An International Conference on

Advances In Mechanisms and Approaches to Neuro-Therapeutics (AIM-AT)
&
XLII Annual Meeting of Indian Academy of Neurosciences 2024 (IAN-2024)

11-14 Nov 2024

Abstract Book

IAN-2024 & AIM-AT

11-14th November 2024

NIMHANS Convention Centre

Halls A, B, and C

NATIONAL INSTITUTE OF MENTAL HEALTH AND NEURO SCIENCES

INSTITUTE OF NATIONAL IMPORTANCE
P.B. 2900, Bengaluru - 560 029 (India)

Dr. Pratima Murthy
MBBS, DPM, MD, FRCP (Glasgow)
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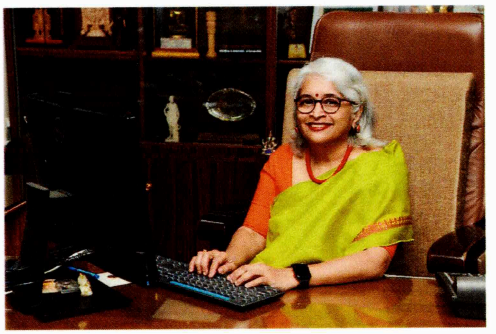
Dear Delegates,



Welcome to the National Institute of Mental Health and Neuro Sciences (NIMHANS)! I am happy to note that you are participating in the **XLII Annual Meeting of the Indian Academy of Neurosciences (IAN) and the International Conference on Advances In Mechanisms and Approaches to Neuro-Therapeutics (AIM-AT)** jointly conducted by the **Department of Clinical Psychopharmacology and Neurotoxicology & the Department of Biophysics at NIMHANS, Bengaluru** from November 12-14, 2024.

I am pleased to see that the scientific program includes presentations by several international and national scientists and researchers. Prof. John Nurnberger, the keynote speaker is a celebrated authority in the field and we are happy to have him for this meeting. The plenary talks, symposia lectures, orations, invited talks and young scientist award-talks on interesting facets of Neurosciences, promise to present the most exciting research findings. I have learnt that approximately 500 participants have registered for the conference including several Ph.D. scholars and clinical residents from NIMHANS and across the country. Besides, national funding bodies like ANRF, DBT, Rohini Nilekani Foundation and International majors like the International Brain Research organization (IBRO) and World Women in Neuroscience are supporting the meeting.

It is pertinent that such a conference is being held at NIMHANS, an institute of national importance, and a tertiary care hospital and referral center for neurological and psychiatric diseases. NIMHANS has been a frontrunner not only in patient care but also in training and research in mental health and neurosciences for several decades.

The last couple of decades have seen research strides in addiction biology, neurodevelopmental brain disorders, aging and associated neurodegenerative diseases among others, via exemplary technological advancements in diagnostics, biomarker discovery, genomics, AI/ML etc. It is interesting that the deliberations during the conference will focus on advancing the field of therapeutics for neuropsychiatric disorders, which is the need of the day!

I wish all of you a comfortable stay and an enriching experience and wish the conference a grand success!

Dr. Pratima Murthy
Director and Senior Professor of Psychiatry
NIMHANS, Bengaluru.

Dr. Pratima Murthy
Director
National Institute of
Mental Health & Neuro Sciences
Bengaluru - 560 029

Registration No.: 79016

INDIAN ACADEMY OF NEUROSCIENCES

(Registered Under Societies Registration Act XXI 1860)

Dr Vinay K. Khanna
PhD, FNASc, FIANS, FST, FAEB
President

November 02, 2024.

Message

It is truly a pleasure that the National Institute of Mental Health and Neuro Sciences (NIMHANS) at Bengaluru, India is hosting the XLII Annual Meeting of the Indian Academy of Neurosciences (IAN) and the International Conference on Advances in Mechanisms and Approaches to Neuro-Therapeutics.

The growing prevalence of neurological and psychiatric disorders is a cause of concern as it not only affects the individuals but also has immense impact on families, healthcare systems and the society. While advances in the technology have improved our understanding on the mechanisms of central nervous system diseases, the complex functioning of the brain continues to present formidable challenges for developing effective treatments and support systems for affected individuals.

I appreciate the endeavours of Dr (Ms) Phalguni Anand Alladi, the dynamic Organizing Secretary and all her colleagues for joining hands together to develop an interesting scientific programme. I am confident that the scientific presentations and discussions at the meeting will offer valuable insights and familiarize researchers with advancements in the area of neuroscience. The discussions will also be helpful in developing strategies to uncover the mysteries of the brain and translate the research findings into meaningful therapies. The participants will have a rewarding experience and the opportunity to build new networks to take up further research with focused efforts for a better future.

Looking forward to a productive and successful meeting.

Vinay Kumar Khanna

Message from the organizers

Dear Colleagues,

Welcome to Bengaluru, the Scientific and Technological hub of India!
While the first part of the 20th century was dominated by pure sciences such as physics and chemistry, the middle part saw the emergence of biochemistry and biology as trending fields of research and academic excellence. The latter part witnessed technological advances in molecular biology with the evolution of genomics and genetic engineering. Everyone believes that the current century belongs to neuroscience. With increased awareness about neurological and psychiatric disorders and scientific inquiry into the complexities of the human nervous system, scientists worldwide are relentlessly pursing neurobiology research ranging from cell biology and biophysics to human cognition, and consciousness.
Every field of neuroscience offers exciting avenues and new challenges in the effort to improve and explore human lives. The tremendous accomplishments in neuroscience are contributed significantly by discussion, deliberation, and collaboration among scientists worldwide, many of which happen in conferences, symposia and workshops.
We are pleased to welcome all of you to NIMHANS, Bengaluru, India, to take part in one such conferences, that is the XLII Annual Meeting of Indian Academy of Neurosciences (IAN) and the International Conference on Advances In Mechanisms and Approaches to Neuro-Therapeutics (AIM-AT). The four-day conference is organized in the NIMHANS Convention Centre (November 11-14, 2024) that aims to discuss the rapid advances in the field of therapeutics for neuropsychiatric disorders. As a part of the scientific program, several international and national scientists will be delivering plenary talks, symposia lectures, and invited talks in diverse fields of Neurosciences. There will be Orations and young scientist award-talks too!
We invite all of you to seize this great opportunity along with your colleagues and students to delve into cutting-edge neuroscience and networking! We assure you of three days of exciting scientific events! We will strive to ensure that you have a pleasant stay in Bengaluru.

Dr. Phalguni A. Alladi
Organizing Secretary

Dr. Bhupesh Mehta
Jt-organizing secretary

Dr. B. Padmanabhan
Organizing Chairperson

Dr. M.M. Srinivas Bharath
Organizing chairperson

List of committee members

Chairperson: Dr. M.M. Srinivas Bharath, Professor & Head, Department of Clinical Psychopharmacology Neurotoxicology; Email: thathachar2010@gmail.com

Joint Chairperson: Dr. B. Padmanabhan, Professor & Head, Department of Biophysics; Email: balapaddy@gmail.com

Organizing Secretary: Dr. Phalguni Anand Alladi, Scientist 'G', Department of Clinical Psychopharmacology Neurotoxicology; Email: alladiphalguni@yahoo.com; Tel: 80-26995108/26995111

Jt. Organizing Secretary: Dr. Bhupesh Mehta, Additional Professor, Department of Biophysics; Email: bhupeshmehta@gmail.com; Tel: +91-080-26995678

Treasurers:

- Dr. Gokulakrishnan K., Associate Professor, Department of Neurochemistry
- Dr. Priyamvada Sharma, Associate Professor, Department of Clinical Psychopharmacology Neurotoxicology

Local Organizing Committee:

- Dr. Sarada Subramanian, Professor & Head, Department of Neurochemistry - Chair SciComm.
- Dr. Anita Mahadevan Professor, Department of Neuropathology, CoChair, SciComm.
- Dr. Nandkumar DN, Professor, Department of Neurochemistry
- Prof. Veena Kumari, Professor & Head, Department of Neuromicrobiology
- Prof. Reeta Mani, Professor & Head, Department of Neurovirology
- Prof. Chethan GK, Professor, Department of Human Genetics
- Dr. Chinnathambi Subashchandrabose, Additional Professor, Department of Neurochemistry
- Dr. Shantala Hegde, Additional Professor, Department of Clinical Psychology
- Dr. Indrani Datta, Additional Professor, Department of Biophysics
- Dr. BN Srikumar, Additional Professor, Department of Neurophysiology
- Dr. Yogananda SM, Associate Professor, Department of Biophysics
- Dr. Sivaraman Padavattan, Associate Professor, Department of Biophysics
- Dr. Kruthika Vinodh, Senior Scientific Officer, Department of Neurochemistry
- Dr. Shilpa Rao, Associate Professor, Department of Neuropathology
- Dr. Manjunatha MV, Additional Professor, Department of Neurovirology
- Dr. Rajeshwarie, Associate Professor, Department of Neuropathology

PROGRAM SCHEDULE

Program	Inauguration; 11-11-2024
16:00 - 18:10	**Hall A: Inaugural Function** **Invocation** **Lamp Lighting** **Welcome Address** **IAN Secretary's Report** **Address by the Guests of Honour** Dr. B.L. Sujatha Rathod, The Director of Medical Education, Govt. of Karnataka Dr. Vinay Kumar Khanna, Chief Scientist IITR, Lucknow & President, IAN **Felicitation of Newly Elected IAN Fellows** **Presidential Address,** Dr. Pratima Murthy, Director, NIMHANS **Vote of Thanks,** Dr. B.S.S. Rao, Registrar, NIMHANS **Prof. P.N. Tandon Oration,** Dr. Pratima Murthy, Director, NIMHANS
18:10 - 18:50	**Hall A: Keynote Address** **Prof. John Nurnberger,** Distinguished Professor Emeritus, Indiana University School of Medicine, USA
19:00 onwards	**Dinner**

Schedule

DAY 1: 12-11-24

08:00	Registration & Breakfast
9:00-9:45	**Plenary Talk:-Hall A** **Title:-** Neural plasticity and brain repair mechanisms - new challenges in treatment of neuropsychiatric disorders; **Chairperson:** Dr. Deepak Nair, IISc, Bangalore, India. Dr Biju Vishwanath, CBM, NIMHANS, India. **Speaker:-** Dr. B.S. Shankaranarayana Rao, Prof. of Neurophysiology, Registrar, NIMHANS, India.
9:45-10:15	**Special Talks:- Hall A** **Title:-** Neuroinflammation, Viral Infection and neurodegeneration: A conversation across borders? **Chairpersons:-** Dr Anita Mahadevan, NIMHANS, Bengaluru Dr Arvind Kumar, CCMB Hyderabad **Speaker:- Dr. Martin Korte,** Department of Cellular Neurobiology, TU Braunschweig Zoological Institute, Germany.
10:15 - 10:45	**Special Talks:- Hall A** **Title:-** The complex GPCR pharmacology of a Southeast Asian natural products **Chairpersons:** Dr. Ravi Yadav, NIMHANS, Bengaluru Prof. Vinay K. Khanna, IITR, Lucknow. **Speaker: Dr. Lance McMahon,** Senior Vice President for Research and Innovation, Professor of Pharmaceutical Sciences and Medical Education, Texas Tech University Health Sciences Center, USA.
	Special Talks:- Hall B **Title:-** Neurobiology of Noncoding RNAs in Alzheimer's Disease and Potential for Translational Prospects **Chairpersons**: Dr. Mathew Varghese, Senior Professor of Psychiatry, NIMHANS, Bengaluru. Prof. Miroslaw Janowski, University of Maryland, Baltimore, USA **Speaker: Dr. Debomoy Lahiri,** Distinguished Professor, Indiana University School Medicine, Indianapolis, USA.
10:45 - 11:15	*Tea*
11:15 - 13:15	**Hall A: Symposium I** **Title:-** Drug Discovery and Development: Focus on Neurological Ailments. **Convener & Chair-** Dr. Aamir Nazir CSIR-CDRI, Lucknow. **Chairperson:** Dr. Netravathi, NIMHANS, Bengaluru **Speakers:-** • Dr. Amir nazir, CSIR - CDRI, Lucknow, U.P. Title:- PTR-10, the C. elegans Homolog of Human PTCHD1, Plays a Crucial Role in Neuroprotection. • Dr. Rajappa Kenchappa, Mayo Clinic, Jacksonville, USA Title:- Antimitotics in Glioblastoma Therapy • Dr. Ravi Yadav, NIMHANS, Bengaluru Title:- Latest therapeutic regimens for Parkinson's disease • Dr. Ishwariya Venkatesh, Centre for Cellular & Molecular Biology, Hyderabad Title:- Molecular Approaches to Treat Spinal Cord Injury • Dr. Syed Shadab Raza, Lucknow Medical College and Hospital, Lucknow Title:- Unmasking a complex regulatory relationship between NLRP3 inflammasome, SIRT3,and the acetylation of SOD2 in ischemic stroke. • Dr Vatsala Thirumalai, NCBS, Banaglore Title:-Assembly and functioning of cerebellar circuits

	Hall B: Symposium II **Title:-** Prion-like properties of Inherently disordered proteins: Effects on the bio-physiological processes in the CNS. **Convener & Chair:** Dr. Sivaraman Padavattan, NIMHANS, Bengaluru. **Chairperson:** Dr. Sangeeta Nath, Manipal Institute of Regenerative Medicine, Bengaluru **Speakers:-** • Dr. Aravind Penmasta, Indian Institute of Science, Bengaluru Title:- Insights into GABA reuptake and inhibitory mechanisms at the neural synapse • Dr. Sivaraman Padavattan, NIMHANS, Bengaluru. Title:-α-Synuclein: unveiling its cellular functions. • Dr. Sangeeta Nath, Manipal Institute of Regenerative Medicine, Bengaluru Title:- Plasma membrane repair upon damage induced by Amyloid-β oligomers • Dr. Anand Srivastava, Indian Institute of Science, Bengaluru Title:- Molecular Basis of Small-Molecule Binding to Intrinsically Disordered Proteins: Design principles from biomolecular simulations and machine learning approaches • Dr. Srinivasa Subramaniam, UF-SCRIPPS Research, USA Title:- Mechanism of cell-to-cell Huntington disease protein transmission • Dr. Deepak Sharma, CSIR-IMTECH Title:- IPD1 prevents α-synuclein pathology and halts neurodegeneration in a mouse model of Parkinson's disease
11:15 - 13:15	**Hall C: Symposium III** **Title:-** Insights into Pathogenic Mechanisms and Treatment Strategies for Neurodegenerative Diseases **Convener & Chair:** Dr. Ashutosh Kumar, AIIMS-Patna. **Chairperson:** Prof. Yasha TC, Dean NIMHANS. **Speakers**:- • Dr. Ashutosh Kumar, AIIMS-Patna. Title:- Continued Hippocampal Neurogenesis in Adult Humans: A Hope for Combating Alzheimer's Disease. • Dr. Akash Gautam, University of Hyderabad, Telangana Title:- Targeting the Brain Renin-Angiotensin System for the treatment of diabetes-induced cognitive disorders • Dr. Anil Kumar Chouhan, University of Iowa, USA Title:- Targeting metabolic enzyme Pyruvate Kinase M2 provides cerebroprotection following ischemic stroke onset • Dr. Ashok K Datusalia, NIPER, Lucknow, U.P. Title:- Targeting Homeostatic plasticity through NMDA Receptor modulation in the treatment of stress Disorders • Dr. Tulika Gupta, PGIMER, Chandigarh Title:- Mitochondrial therapy to combat the metabolic dysfunctions in Alzheimer's disease
13:15-14:00	Lunch

14:00 -16:00	**Hall A: Symposium IV** **Title:-**"Sleep Counts" for a healthy brain: Insights from autonomic, neurovisceral and muscular integration **Convener & Chair:** Dr. Kamalesh Gulia, SCTIMST, Thiruvananthapuram. **Chairperson**: Dr. Bindu M. Kutty, NIMHANS, Bengaluru **Speakers**: • Dr. Kamalesh Gulia, SCTIMST, Thiruvananthapuram Title: Role of prenatal sleep in shaping the behavioural phenotypes of offspring: Complex modulation of heart-brain networks • Dr. HN Mallick, AIIMS, New Delhi Title:- Electroencephalographic arousal is earlier than electromyographic arousal • Dr. Ravindra N, NIMHANS, Bengaluru Title:- Randomness is characteristics of sleep-in meditators • Dr. Sushil Jha, JNU, New Delhi Title:- Why does memory consolidation require sleep? • Dr. Nasreen Akthar, AIIMS, New Delhi Title:- Memory Encoding and Sleep in Older Adults: A Neurocognitive perspective
	Hall B: Symposium V **Title:-**Women Clout!! Prominent and Rising Women Speakers **Convener & Chair:** Dr. Sumana Chakravarty, IICT, Hyderabad. **Chairperson:** Dr. Gurcharan Kaur, Panjab University, Punjab **Speakers**: • Dr. Sumana Chakravarty, CSIR-IICT, Hyderabad. Title: Differential levels of post-cerebral ischemia recovery in males and females are mediated by Sex-distinctive epigenetic modifications • Dr. Indrani Datta, NIMHANS, Bengaluru Title:- Advancing Parkinson's Disease Modeling for Personalized Medicine: Insights from patient-derived iPSCs with the LRRK2 I1371V Mutation • Dr. Aditi Naskar, Yale University, USA Title:- "Hitchhiking" on lysosomes: lysosome-dependent and independent mechanisms underlying axonal transport of TDP43-RNP condensates • Dr. Rugmani Meenambal, Christ University, Bengaluru Title:- Influence of europium doping on neuroprotective potential of polyacrylic acid functionalized cerium oxide nanoparticles • Dr. Chanda Kulkarni, IDD Research Solutions INC, Bengaluru, India Title:- Monitoring age-related factors influencing pharmacotherapy with anti-seizure medications [ASMs] among elderly persons with epilepsy [EPWE]: Challenges and solutions for corrective and preventive measures. • Dr. Meera Purushottam, NIMHANS, Bengaluru Title:- Study of Neuropsychiatric Illness : A journey

14:00 -16:00	**Hall C: Symposium VI** **Title:-** Genetics and epigenetics of neurodevelopmental and psychiatric disorders **Convener:** Dr. Arpita Konar, Presidency College, Kolkata. **Chairperson:** Dr. Jackson James, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapura **Speakers:** • Dr. Arpita Konar, Presidency College, Kolkata. Title:- Epigenetic memories of stressful experiences and impact on Aggression • Dr. Amrutha Swaminathan, IISER , Thiruvananthapuram Title:- Understanding the contribution of immune factors to stress-responsive behaviour • Dr. Bharath Holla, NIMHANS, Bengaluru Title:-A cross ancestry genetic study of psychiatric disorders from India • Dr. Bhavana M, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru Title:-Dissecting Molecular Mechanisms of Neurodevelopmental Chromatinopathies • Dr. Mainak Sengupta, University of Calcutta, Kolkata Title:- Genetics of cognition in disease and well-being • Prof. Amal Kanti Bera, IIT Madras, Chennai Title:- Pannexin and P2X7 Receptor Crosstalk: A Key Determinant of Cell Fate
16:00 -17:30	Tea & Poster session
17:30-19:00	**Hall A** **Title:-** World Women in Neuroscience Program: Resilience in Science **Panelist:** Prof. Suvarna Alladi Dr. Shantala Hegde Dr. Nisha Patro panelist
	Hall C: Symposium VII **Title:- Insights into Stroke, Tumorigenesis and Autophagy** **Oral Presentation-1** **Chairperson:** Dr Yoganarasimha, NIMHANS, Bengaluru Dr B N Srikumar, NIMHANS, Bengaluru **Speakers:** • Dr. Pramod Avti, PGIMER, Chandigarh Title:- Regulation of PPAR-γ and TLRs Expression in Ischemic Stroke Model Through PPAR-γ Agonist: A New Paradigm in Stroke Treatment • Dr. Ashok Kumar Rastogi, AIIMS, Patna Title:- Hypothalamus centered Pathogenesis of Heat Stroke Deaths- A Postmortem Study • Dr. Mehdi Hayat Shahi, Aligarh Muslim University, Aligarh Title:- Heavy metal Cadmium may induce potential brain tumor development by up-regulating mitogenic Shh-Gli1 (Sonic Hedgehog-Gli1) cell signaling pathway and stem cell marker BMI1(B lymphoma Mo-MLV insertion region 1 homolog) • Dr. Abhishek Kumar Singh, Manipal Academy of Higher Education, Manipal Title:- Rapamycin alleviates amyloid-beta-induced disruptions in redox balance and synaptic neurotransmission by activating autophagy and pro-survival signaling pathways • Dr. Ravish H, NIMHANS, Bengaluru Title:-Status of serum vitamin B12, homocysteine, folate and Hindi mental examination scale (HMSE) in older adults with psychiatric illness: A chart review from a tertiary care centre
19.00-20:0	Dining area: IBRO Networking & Refreshments! Followed by Dinner...

Day 2: 13-11-24

08:00-08:30	Registration & Breakfast
08:30-09:15	**Hall A: Prof. SS Parmar Oration** **Dr. Sandhya Kaushika,** Associate Professor,Dept. of Biological Sciences, Tata Institute of Fundamental Research, Mumbai. **Chairpersons:** Dr. Pankaj Seth, NBRC, Manesar, Dr. Subhash C Pandey, Department of Psychiatry, University of Illinois, Chicago, USA Dr. Phalguni Anand Alladi, NIMHANS, Bengaluru.
09:15-10:30	**Hall A:** Presentations for **"Tulsabai Somani Educational Trust Award"** **Chairperson** Kavita Seth, CSIR-IITR, Lucknow Nisha Patro, Jiwaji University, Gwalior
10:30 - 11:00	Tea
11:00 -13:00	**Plenary Talks: Hall A** **Title:-** Essentials of Bed-side and Bench **Chairpersons:-** Prof. Rajat Sandhir, Panjab University Dr Vivek Benegal, NIMHANS, Bengaluru **Speakers** **Dr. Mirosław Janowski**, Co-Director, Program in Image Guided Neurointerventions, Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, USA.Neuromuscular Disorders Title:- Guideomics - beyond image guidance for neuroscience. **Dr. A. Nalini,** Department of Neurology, NIMHANS, Bengaluru. Epigenetics of Depression and Neuro-Psychiatric disorders Title:- Amyotrophic Lateral Sclerosis: Current Concepts and Therapeutic Approaches **Dr. Arvind Kumar**, former Principal Scientist, CCMB, Hyderabad. Title:- Epigenetics of Depression and Neuro-Psychiatric disorders **Dr. Subhash Pandey**, Director, Alcohol Research Center, Dept. Psychiatry, University of Illinois, Chicago. Title:- Neuroepigenetics of Alcohol Use Disorder: Mechanisms, Phenotypes, and Treatment
13:00 - 13:45	Lunch
13:45 - 15:15	**Hall A: Symposium VIII** **Title:-** From animate to inanimate - to brain! Trends in Neuro-Virology **Chairpersons:** Prof. Yasha TC, NIMHANS, Bengaluru Dr.Reeta Mani, NIMHANS, Bengaluru **Speakers**: • Dr. Manjunatha MV, NIMHANS, Bengaluru Title:- Probing the in vitro neuropathogenesis of SARS-CoV-2 to understand neurological complications of COVID-19! • Dr. Pankaj Seth, NBRC, Gurgaon Title:- Insights into SARS-CoV2 mediated Neuronal Damage - Possible Mechanisms of Brain Fog in Long COVID-19 cases • Dr. Jayasri Das Sarma, IISER, Kolkata Title:- Neuroinflammation to Neurodegeneration: Finding the Roadmap for Developing Anti-β Coronaviral Therapeutics • Dr. Gurudutt Pendyala, USA Title:- Mechanisms underlying prescription opioid use post social defeat in HIV+ adolescents. • Dr. Dinesh Upadhya, Manipal Academy of Higher Education, Manipal Title:- Glucuronoxylomannan from Cryptococcus neoformans preferentially targets neurons in immune-deficient human cerebral organoids

13:45 - 15:15	**Hall B: Symposium IX** **Title:-**Stars of Neurosciences – Recognized and Rising!! **Chairperson & Convener:** Dr. Varun Bhaskar, JNCASR, Bengaluru. **Chairperson:** Dr. Ravi Manjithaya, JNCASR, Bengaluru. • Dr. Varun Bhasker, JNCASR, Bengaluru Title:- Elucidating the combinatorial effects of C9ALS/FTD-associated disease factors on RNA metabolism! • Dr. Pradeep Kumar, WITS, South Africa Title:- Functionalized Nano-medicinal Strategies and Interventions for Neurodegenerative Disorders • Dr.Senthil Kumar Thangaraj, NCCS Pune Title:- Understanding Brain Diseases: Elucidation of Disease Mechanisms and Essentials of Drug Discovery Research • Dr. Vaibhav Vemuganti, University of Wisconsin, USA Title:- Microbially modulated metabolites are risk factors of Alzheimer's disease and related dementias. • Dr. Subhadeep Datta Gupta, NIH, USA Title:- Understanding Reserve and Resilience in Aging Through Social Cognitive Lens. • Dr. Rajesh Singh Yadav, National Forensic Sciences University, Bhopal Title:- Neurotoxic effect of nano-formulation of neonicotenoid pesticides in mice.
	Hall C: Symposium X **Title:-** Neurotrophic Signaling and Neurodegeneration: New Frontiers in Neuronal Survival and Neurodegeneration **Oral Presentation-2** **Chairperson & Convener:** Dr. Sharmistha Dey, AIIMS, New Delhi **Chairperson: D**r. Sabita Mishra, Maulana Azad medical College, New Delhi • Dr. Kavita Seth, CSIR Indian Institute of Toxicology Research, Lucknow Title:- Nanoparticle Mediated Management of Dopaminergic Neurodegeneration • Dr. Sanjay Das, Drexel University, USA Title:- Activation of EAAT2 impacts impulsive behavior by reducing glutamate excitotoxicity in Parkinson's disease • Dr. Adil Asghar, AIIMS, Patna Title:- Olfactory Bulb Shrinkage in Parkinson's Disease: Insights from a Meta-Analysis • Dr. Richa Gupta, Nirma University, Ahmedabad Title:- Cadmium and Movement Disorders: Molecular Insight to Preventive Intervention. • Dr. Amrita Pathak, Amity University, Noida Title:- Retrograde death signaling in neurons by pan neurotrophin receptor p75NTR • Dr. Soumya Pati, Shiv Nadar University, Gautam Buddha Nagar, Title:- Small-molecule nutraceuticals, rescued the NADPH Metabolism in Glucose-6-Phosphate Dehydrogenase deficient (G6PDd) microglia; thus suggested the new-age neurotherapeutics for ASD
15:15 - 16:45	Tea & Poster session
16:45 - 18.15	**Hall A: Symposium XI** **Title:-**Riders of Aging, Cognitive decline, and Alzheimer's disease **Chairperson & Convener:** Prof. Suvarna Alladi, NIMHANS Bengaluru **Chairperson:** Prof. Sarada Subramanian, NIMHANS Bengaluru • Dr. Suhail Rasool,TrueBinding Inc. California, USA Title:- Potential reversal of Alzheimer's Disease pathology by novel TB006 antibody • Dr. Rajashekhar Gangaraju, University of Tennessee Health Science Cente, USA Title:- Engineered Exosome-driven Therapy: Combatting Visual and Cognitive Decline with Anti-Inflammatory TSG-6 • Dr. Latha Diwakar, CBR-IISc, Bengaluru Title:- Rodent model of small vessel dysfunction in understanding molecular aspects of dementia. • Dr. Reddy P. Kommaddi, CBR-IISc, Bengaluru Title:- Synaptic actin cytoskeleton: Implications in Alzheimer's disease • Dr. Muddanna Rao, Kuwait University, Kuwait Title:- Impaired insulin signaling decreases the Hippocampal neurogenesis by decreasing pro-proliferative factor and neuronal determination markers -development of sporadic Alzheimer's disease.

	Hall B: Symposium XII **Title:-** Glia: The Trapeze artists! **Chairpersons:** Dr. Ishan Patro, Jiwaji University, Gwalior Dr. Nandakumar DN, NIMHANS, Bengaluru • Dr. Mohammad Moshahid Khan, University of Tennessee Health Science Cente, USA Title:- Persistent DNA damage response drives neuroinflammation after traumatic brain injury in mice • Dr. Subhas Chandra Biswas, IICB, Kolkata Title:- ICAM-1 reprograms microglia to ameliorate amyloid pathology and cognitive functions in a model of Alzheimer's disease. • Dr. Sudip Sen, AIIMS, New Delhi Title:- Deciphering the neuroprotective role of astrocytes in hypoxic brain injury by understanding glial cholesterol redistribution to sustain oligodendrocytes in vitro • Dr. Kaushik P Sharma, Swami Rama Himalayan University Uttarakhand, India Title:- Exploring Non-Neuronal Therapeutic Targets for Epilepsy: A Novel Approach to Regulating Hyperexcitability • Dr. Kanchan Bisht, Swami Rama Himalayan University Uttarakhand, India Title:- Unveiling Microglial Heterogeneity: Multifaceted Guardians of Brain Health and Disease
16:45 - 18.15	**Hall C: Symposium XIII** **Title:- Exploring Metabolic, Biochemical and Neurobiological Correlates in Neuropathology and Mental Health** **Oral Presentation-3** **Chairperson:** Dr Subhasree Ramakrishnan, NIMHANS, Bengaluru Dr. T. N. Sathyaprabha, NIMHANS, Bengaluru Dr Bhupesh Mehta, NIMHANS, Bengaluru **Speaker** • Dr. Yogitha Adlakha, Amity University, Noida Title:- Vitamin D signaling modulates human neural stem cell fate • Dr. Simantini Ghosh, Ashoka University, Rai Sonepat Title:- Chymase and tryptase from mast cells mediate blood-brain barrier and neurobehavior dysfunction in a rodent model of anxious depression • Dr. Gayathri S Prabhu, Manipal Academy of Higher Education, Manipal Title:- Neuro-protective Effects of Choline and DHA or Environmental Enrichment on Hippocampal Neural Cells in Early Life High Fat Diet-Induced Obese Adult Rats • Dr. Gulshan Kumar, NIMHANS, Bengaluru Title:- Neurophysiological correlates of dream recall: Insights from serial awakening paradigm in REM and NREM Sleep • Dr Anil Annamneedi, SRM Institute of Science and Technology, Tamil Nadu, India Title:- Biochemical Changes Linked to the altered social Environment and its Effect on social, Behavioral Alterations Related to neuropathology
18:15 - 19.15	Hall A: Governing Body Meeting
19.15 onwards	Hall A: Cultural Program Followed by Dinner

Day 3: 14-11-24

08:00-08:30	Registration & Breakfast
08:30-09:45	**Hall A** **Presentations for the D.M. Kar Prize** **Chairpersons:** Dr. Phalguni Anand Alladi, NIMHANS, Bengaluru Dr. Prachi Srivastava, AMITY UNiversity, Lucknow
09:45 -10:30	**Hall A** **Prof. K.T Shetty Memorial Oration** **Dr. Samarjit Bhatacharrya,** Professor, Department of Biological Sciences, Indian Institute of Science Education and Research (IISER) Mohali. **Chairpersons:** Dr Akshay Anand, PGIMER, Chandigarh Dr M M Srinivas Bharath, NIMHANS, Bengaluru
10:30 - 11:00	Tea
11:00 -11:30	**Plenary Talk:-** **Hall A** **Title:-** Epigenetics: Application in spinal injuries **Chairpersons:** Dr M M Srinivas Bharath, NIMHANS, Bengaluru Dr B Padmanabhan, NIMHANS, Bengaluru **Speaker:** Dr. Tapas Kundu, Professor, JNCASR, Bengaluru.
11:45 - 13:45	**Hall A: Symposium XIV** **Title:-** Neuromodulation and Neurological Disorders: Role of the Gut Brain Axis **Chairperson & Convener:** Prof. Suman Jain, AIIMS, New Delhi. **Chaiperson:** Dr Akshay Anand, PGIMER, Chandigarh **Speakers** • Prof. Suman Jain, AIIMS, New Delhi Title:-Modulation of cortical excitability, plasticity and gut motility in hemiparetic Cerebral Palsy patients: Role of Probiotics • Dr. Vinod Tiwari, IIT-BHU, Varanasi Title:- Gut microbiome and neuropathic pain • Dr. Gokulakrishnan K, NIMHANS, Bengaluru Title:-Gut Microbiome Patterns: Assessing Clinical Relevance in Schizophrenia • Dr. Manorama Patri, Central University Himachal Pradesh, Dharamsala Title:- Computational system biology approaches to understand the gut-brain connections in neurodegenerative diseases • Dr. Prachi Srivastava, Amity Institute of Biotechnology, Lucknow Title:- Diving into Microbiome Gut-Brain Axis to Predict Biomarkers Through AI • Dr. Akshay Anand, PGIMER, Chandigarh Title:- Number of hUCB-derived Lin-ve stem cells is crucial for effective amelioration of retinal injury and improvement in associated memory
11:45 - 13:45	**Hall B: Symposium XV** **Title:-** Essentials of Protein aggregation in neurodegenerative diseases **Chairperson & Convener:** Dr. Poonam Thakur, IISER-Thiruvananthapuram, Kerala **Chairperson:** Dr Nitish Kamble, NIMHANS, Bengaluru **Speakers** • Dr. Poonam Thakur, IISER, Thiruvananthapuram. Title:- Influence of glycation modification on alpha-synuclein structure and pathology • Dr. Deepak Nair, Indian Institute of Science, Bangalore Title:-Heterogeneity of molecular organization at single synapses drives onset of Alzheimer's disease • Dr. Neha Jain, IIT Jodhpur, Jodhpur, Rajasthan Title:-Modulation of amyloid assembly by chaperone-like proteins

11:45 - 13:45	**Hall B: Symposium XV (Continued..)** **Title:-** Essentials of Protein aggregation in neurodegenerative diseases **Chairperson & Convener:** Dr. Poonam Thakur, IISER-Thiruvananthapuram, Kerala **Chairperson:** Dr Nitish Kamble, NIMHANS, Bengaluru **Speakers** • Dr. Subashchandrabose Chinnathambi, NIMHANS, Bengaluru Title:- LC-3-associated phagocytosis facilitates extracellular Tau internalization and degradation in microglia • Prof. Rajnikant Mishra, Institute of Science, Banaras Hindu University, Varanasi Title:- Pax6 regulates genes associated with motor and non-motor function in brain of MPTP-treated mouse model of Parkinson's disease
11:45 - 13:45	**Hall B: Symposium XVI** **Title:-**Advances in molecular medicine- Seizures, Schizophrenia and more **Chairperson & Convener:** Dr Pradeep Punnakkal, PGIMER, Chandigarh **Chairperson:** Dr Sanjib Sinha, NIMHANS, Bengaluru **Speakers** • Dr. Pradeep Punnakkal, PGIMER, Chandigarh Title:- Third-generation antiseizure medication: Effects on excitatory and inhibitory currents and synaptic plasticity in the hippocampus. • Dr. Christhunesa Soundarajan, Christian Medical College, Vellore Title:- Biology of the Blood-Brain Barrier • Dr. Shobi Veleri, ICMR-National Institute of Nutrition, Hyderabad Title:- Insights into the molecular signature of neurodegeneration in WNIN/Ob rat • Dr. Subash Susai, Beaumont Hospital, Ireland Title:-Therapeutic importance of complement pathway proteins in early intervention in psychosis: A proteomic based validation study in Clinical High Risk and First Episode Psychosis patients • Dr. Suneel Kateriya, Jawaharlal Nehru University, New Delhi Title:- Development of optogenetic tools for delineating neural signaling and associated diseases
13: 45 -14:30	Lunch
14:30 -16:30	**Hall A: Symposium XVII** **Title:-** Autism Spectrum Disorder: Genetic and neural circuit dysfunction of developing brain **Chairperson & Convener:** Dr. Sourav Banerjee, NBRC, Manesar. **Chairperson:** Prof. Rajat Sandhir, Panjab University, Punjab **Speakers** • Dr. Sourav Banerjee Title:- RNA-based mechanism of inhibitory synapse development: Implications in autism. • Dr. Sharba Bandopadhyay, IIT Kharagpur Title:- Alterations is cortical processing of context specific vocalization sequences in a mouse model of autism spectrum disorders • Dr. Sheffali Gulati, AIIMS, New Delhi Title:-Etiopathogenesis of Autism Spectrum Disorder: A Multifactorial Approach based on genetics and epigenetics • Dr. Soumya Iyengar, National Brain Research Centre, Manesar Title:- Using Zebra finches as a model system to study Vocal Deficits in Neurodevelopmental Disorders • Dr. Soumya Sundaram, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Kerala Title:- Autism spectrum disorder and epilepsy -A complex interplay!

14:30 -16:30	**Hall B: Symposium XVIII** **Title:-** Horizons & Expanse of Neurosciences! **Chairperson & Convener:** Dr. Anita Jagota, University of Hyderabad, Hyderabad **Chairperson:** Dr. TR Raju, Sankara Academy of Vision **Speakers** • Dr. SP Arun, IISc, Bengaluru Title:- Neural basis of real-world vision • Dr. Tapas Chandra Nag, AIIMS, New Delhi Title:- A presynaptic autophagic dysregulation that underlies photoreceptor cell vulnerability in aging human retina • Dr. Meenakshi Bawari, Assam University, Assam Title:- In silico analysis of phytoconstituents targeting N-methyl-D-aspartate, acetylcholine, γ-aminobutyric acid, and dopamine receptors for therapeutic use in learning and memory • Dr. Tony Jacob George, AIIMS, New Delhi Title:- The penguin brain: a morphological and magnetic resonance imaging • Dr. Radha Chaube, BHU, Varanasi Title:- Identification, Localization and significance of neuropeptides in non-mammalian vertebrates • Dr. Anita Jagota, University of Hyderabad Title:- Circadian Misalignment in Aging and Neurodegeneration : Therapeutic Interventions
	Hall C: Symposium XIX **Title:-** Artificial Intelligence and Machine Learning in Neurosciences **Chairperson & Convener:** Dr. Sudip Paul, NEHU, Shillong. **Chairperson:** Dr Nandeesh B N, NIMHANS, Bengaluru **Speakers** • Dr. Sudip Paul, NEHU, Shillong. Title:- Parkinson's Disease Risk Classification: A Deep Learning-based Artificial Intelligence Approach • Dr. Sridharan Devrajan, Indian Institute of Science, Bangalore Title:-Identifying connectivity markers of brain aging and cognitive decline with deep learning models • Dr. Mahesh Maindarkar, Maharashtra Institute of Technology, Pune Title:-CVD risk stratification in PD patients using AI • Dr. Sanjay Saxena, International Institute of Information Technology, Bhubaneswar Title:- An Integrated Radiomics-Attention-Graph Network for Prognostic Prediction in IDH-Wildtype Glioblastoma Multiforme (GBM) Patients • Dr. Vivek Tiwari, IISER Berhampur, Odisha Title:- 'Radiomics and RadioGenomics in Aging Associated Disorders and Gliomas'
16:30 - 17:30	Tea & Poster session
17:30-18.30	**Hall A: Symposium XX** **Title:-**Neurobiological Insights and Biomarker Alterations in Neuropsychiatric Disorders and Neurodegenerative Disorders **Oral Presentation- 4** **Chairperson:** Dr Veena Kumari, NIMHANS, Bengaluru Dr Tony Jacob, AIIMS, New Delhi **Speakers** • Dr. Sampath Kumar Madhyastha Uppoor Title:- Serotonergic Neuroreceptor manipulation ameliorates ADHD Symptoms in Spontaneously Hypertensive Rats by altering the expression of Dopamine DA1 and DA2 Neuroreceptors in the Prefrontal cortex and the Striatum • Dr. Swagata Ghatak, NISER, Bhubaneshwar Title:- Hyperexcitability in early stages of Alzheimer's Disease causes aberrant expression of two pore domain leak potassium channels. • Dr. Suryanarayan Biswal, Central University of Punjab, Bathinda Title:- Unravelling Depression: A Molecular Meta-Analysis of Blood Biomarkers in MDD. • Dr. Uttam Kumar, Center of Biomedical Research, Lucknow Title:-Resting-State Brain Networks and Graph Theory: Unlocking Signatures to Differentiate Adolescent Mood Disorders

17:30-19.00	**Hall B: Symposium XXI** **Title:- Innovations in Neurotherapeutics: Systems Biology, Nutraceuticals, and Pharmacology** **Oral Presentation -5** **Chairperson:** Dr. Vivek Jain, IISER Berhampur, Odisha Dr. Prem N Yadav, CSIR-CDRI, Lucknow **Speakers** • Dr. Kumari Preeti, Dayananda Sagar University, Bangalore Title:-Lipid metabolism predictive analysis: Implying in finding genetic commonality Between Alzheimer's Disease and Metabolic Syndrome • Dr. Prabha M, Ramaiah Institute of Technology, Bengaluru Title:-Investigation for Anticancerous agents with Lithium and Turmeric extract on specific activity of β-galactosidase and Acid Phosphatase in glioblastoma (LN229) cell lines • Dr. Bhagawati Saxena, Nirma University, Ahmedabad Title:-Mechanistic investigation of Trigonelline hydrochloride for alleviating the oxidative stress, neuroinflammation and functional disabilities in rat model of traumatic brain injury • Dr. Chettiar Ganesh Kumar, Kasturba Medical College, Mangalore Title:-Efficacy of Spondias pinnata bark extract as an adjuvant for the management of chemobrain by alleviation of oxidative stress in etoposide administered Wistar rats • Dr. Kaushik Kumar Dey, St. Jude Children's Research Hospital, Memphis, USA Title:-Multi-omics & Systems Biology Approach reveals mitochondrial associated proteins in Alzheimer's disease progression • Dr. Somasish Ghosh Dastidar, Manipal Academy of Higher Education, Manipal Title:- Exploring the therapeutic potential of natural Nutraceutical in reducing neuroinflammation and enhancing motor function in Parkinson's Disease.
17:30-19.00	**Hall C: Symposium XXII** **Title:- From Retina to Brain: Unveiling Pathological Mechanisms and Therapeutic Targets** **Oral Presentation -6** **Chairperson:** Dr Sheeba Vasu, JNCSR, Bengaluru Dr. Rajeswarie RT, NIMHANS, Bengaluru **Speakers** • Dr. Mayanglambam Dhruba Singh, National Brain Research Centre, Manesar Title:-Downregulation of Pten ameliorates Huntington's disease in Drosophila model • Dr. Pankaj Kumar, Indira Gandhi Institute of Medical Sciences, Patna Title:-Quercetin role in tackling endothelial cell degeneration of retinal capillaries in DR. • Dr. Anwesha Bhattacharyya, Amity University, Noida Title:-Changes in the primary visual cortex (V1) during retinal degeneration in rd1 mice model • Dr. Madhumita P. Ghosh, Amity University, Noida Title:-Regulation of Vascular Endothelial Growth Factor is significant in the pathology of glaucoma, diabetic retinopathy and retinoblastoma • Dr. Goutam Chandra, Mahatma Gandhi University, Kottayam Title:- Dysregulation of lysosomal pH and cathepsin processing contribute to the pathogenesis of infantile Batten disease
19.00 Onwards	**Hall A:** Valedictory Function & High Tea

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Prof. B.K. Bachhawat Life Time Achievement Award is conferred on a Neuroscientist for their scientific accomplishments and research contributions in the area of Neurosciences.

Dr. Shashi Bala Singh
Former Distinguished Scientist and DG-Life Sciences, DRDO and Director, NIPER, Hyderabad

Dr. Shashi Bala Singh was a Distinguished Scientist and Director General (Life Sciences) at DRDO HQS, New Delhi. In addition, Dr Singh has the distinction of serving as the Director of two premier research institutions, namely, the Defence Institute of HighAltitude Research (DIHAR), Leh and the Defence Institute of Physiology and Allied Sciences (DIPAS) Delhi. She has also served as the Director of the National Institute of Pharmaceutical Education and Research (NIPER) Hyderabad.

She is an alumnus of All India Institute of Medical Sciences (AIIMS), where she obtained her MSc and Ph.D. degrees in Human Physiology and won the Dr. B.K. Anand Gold Medal as the best graduating student. She received her D.Sc. from Bharathiar University, Coimbatore.

Dr Shashi's active involvement in research led to "using translational research for improving life of troops at high altitude." Her endeavours have made "the life of troops comfortable in the most difficult-to-inhabit terrains." During her tenure as Director at Leh, she created an innovative agricultural ecosystem that enabled Ladakh's socio-economic development via science and technology.

Under her guidance, various technologies/ products like oxygen enrichment facilities, Sourja (solar shelter), Bukhari, and Alocal (for frostbite) were improvised. In addition, she has been instrumental in customising various yoga packages for high altitude and hot desert conditions.

For her significant contribution to Defence technologies, Dr Singh received many awards and honours, including the Scientist of the year award from the Hon'ble Prime Minister of India, the Macro innovation foundation Award, and the CSIR award for Innovation and Technology spin-off award. Under her leadership, DIHAR & DIPAS were awarded the Titanium Trophy by the Hon'ble PM for the best Science Laboratories of DRDO.

She is also an elected Fellow of the National Academy of Medical Sciences **(FNAMS, National Academy of Sciences, India, FNASC) and the Indian Academy of Neurosciences (FIAN).** She has nearly 270 publications in national and international journals. She has successfully commercialised and transferred several of her technologies and has 22 patents to her credit. Technology transfers of 10 products given to industries are under commercial production. In addition, she has supervised 24 PhD students.

Prof Pratima Murthy
Director, National Institutes of Mental Health and Neurosciences awarded the Prof PN Tandon Oration

2024

Prof PN Tandon Oration is bestowed to a Neuroscientist for his/her scientific accomplishments and contributions in clinical neurosciences and allied sciences in India

Dr Pratima Murthy,
MD, DPM, FRCP (Glasgow)
Senior Professor of Psychiatry National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029

Dr Murthy was educated in Bangalore, she graduated from the Bangalore Medical College batch of 1979. Subsequently Dr Murthy completed Diploma (1985-87) and MD (1987-89) in Psychiatry from NIMHANS and received the outstanding student award in both courses.

She obtained a Diploma in Psychological Medicine from the University of Manchester, UK in 1992 and returned to India. She has been a faculty in the Department of Psychiatry since 1994, as Assistant, Associate Professor, Professor and is presently Senior Professor of Psychiatry since May 2021. She served as the head of the Centre for Addiction Medicine for eight years, Head of the Forensic Psychiatry Services for four years and Head of the Department of Psychiatry for two years (at NIMHANS), until her appointment as Director, NIMHANS in June 2022. Dr Murthy is a Fellow of the Royal College of Physicians and Surgeons, Glasgow.

Dr Murthy's areas of clinical work and research has been in the areas of addiction, mental health, post-graduate training and the history of psychiatry. She has been involved in about 40 research projects, has about 330 peer reviewed publications, made more than 400 presentations and guided more than 50 PG dissertations. She has received about 17 distinguished awards and delivered 8 orations. She has been a consultant to various international organizations, including the WHO, where she has been a member for developing mhGAP guidelines, member of the Guidelines Development Group (GDG) for mental, neurological and substance use disorders (MNS), co-chair of the expert group on guidelines for tobacco cessation and has also carried out consultancies for the UNODC and ILO.

As the Director of NIMHANS, she has been instrumental in bringing about several improvements in clinical services, introducing new departments and centres of excellence, NABH accreditation and re-accreditation and national and international accolades for NIMHANS. During her directorship, NIMHANS was awarded the WHO Geneva Nelson Mandela Prize for Health Promotion in 2024.

Psychiatric Genetics: Scientific Advances and Clinical Applications

John Nurnberger *MD PhD* [1]

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Indianapolis, Indiana, USA

Background: It has long been known that psychiatric disorders travel within families. Structured family studies, twin studies, and adoption studies have suggested that genetic factors are important, and the heritability of different disorders has been estimated to range between 40% and 90%. In recent years, genomewide association studies (GWAS) have become possible and large cohorts (10,000-200,000) of cases have been studied in relation to comparison groups. These studies have affirmed the genetic contribution to various disorders, including schizophrenia, bipolar disorder, major depression, autism spectrum disorder, attention deficit hyperactivity disorder, alcohol use disorder, and other similar conditions. These disorders have been demonstrated to be genetically complex and clues to their pathophysiology have been identified. An individual index of risk, termed a polygenic risk score (PGS) has been developed for each disorder. Other advances include the use of whole genome and whole exome sequencing to identify rare variants of large effect. Treatment selection may sometimes be aided by typing of genes for metabolic enzymes involved in processing of psychiatric medications or other markers of physiologic response.

Purpose: To review the recent developments in GWAS and the utility of PGS in research ponse potentially in clinical care. To consider the role of rare variants in neurodevelopmental disorders. To evaluate the utility of pharmacogenomic screening in clinical treatment.

Methods: The development of GWAS, PGS, rare variant assessment, and pharmacogenomic testing will be described.

Results: Rare variant screening in neurodevelopmental disorders, including some psychotic disorders, is now available and recommended for clinical use. Pharmacogenomic screening is now available and may be helpful with choice of antidepressants in some instances. Screening should be used for Human Leukocyte Antigen typing prior to carbamazepine and oxcarbazepine treatment. PGS has been used in numerous medical conditions including types of cancer and cardiovascular disease. It should be available to help with prognosis and treatment selection in various types of psychiatric disorders in the next few years.

Conclusions: Psychiatric Genetics has made major strides in the last decade. It is now useful for many clinical situations and should be increasingly relevant to clinical psychiatric care.

Neural plasticity and Brain Repair Mechanisms: New Challenges in Treating Neurological and Psychiatric Disorders

B.S. Shankaranarayana Rao
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and Registrar
National Institute of Mental Health and Neuro Sciences (NIMHANS)
Institute of National Importance
Bengaluru, INDIA

Neuronal plasticity is an extraordinary property of the brain and refers to the morphological, biochemical, behavioral and electrophysiological alterations in both the adult and developing nervous system. Thus, it is becoming increasingly clear that a regenerative and continuing mechanism for adaptive reorganization of the brain occurs because of the property of neuronal plasticity. This unique property of the nervous system may be responsible for the recovery of functions in several brain disorders including stress, anxiety, depression, epilepsy, aging, stroke and mental retardation. Stress is a condition that seriously perturbs physiological and psychological homeostasis, resulting in disorders ranging from anxiety to post traumatic stress disorder. Severe traumatic or repeated stress can result in long-term deleterious effects leading to depression and cognitive deficits. Prolonged stress induces learning and memory impairments, dopaminergic and cholinergic dysfunction, dendritic atrophy, decreases neurogenesis and long-term potentiation (LTP), alters sleep-wake cycle, and enhances degeneration of the hippocampal and medial prefrontal cortical neurons. These degenerative changes in the brain are associated with decreased neurotrophic factors mainly brain-derived neurotrophic factor (BDNF), alterations in NMDA receptors and tissue plasminogen activator (tPA) in the hippocampus. Thus, stress leads to regressive plasticity in the hippocampal and cortical neurons, the crucial brain regions involved learning and memory.

In contrast, brain stimulation rewarding behavioral experience (BSR) is known to increase dendritic arborization, spine and synaptic density, and increase neurotransmitter levels in the hippocampus. In addition, BSR facilitates operant and spatial learning, and ameliorates fornix-lesion induced behavioral deficits. Further, exposure to enriched environment results in an increase in dendritic arbors, spines, synapses and enhances dopaminergic and cholinergic transmission, neurogenesis and facilitates acquisition and performance in several learning tasks. Thus, BSR and enriched environment induces a robust plasticity in the hippocampus and frontal cortex. In addition, the cholinergic and dopaminergic drugs are also known to induce progressive plasticity. Accordingly, we have used multiple novel approaches to restore stress-induced cognitive deficits by inducing progressive plasticity at multiple levels of neural organization; namely, (i) Intracranial electrical stimulation of rewarding experience, (ii) Chronic exposure to enriched enrichment, (iii) Pharmacological manipulation of dopaminergic and cholinergic transmitter systems, (iv) herbal drugs, (v) Enhancing BDNF levels in the forebrain regions including hippocampus and cortex, (vi) Inactivation of amygdalar neurons, and (vi) Altering tPA levels.

Our results demonstrate reversal of stress induced cognitive deficits and depression, dopaminergic and cholinergic dysfunctions, decreased neurogenesis, hippocampal LTP and neurodegeneration by BSR / EE. In addition, enhancement of dopaminergic and cholinergic neurotransmission in the hippocampus and frontal cortex in stressed rats by administration of dopaminergic or cholinergic agonists, antidepressants or herbal drugs ameliorated the stress-induced learning and memory deficits. The overexpression of BDNF or inactivation of amygdalar neurons prevents stress-induced hippocampal neurodegeneration and ameliorates cognitive deficits. Interestingly, stress-

induced altered synaptic plasticity is regulated by tPA. Thus, multiple strategies are necessary to prevent / restore stress-induced cognitive deficits by restoring hippocampal and cortical neuronal dendritic atrophy, cholinergic and dopaminergic neurotransmission, synaptic plasticity in the hippocampus in terms of restoring long-term potentiation and activation of resident stem cells in the adult brain.

Chronic and prolonged stress is known to cause anxiogenesis and depression. Severe depression compromises structural and functional integrity of the brain and results in cognitive deficits, maladaptive synaptic plasticity as well as degenerative changes in the hippocampus, amygdala and prefrontal cortex. The precise mechanisms underlying cognitive dysfunctions in depression remain largely unknown. Accordingly, we have attempted to address this issue by investigating behavioral, structural and hippocampal synaptic plasticity in an animal model of endogenous depression induced by neonatal clomipramine administration. Furthermore, we have also looked into the possible means of ameliorating depression induced cognitive deficits and anxiety. The first line of defense in depressive illness is antidepressant drugs. However, it is associated with poor response, side effects and recurrence of depressive episodes. Recent studies suggest that antidepressant response can be augmented by positive environments. Therefore, in this study we studied the effect of sub effective doses of either escitalopram (an SSRI) or reboxetine (an SNRI) combined with short duration of enriched environment (EE) on depression induced deficits. Our results demonstrate that depression is associated with impaired spatial learning and enhanced anxiety-like behavior which is correlated with hypotrophy of the dentate gyrus and amygdalar hypertrophy. We also observed a gross reduction in hippocampal long-term potentiation (LTP). In depressive rats subjected to concomitant escitalopram / reboxetine - EE treatment, we observed complete behavioral recovery with reduced indices of anhedonia and behavioral despair, reduced anxiety-like behavior and improved spatial learning along with a complete restoration of dentate gyrus and amygdalar volumes. The combination treatment also facilitated CA3-Schaffer collateral LTP. Our study proves convincingly that depression induces learning deficits and impairs hippocampal synaptic plasticity. It also highlights the role of restorative environmental stimuli in enhancing antidepressant response which might prove vital in outlining more effective strategies to treat major depressive disorders.

Our recent studies have demonstrated the cellular and molecular basis of fragile X mental retardation and autism in transgenic and knockout mouse models. The selective synaptic manipulation by p21 activated kinase or metabotropic glutamate receptors ameliorated major symptoms of mental retardation and autism. This discovery led to the development of drugs to treat mental retardation and autism, which are in different stages of clinical trials. Thus, understanding the mechanisms of plasticity will provide an insight in developing new therapeutic strategies in treating neurological and psychiatric disorders. In spite of recent developments in novel research approaches and technologies, the clear understanding of the pathophysiological basis of complex brain dysfunctions is yet to emerge. Accordingly, it is becoming increasingly difficult and challenging to treat several brain disorders including cognitive deficits.

Keywords: Neural plasticity and brain repair mechanisms, Chronic stress, Anxiety, Depression, Epilepsy, Mental retardation, Aging, Prefrontal cortex, Hippocampus, Inactivation of basolateral amygdala, Corticosterone, Glucocorticoid receptors, Glial plasticity, Neurodegeneration, Neurogenesis, Activity-dependent synaptic plasticity, Cognitive deficits, Dendritic remodelling, Learning and memory deficits, Novel treatment strategies.

Acknowledgements: We acknowledge financial support from CSIR, DST, ICMR, DBT and NIMHANS

Guideomics - beyond image guidance for neuroscience

Miroslaw Janowski

Co-Director, Program in Image Guided Neurointerventions, Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland, USA

Dr. Janowski completed his residency in neurosurgery at the Medical University of Warsaw, Poland in 2009, and a year later he defended his PhD thesis in neuroscience at the Mossakowski Medical Research Centre, PAS, Warsaw, Poland. In 2011 he joined the Department of Radiology at Johns Hopkins University as a post-doctoral fellow and his career progressed to Associate Professor in 2016. In 2019 he moved to the Department of Diagnostic Radiology and Nuclear Medicine at the University of Maryland, Baltimore. Dr Janowski's research interests center on adding advanced imaging to accomplish precision medicine in neurointerventions. He is using radiolabeling and magnetic labeling of therapeutic agents to deliver them to the central nervous system using real-time interventional PET and MR imaging.

Dr. Janowski is the Co-Director of the Program in Image Guided Neurointerventions (PIGN).

Amyotrophic Lateral Sclerosis / Motor Neuron Disease: Current concepts and Therapeutic targets

Nalini Atchayaram, *DM, PhD*
Professor of Neurology, Neuromuscular Specialist
National Institute of Mental Health and Neurosciences

Amyotrophic lateral sclerosis (ALS) or Motor Neuron Disease (MND), is a progressive neurodegenerative disease that affects motor neurons in the Brain and spinal cord. ALS primarily affects voluntary muscles, leading to muscle weakness and wasting that may start in the hands, feet, or legs and spread or involve the bulbar muscles with difficulty in swallowing and speaking. There is increased muscle tone. In the later stages patient become bed bound and have respiratory distress and death due to respiratory failure. While ALS mainly affects motor neurons, some also experience cognitive impairment (FTD / AD), Parkinsons features and overlap syndromes. The hallmark of ALS is degeneration of motor neurons, both in the brain and spinal cord. Recent studies have highlighted the important role of dysfunctional astrocytes that contribute to motor neuron death through glutamate toxicity. Elevated levels of glutamate can overstimulate motor neurons, leading to excitotoxicity and eventual cell death. Microglia also, are chronically activated, contributing to neuroinflammation and neuronal death. One of the most critical discoveries in ALS is the role of TDP-43 protein. In most ALS cases (familial and sporadic), TDP-43 undergoes abnormal aggregation and accumulation in neurons and glial cells. In ALS, it misfolds, forms cytoplasmic inclusions, and disrupts cellular functions leading to neurodegeneration and targeting these aggregates could be a potential therapeutic approach. Common gene involved in familial ALS are FUS (Fused in Sarcoma), SOD1 (Superoxide Dismutase 1), C9orf72 hexanucleotide repeat expansion (GGGGCC). Counteracting the toxic effects of this repeat expansion, has promising approaches with antisense oligonucleotides (ASOs) that aim to reduce the repeat RNA. Thus, latest pathology of ALS reveals a multi-faceted and complex disease that involves the interplay of genetic mutations, protein aggregation, mitochondrial dysfunction, neuroinflammation, and disrupted RNA/protein quality control. With ongoing advances in genetics, cellular biology, and neuroimmunology, we hope to identifying potential targets for new therapies, including gene therapy, protein-based interventions, and immune modulation.

Epigenetics of major depressive disorder and related neuropsychiatric disorders

Arvind Kumar[1]

[1]*CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India*

Background: Major depressive disorder (MDD) is a highly debilitating psychiatric disorder and most cases are sporadic induced by chronic stress. Studies using stress-induced MDD rodent models show that the hippocampal dentate gyrus (DG) neurogenesis is adversely affected, which in turn, altered the circuitry causing affective and cognitive disorder phenotype. These stress effects are mediated by diverse epigenetic mechanisms involving histone lysine methylation, the most studied one. But another abundant neural epigenetic mechanism, histone arginine methylation and the regulators protein arginine methyltransferases (PRMTs) are least studied, which warranted this study for better insight into the underlying molecular mechanism.

Purpose: The study envisages unravelling how PRMT5 affects hundreds of genomic targets by altering its target epigenetic mark H4R3me2 on the regulatory regions of critical genes that are involved in mediating stress-induced neural changes in MDD and related neuropsychiatric disorder phenotype.

Methods: Using C57bl/6 mice and chronic stress induced paradigms, MDD-like phenotype was induced, as assessed by hallmark features anhedonia and helplessness, by analyzing the data from a battery of behaviour tests. To uncover the role of PRMT5, ChIP-Seq using antibodies against PRMT5 and H4R3me2 were performed on the DG neural progenitor cells (NPCs), followed by ChIP-qPCR validation. For regulation of gene expression by these epigenetic regulators, RT-qPCR was done.

Results: PRMT5 appears to play a critical role in DG proliferation and differentiation. The Ingenuity Pathway Analysis on hundreds of overlapping genomic regions showing enrichment by both PRMT5 and its epigenetic target H4R3me2 gave us novel molecular insights into the affected neurogenesis, altered circuitry and the underlying MDD etiopathology.

Discussion & Conclusion: Histone arginine methylation involving PRMT5 appears critical not only for normal or physiological DG neurogenesis by controlling expression of genes involved in regulation of NPCs' proliferation and differentiation, this epigenetic mechanism also seems to mediate underlying molecular changes in chronic stress response, neural as well as neurogenic ones.

Neuroepigenetics of Alcohol Use Disorder: Mechanisms, Phenotypes, and Treatment

***Subhash C. Pandey**, PhD*
Joseph A. Flaherty, MD Endowed Professor of Psychiatry & Director
Alcohol Research Center, Dept. of Psychiatry, University of Illinois Chicago
Jesse Brown VA Medical Center Chicago, IL 60612 USA

Acute ethanol produces anxiolysis, but anxiety that appears during withdrawal, is crucial in driving alcohol use disorder (AUD). Using RNA-seq and ATAC-seq, we found that chromatin accessibility and transcriptomic changes in the amygdala are associated with acute ethanol-induced anxiolysis in rats. In depth analysis of the cellular heterogeneity of these transcriptomic changes in the central amygdala (10x Genomics) revealed that differentially expressed genes are more abundant in PKC-delta positive GABAergic neurons after acute ethanol exposure. Chronic ethanol exposure and subsequent withdrawal produces anxiogenic effects and bulk RNA-seq and ATAC-seq data identified critical epigenetic regulators of gene network pathways associated with excitatory and inhibitory neurons in the amygdala during ethanol withdrawal after chronic exposure that may be involved in the development of anxiety-like behaviors in rats. Some of these findings have also been corroborated in human post-mortem amygdala of AUD subjects. Furthermore, targeted epigenomic editing of selected genomic regions in the central amygdala or HDAC inhibitors treatment prevented ethanol withdrawal related anxiety in preclinical model of AUD. Together, these studies have identified several potential molecular targets in the central amygdala that can be used to develop therapeutic interventions for AUD (Supported by NIH-NIAAA grants and senior research career award from department of Veterans Affairs).

Epigenetic Regulation of Neurological Disorders: Role of Lysine Acetyltransferases p300/CBP

Tapas K. Kundu

Transcription and Disease Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur P.O, Bangalore 56064, INDIA

Epigenetics is gene function beyond the DNA sequence, operated by DNA modifications, DNA-associated protein modifications, and noncoding RNA. It is reversible and metabolically regulated, thus directly related to habit and lifestyle. Reversible histone acetylation is one of the most investigated epigenetic modifications shown to be involved in diverse physiological as well as pathological phenomena. However, its role in memory and neurological disorders is not fully understood. Several studies have demonstrated that the master Lysine acetyltransferases CBP/p300 catalytic activity could be critical for long-term memory formation. We have shown that specific activation of p300/CBP KAT activity significantly prolongs the long-term memory in mice. We have discovered a small molecule (TTK21) activator of CBP/p300, which, after conjugating to the glucose-derived carbon nanospheres (CSP), crosses the blood-brain barrier and reaches different parts of the brain without apparent toxicity. It induces adult neurogenesis and long-term memory. By administrating this activator to the tauopathy mouse model of Alzheimer's Disease (AD), we could significantly reverse the memory loss in young and older mice. In the course, we identified that the cholesterol biosynthesis pathway is severely deregulated in older AD mice, which could be correlated with available human patient data. Activating p300/CBP KAT activity could normalize cholesterol biosynthesis, reversing cognitive function. Recently, we have found that in Syngap1+/-, a mouse model on intellectual disability (ID) and autism spectrum disorder (ASD), the p300 KAT activity is dramatically reduced in the CA1 region of the hippocampus. Our results demonstrate that the oral administration of CSP-TTK21 in adult *Syngap1*+/-mice rescued physiological and cognitive/emotional functions, presumably through restoring p300/CBP mediated histone acetylation and adult neurogenesis. The molecular pathways of the amelioration of symptoms are being elucidated.

Traffic rules in neurons

Sandhya P. Koushika
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Cargo movement in neurons is essential to maintain complex neuronal architectures and function of the nervous system. We asked if there are rules for cargo traffic in neurons. We identify that cargo type, numbers of motors and the axonal environment are all critical for both transport in general & choice of transport path at branch points in axons. Through an interdisciplinary collaboration we learnt that the design principles of the axon lead to traffic jams occur in healthy neurons in part due to physical crowding. Movement of vehicles on roads, of ants in confined spaces and of neuronal cargo within axons all appear to share some of the same traffic rules. These rules have implications in the progression of neurodegenerative disease.

Trafficking of glutamate receptors: Implications in the brain

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Background: In the brain, a variety of neurotransmitters and neuromodulators act on target receptors to activate cellular signaling events which transfer information from one cell to the next. Normal signaling depends on accurate localization of such receptors in specific regions of the cell, and the process of receptor trafficking plays a critical role in controlling this localization. In addition, in case of most G-protein-coupled receptors (GPCRs), receptor trafficking also plays crucial roles in the regulation of the receptor. Despite the obvious significance of this process, we still know very little about the molecular mechanisms that mediate trafficking of neurotransmitter receptors in the brain.

Purpose: Our labs specific interest lies in studying the cellular and molecular mechanisms that regulate the trafficking of glutamate receptors in the central nervous system. These trafficking events are thought to be critical for virtually all forms of experience-dependent plasticity, including learning and memory and are believed to play crucial role in various neuropsychiatric disorders.

Methods: Our laboratory employs multi-disciplinary approaches ranging from biochemistry and molecular biology to cell biology, imaging in primary hippocampal neurons to address these questions.

Results: Our studies unravelled the role of various postsynaptic density proteins in the ligand-mediated trafficking of metabotropic glutamate receptors (mGluRs) and mGluR-mediated AMPA receptor endocytosis.

Conclusion: The talk will be focused on the cellular and molecular mechanisms that govern the trafficking of glutamate receptors in neurons and implications of these processes in the brain.

The bright and dark side of neuroinflammation and neurodegeneration in the brain

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Acute inflammatory reactions can lead to life-threatening conditions such as septic shock, while chronic inflammation has the potential to worsen the condition of body tissues and ultimately lead to significant impairment of their functionality. Although the brain has long been considered immune privileged to peripheral immune responses, recent research has shown that strong immune responses in the periphery also affect the CNS, which can be shown by the long-lasting activation of reactive microglia, which belong to the innate immune system and reside in the brain. Excessive and chronic inflammation can have negative effects on neuronal and glia structure and function. In fact, neuroinflammation underlies the pathogenesis of many neurological and neurodegenerative diseases and can accelerate their progression. Consequently, targeting inflammatory signaling pathways offers potential therapeutic strategies for various neuropathological conditions, namely MS, Parkinson and Alzheimers' disease (AD), by curbing inflammation. Here the BBB is a major barrier for possible therapeutic strategies, therefore it would be highly advantageous to foster and utilize brain innate anti-inflammatory mechanisms. We elucidated if the tricarboxylic acid cycle (TCA)-derived metabolite itaconate and mesaconate can be utilized in the is endeavor, since it is highly upregulated in activated macrophages and has been shown to act as an immunomodulator with anti-inflammatory and antimicrobial functions. In this study we investigated the immunomodulatory and therapeutic potential of endogenously synthesized itaconate and its isomer mesaconate in lipopolysaccharide (LPS)-induced neuroinflammatory processes (Ohm et al. 2024). Our results show that both itaconate and mesaconate reduce LPS-induced neuroinflammation, as evidenced by lower levels of inflammatory mediators, reduced microglial reactivity and a rescue of synaptic plasticity, the cellular correlate of learning and memory processes in the brain. Overall, this study emphasizes that both itaconate and mesaconate have therapeutic potential for neuroinflammatory processes in the brain and are of remarkable importance due to their endogenous origin and production, which usually leads to high tolerance. In addition we also study long covid after a SARS-CoV2 infection. Cognitive decline following viral infection may be caused by direct damage to the brain by the virus or due to the immune response to a pronounced infection. Since aging affects the immune system at the cellular and molecular levels, the elderly are particularly affected by SARS-CoV-2 infection and are at increased risk of severe COVID-19 disease. Moreover, the aged brain is more sensitive to inflammatory stimuli, leading to more severe and long-term impairments in brain function. We could show here, that an increased activation of the immune response in the periphery or in the CNS upon SARS-CoV-2 infection leads to chronic neuroinflammation and subsequent neuronal dysfunction. This is of particular interest, since there is growing evidence of a link between frequent infections and dementia risk, because inflammation and oxidative stress are key features of many neurodegenerative diseases. Therefore, using previously established mouse models of (AD and infection, we are particularly interested in deciphering the potential impact of SARS-CoV-2 and influenza infection on the onset and progression of AD.

The complex GPCR pharmacology of a Southeast Asian natural product

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Mitragyna speciosa (kratom) leaves have been consumed in Southeast Asia to manage pain and increase energy, and more recently as a remedy for opioid withdrawal. Kratom-related products are now widely available in the United States and other Western countries. More than 45 kratom alkaloids have been isolated, and many appear to have a distinct and complex pharmacology. This presentation will highlight the pharmacology of several CNS active kratom alkaloids, including mitragynine and its metabolite 7-hydroxymitragynine. Data to be shared include G-protein coupled receptor (GPCR) binding affinity and functional activity in vitro, cytochrome P450 enzyme activity in microsomes, pharmacokinetics *in vivo*, and behavioral effects in preclinical assays of opioid activity including tests of antinociception, abuse, and respiratory depression. The data will show that mitragynine has sub-micromolar binding affinity at mu-opioid receptors and little or no agonist activity, whereas 7-hydroxymitragynine shares effects with mu-opioid receptor agonists (e.g., morphine). The data further suggest that the amount of 7-hydroxymitragynine generated from metabolism of mitragynine *in vivo* is not sufficient to exert behavioral activity. Several additional kratom alkaloids will be shown to have activity at other GPCRs, such as adrenergic and serotonin receptors. The emerging pharmacological profile of individual alkaloids provides the starting point for understanding the more complex profile of activity to be expected from mixtures of alkaloids within kratom leaves.

Neurobiology of Noncoding RNAs in Alzheimer's Disease and Potential for Translational Opportunities

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Background: Small non-coding RNAs, such as microRNA (miRNA), play a vital role in brain and neurodegenerative diseases, including Alzheimer's disease (AD). AD mitigation presents a significant unmet problem. Our aim is to identify biochemical changes that lead to neuropathological features of AD and related dementias (ADRD). AD results from alterations of key biochemical pathways leading to AD pathology: neuritic plaques generated from aggregates of amyloid-β peptide (Aβ), which is cleaved from Aβ precursor protein (APP), and neurofibrillary tangles of hyperphosphorylated tau (or MAPT). Dysregulation of proteins involved in Aβ production, e.g., APP and β-secretase (or BACE1), and/or Aβ degradation, e.g., membrane metalloendopeptidase (MME), contribute to excess Aβ deposition. MicroRNAs (miRNAs) are non-coding small RNAs that typically regulate mRNA translation via mRNA 3'-untranslated region (UTR) and, subsequently, many cellular processes. We have shown that miRNA expression is dysregulated in AD (PMC8758483; PMC8866491). Herein, we highlight our recent findings on human-specific miRNA species regulating genes involved in AD.

Methods: We obtained autopsy brain tissues from non-cognitively impaired (NCI) and AD subjects. We measured levels of miR-20b and miR-298 and AD-related mRNA and proteins in cortical samples from these subjects. For mechanistic studies, we used human primary cell cultures and induced pluripotent stem cells (iPSCs) from control and AD subjects.

Results: We observed regulation of APP by miR-20b, miR-101, and miR-153; BACE1 by miR-9 and miR339-5p; and MME by miR-181d. These miRNAs regulate protein expression via the respective target's mRNA-3'UTR (see an exception below). Interestingly, we observed that overexpression of miR-298 reduced levels of APP, BACE1, and specific tau protein moieties. Further, we found that miR-346 uniquely *upregulates* APP levels via the APP mRNA *5'UTR* in human cultures and that this activity was part of iron (Fe) homeostasis. Our results reveal fundamentally novel regulatory interactions.

Conclusions: Together, these multiple unique regulatory interactions may serve as novel therapeutic targets and enable the development of beneficial treatment strategies against human diseases, including AD.

Significance: This year's Nobel Prize in Physiology or Medicine was awarded to scientists Victor Ambros and Gary Ruvkun for discovering microRNA, highlighting these tiny RNA molecules' crucial role play in regulating gene expression and cell function. Sincere thanks to grant support from NIH.

PTR-10, the *C. elegans* Homolog of Human PTCHD1, Plays a Crucial Role in Neuroprotection

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The role of glial cells in neuroprotection and the progression of neurodegenerative diseases is increasingly recognized, particularly in the context of aging. In *C. elegans*, the glia-enriched gene PTR-10 (human orthologue PTCHD1) plays a crucial role in maintaining neuronal integrity. This study explores PTR-10 and its downstream targets, *basl-1* (orthologue of dopa decarboxylase, DDC) and daf-18 (orthologue of PTEN), to understand their roles in neurodegeneration and neuroprotection during aging. Using wild-type and transgenic *C. elegans* strains, we performed behavioral assays, lifespan studies, and assayed 6-OHDA-based injury models. Transcriptomic analysis of the PTR-10 knockout strain (RB1693) revealed significant downregulation of *basl-1* and *daf-18*, both implicated in axonal regeneration pathways. Our results show that knockdown of basl-1 increases alpha-synuclein expression, shortens lifespan, and disrupts dopaminergic neuron function, all of which are associated with aging and neurodegeneration. Similarly, *daf-18* knockdown also led to increased alpha-synuclein expression and reduced lifespan. PTR-10 expression itself declines with age exacerbating these effects and its absence impacts neuronal repair even in the presence of neuronal repair agents. In summary, PTR-10 and its downstream targets are critical in age-related neurodegeneration and neuroprotection. These findings highlight the potential of this axis for therapeutic strategies aimed at mitigating neurodegenerative diseases by promoting axonal regeneration and maintaining neuronal health thereby promoting healthy aging.

Antimitotics in Glioblastoma Therapy

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Background: The prognosis for glioblastoma (GBM) remains dismal, so there is a desperate need to develop more effective therapies. An example is illustrated by a group of antiproliferative drugs refer as mitotic spindle inhibitors that target the mitotic spindle without affecting microtubules. These drugs are devoid of the neurotoxicity of microtubule poisons, and include ispinesib, alisertib, and volasertib, which inhibit Kif11, Aurora Kinase A, and Polo Like Kinase, respectively. Although these drugs are CNS penetrant and are active against a variety of tumor cells, including GBM stem cells, the emergence of treatment resistance has limited their clinical utility.

Purpose: Identifying resistance mechanisms underlie against mitotic spindle inhibitors to reverse resistance with clinically available CNS permeant drugs.

Methods: We used phospho-proteomics and bulk and single cell RNASeq to identify resistance pathways, and used patient derived GBM stem cells, genetically engineered mouse (GEM) and patient derived xenograft (PDX) models to evaluate and reverse resistance.

Results: Treating glioblastomas with the spindle inhibitors ispinesib, alisertib, or volasertib creates a subpopulation of therapy induced senescent cells that resist these drugs by relying upon the anti-apoptotic and metabolic effects of activated STAT3. STAT3 is activated by phosphorylation at residues Y705 and S727, mediated by SRC and epidermal growth factor receptor (EGFR), respectively. Furthermore, these senescent cells expand the repertoire of cells resistant to these drugs by secreting an array of factors, including TGF-beta, which induce proliferating cells to exit mitosis and become quiescent—a state that also resists spindle inhibitors. Targeting STAT3 restores sensitivity to each of these drugs by depleting the senescent subpopulation and inducing quiescent cells to enter the mitotic cycle.

Conclusion: These results support a therapeutic strategy of targeting STAT3-dependent therapy-induced senescence to enhance the efficacy of spindle inhibitors for the treatment of glioblastoma.

Latest therapeutic regimens for Parkinson's disease

Ravi Yadav

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Dr. Ravi Yadav, Professor, Department of Neurology, NIMHANS; his areas of interest include Movement disorders (Parkinson's disease and other Parkinsonian syndromes, Dystonia, tremors), Headache (Secondary headaches), NeuroSjogren's Syndrome, Sleep in Parkinsonsian and Movement disorders, Neurocritical Care.

Molecular Approaches to Treat Spinal Cord Injury

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The core question that drives our research program is - How is axon growth regulated during development and regeneration in mammals? Communication in the nervous system is achieved via long cables called axons which connect neurons in the brain with the rest of the body. Intact axons are critical for proper nervous system function. When injured, young neurons are remarkably good at regeneration and repair. In contrast, adult neurons fail to regenerate resulting in permanent irreversible nervous system damage. What molecular pathways drive the observed loss of regenerative capacity across development? What regulatory mechanisms modulate developmental axon growth? Does successful CNS regeneration in adult neurons require a faithful recapitulation of developmental mechanisms? Are there development independent pathways that co-ordinate repair? These are some of the questions we are currently tackling. To get at these questions, we use a combinatorial approach which includes Bioinformatics, Functional Genomics (Single-cell RNA-Seq, ATAC-Seq, Hi-C, ChIP-Seq), in vitro assays of growth, in vivo mouse models of injury and behavioral assessments.

Unmasking a complex regulatory relationship between NLRP3 inflammasome, SIRT3, and the acetylation of SOD2 in ischemic stroke

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Background: Ischemic stroke, marked by high morbidity and mortality, is characterized by significant inflammation and oxidative stress.

Purpose: This study aims to investigate the relationship between Nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome activation and NAD-dependent deacetylase sirtuin-3 (SIRT3) expression in the context of ischemic stroke. By examining how these two factors interact to influence inflammation and oxidative stress, this study aims to uncover the underlying mechanisms that contribute to neuronal damage during ischemic stroke. The study also aims to find possible therapeutic targets that could change these pathways, thereby providing new ways to lessen the harmful effects of ischemic stroke and related conditions.

Methods: Utilizing in vitro, in ovo, and in vivo models of ischemia-reperfusion, our research employed a combination of biochemical assays (several florescent chemicals) and molecular biology techniques (such as, Western blotting, immunofluorescence, flow cytometry, etc.) to assess the expression levels of NLRP3 and SIRT3 in ischemic stroke models. We also looked into the acetylation status of superoxide dismutase 2 (SOD2), a key antioxidant enzyme, to see how its activity relates to the expression of SIRT3 and NLRP3.

Results: We observed a significant increase in NLRP3 expression following ischemic stroke, indicating heightened inflammatory activity. Simultaneously, there was a marked depletion in SIRT3 expression, indicating a compromise in the oxidative stress response. Notably, decreasing NLRP3 did not change the levels of SIRT3. However, decreasing SIRT3 caused NLRP3 expression to rise, showing a one-way regulatory feedback loop. We found that both NLRP3 and SIRT3 influence the acetylation of SOD2. When SIRT3 levels dropped, acetylation of SOD2 went up.

Conclusion: This study highlights a previously unknown mechanism of ischemic stroke pathology, providing a promising target for intervention in neurodegenerative diseases.

Assembly and functioning of cerebellar circuits

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Background: The cerebellum is an important organ in the brain responsible for motor coordination and balance. The cerebellum is well conserved among vertebrates in terms of its circuitry, gene expression patterns and developmental trajectories. In the cerebellum, the climbing fibre (CF) to Purkinje neuron synapse is among the strongest of synapses known and plays a critical role in shaping Purkinje neuron output. In mammals, Purkinje neurons are innervated by multiple CFs in the neonate which are then pruned away to leave one CF innervating each Purkinje neuron in the adult.

Purpose: While molecular mechanisms governing synapse elimination are well known, what is not clear is how synapse elimination in the olivo-cerebellar system affects circuit function and motor behavior.

Methods: The larval zebrafish is an ideal model organism to study this because larvae exhibit multiple motor behaviours and are independent organisms soon after they hatch. We used whole-cell patch clamp recordings from Purkinje neurons while providing electrical and visual stimulation to recruit the olivo-cerebellar pathway.

Results: We first established that in the early stage larvae, multiple CFs innervate each Purkinje neuron. At 4-5 days post fertilisation (dpf), Purkinje neurons are poly-innervated by CFs while by 11-12 dpf, they are largely mono-innervated. We find that poly-innervated Purkinje neurons are poorly tuned to directional visual stimuli and to motor errors, while mono-innervated Purkinje neurons are sharply tuned. This in turn translates to poorer representation of predictions and prediction errors in learning stimulus patterns. Finally, all of these reflect in the larval behavior as well: early stage larvae are unable to modulate swim latencies and this correlates strongly with weaker predictive signals in Purkinje neurons.

Conclusions: In sum, our data strongly argue for a role of synapse elimination in the olivo-cerebellar circuit in sensori-motor tuning and behavioural adaptability.

Insights into GABA reuptake and inhibitory mechanisms at the neural synapse

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Background: The neurotransmitter transporter, GAT1 is responsible for clearance of inhibitory neurotransmitter g-aminobutyric acid (GABA) from synaptic cleft. Targeting GABA reuptake by inhibiting GAT1, hence prolonging GABAergic signaling is one of the strategies to treat disorders arising due to imbalance in inhibitory neurotransmission like epilepsy and anxiety.

Methods: To understand the mechanism of GABA recognition and transport, initially we used an engineered *Drosophila melanogaster* dopamine transporter to resemble GAT1 ($dDAT_{GAT}$) and determined high-resolution X-ray structures of the modified transporter in the substrate-free state and in complex with GAT1-inhibitors NO711 and SKF89976a. We further determined the cryo-EM structure of GAT1 from *Rattus norvegicus* at 3.1 Å resolution in a cytosol-facing conformation utilizing a strategy of transferring the epitope for a fragment-antigen binding (Fab) interaction site, from *Drosophila* dopamine transporter (dDAT) to rGAT1, to assist structure determination through Fab binding to rGAT1 epitope construct.

Results: The structure captured a transport cycle intermediate step of rGAT1 with substrate GABA, tightly bound chloride, and a partly displaced sodium from site 1. GABA interacts in the binding pocket in a pose similar to GAT1 specific inhibitors in the $dDAT_{GAT}$ structure.

Conclusion: This study highlights important details of the GABA recognition, transport activity and inhibition.

α-Synuclein: Unveiling its cellular functions

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Background: α-Synuclein (αSyn) plays a critical role in the pathogenesis of Parkinson's disease (PD) and other Synucleinopathies. Although many cellular functions have been proposed for αSyn, its precise physiological role remains elusive. Multiple lines of evidence indicate that under pathological conditions, the nuclear αSyn level increases, eliciting neurotoxicity in dopaminergic neurons and mouse models independent of its aggregation property. These findings raise a fundamental question regarding the mechanism of αSyn toxicity in PD: the underappreciated nuclear function versus its aggregation property. Therefore, determining αSyn's physiological role in the nucleus is of particular interest.

Purpose: So far studies on nuclear αSyn are limited to its interaction with individual histones and dsDNA, leaving a significant gap in our understanding of its nuclear functions and role in chromatin regulation.

Methods: We employed a combination of biochemical, biophysical, structural (X-ray crystallography), and cellular techniques.

Results: Our earlier study showed that αSyn's interaction with dsDNA is weak and non-specific, whereas its interaction with individual core histones H3 is specific; based on this study, we proposed that the nuclear function of αSyn is possibly driven through histone interaction. In the current study, we provided molecular-level details and structural insights into αSyn nuclear physiological function for the first time.

Conclusion: This study offers detailed structural and functional insights into αSyn's precise nuclear physiological functions and sheds newer light on its physio-pathological role.

Plasma membrane repair upon damage induced by Amyloid-β oligomers

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Background: The interaction of amyloid-β (Aβ) peptides with the plasma membrane (PM) is a potential trigger that initiates the formation of higher-order aggregates, membrane alterations/damage, and progressive neurotoxicity in Alzheimer's disease (AD).

Purpose: In our previous study we showed that oligomers of $A\beta_{1-42}$ ($oA\beta_{1-42}$) induced PM damage, resulting in PM repair (PMR) cascade via lysosomal exocytosis coupled with endocytosis. However, the molecular players involved in PMR in response to Aβ-oligomers induced damage were unknown.

Methods: We have demonstrated the kinetics of Rab3a-mediated PMR in response to oligomers Aβ peptides induced PM damage using total internal reflection fluorescence (TIRF) microscopy. EGFP-Rab3a vesicles fuse faster to PM upon treatment with $oA\beta_{1-42}$ than control and $oA\beta_{1-40}$ treated neuronal cells. IPA-3, a selective non-ATP competitive inhibitor of PAK1, inhibits Rab3a-dependent PMR. Further, shRNA-mediated knockdown of the Rab3a gene inhibits pPAK1 and disrupts PMR. Disruption in PMR leads to neuronal cell death.

Results: The study revealed that endocytosis mediated by phosphorylated p21-activated kinase1 (pPAK1) is involved in regulating Rab3a-dependent vesicle fusion/exocytosis to repair oAβ-induced PM damage in SH-SY5Y and SK-N-SH neuronal cells. The aggregation-prone peptide $A\beta_{1-42}$ oligomers significantly increase pPAK1-dependent endocytosis and Rab3a-dependent exocytosis to facilitate PMR compared to $oA\beta_{1-40}$.

Conclusion: Several studies have indicated that Rab3a and PAK1 may have crucial roles in AD. However, there was no explicit understanding. This study revealed the interconnected action of Rab3a and PAK1 in PMR induced by oAβ, along with their potential correlation with the propagation of amyloid pathology and neurotoxicity.

Molecular Basis of Small-Molecule Binding to Intrinsically Disordered Proteins: Design principles from biomolecular simulations and machine learning approaches

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Background: Highly labile intrinsically disordered proteins (IDPs) are not directly amenable to conventional drug-designing strategies that hinge upon the knowledge of a reference 3-dimensional structure.

Purpose: Physics and machine learning based computational tools, particularly those that incorporate the available experimental information, can be effectively used to generate high-resolution ensemble structures of IDPs and rationally design small molecule inhibitors for these ensemble conformations.

Methods: I will discuss our recent work on small molecule binding properties of Aβ42 and α-synuclein, proteins involved in the neurodegenerative proteinopathies, namely, Alzheimer's and Parkinson's diseases, respectively.

Results: Our all-atom resolution binding geometries data with accurate conformational ensembles of IDPs in complex with small molecules provides critical insight towards the rational design of IDP inhibitors.

Conclusion: We believe that the pipeline developed by us is general in nature and can be used to cluster and visualize IDP ensembles across systems with varying degrees of structural heterogeneity and assist in detailed structural, thermodynamic, and kinetic analyses of IDP conformations in APO and bound states with small molecules and other partners biomolecules.

Mechanism of cell-to-cell Huntington disease protein transmission

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Background: The CAG/CAA expansion encoding polyQ huntingtin (mutant huntingtin [mHTT]) causes Huntington's disease (HD), which is characterized by atrophy and loss of striatal medium spiny neurons (MSNs), which are preceded by neuropathological alterations in the cortex.

Purpose: Previous studies have shown that mHTT can spread in the brain, but the mechanisms involved in the stereotyped degeneration and dysfunction of the neurons from the striatum to the cortex remain unclear.

Methods: In this study, we used cellular, molecular and animal models, combined with reporter gene expression and state-of-the art microcopy tools to address biological questions.

Results: We found that the mHTT expression initially restricted in the striatum later spread to the cortical regions in mouse brains. Such transmission was diminished in mice that lacked the striatal-enriched protein Ras-homolog enriched in the striatum (Rhes). Rhes restricted to MSNs was also found in the cortical layers of the brain, indicating a new transmission route for the Rhes protein to the brain. Mechanistically, Rhes promotes such transmission via a direct cell-to-cell contact mediated by tunneling nanotubes (TNTs), the membranous protrusions that enable the transfer of mHTT, Rhes, and other vesicular cargoes. These transmission patterns suggest that Rhes and mHTT are likely co-transported in the brain using TNT-like cell-to-cell contacts.

Conclusion: On the basis of these new results, a perspective is presented in the IAN 2024 meeting: Rhes may ignite the mHTT transmission from the striatum that may coincide with HD onset and disease progression through an anatomically connected striato-cortical retrograde route.

IPD1 prevents α-synuclein pathology and halts neurodegeneration in mouse model of Parkinson's disease

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Background: The presence of Lewy bodies, primarily consisting of α-synuclein (α-syn) aggregates, in the substantia nigra region of the brain is the pathological hallmark of Parkinson's disease (PD). The disease remains incurable, and various therapeutic options are currently under investigation. In the current study, we identified a cell-penetrating peptide IPD1 that potently inhibits α-syn amyloid aggregation and improves locomotor coordination in mice models of PD.

Purpose: The primary aim of the present study is to identify inhibitors of α-syn fibrillation that are able to cross blood brain barrier, and provide therapeutic effect in mouse model of Parkinson's disease.

Methods: We employed phage displayed peptides as well as cell-penetrating to screen peptide that interact with α-synuclein. Among the interacting peptides, we identified those that inhibit α-syn fibrillation. The ability of the peptide to inhibit α-syn aggregation was confirmed using various biophysical methods and also in different models such as *C. elegans*, and transgenic mouse model of PD. The mechanism of action was examined using NMR and Molecular Dynamics study.

Results: We identified IPD1 as one of the potent peptide that inhibited α-syn fibrillation. We also designed various potent derivatives of the IPD1, and found that similar to the parent peptide, its cyclic derivative also inhibits α-syn fibrillation. Both IPD1 and its cyclic derivative restored dopamine signaling and improved motility in *C. elegans* model of PD. The PD mouse treated with IPD1 showed improved motor phenotypes as well as histological features including neuronal density, reduction in lewy bodies, and restoration of tyrosine hydroxylase.

Conclusion: The study thus reveals a potent peptide that could serve as a template for the design of potential therapeutic agents for PD treatment.

Continued Hippocampal Neurogenesis in Adult Humans: A Hope for Combating Alzheimer's Disease

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Background: It is not well established that continued hippocampal neurogenesis is a protective mechanism against age-associated dementia and Alzheimer's disease

pathology. We examined immunohistochemical and genomic evidence of continued hippocampal neurogenesis in aged individuals, including those with evident beta- amyloidopathy, in postmortem samples.

Purpose: To detect immunohistological and genomic evidence of continued hippocampal neurogenesis in aged humans.

Methods: Post-mortem hippocampal tissue samples from adult individuals (> 50 years old) were examined and compared with younger age-healthy individuals (<50 years old). The tissue samples were fixed in 4% paraformaldehyde, and H&E and Nissl (cresyl-violet) staining was performed. Further immunohistochemistry (IHC)/Immunofluorescence (IFC) was performed to detect a panel of neurogenesis and senility markers. The stained slides were examined with a bright-field light/ fluorescence microscope, and images were acquired with an in-built imaging system. In addition, transcriptomic analysis was performed in fresh frozen samples.

Results: Newborn neurons were detected in the sub-granular zone of the hippocampus's dentate gyrus (DG) in individuals up to 80 years. The migration and integration of the new neurons to the DG cortex were also noted. The number of newborn neurons significantly decreased with aging. Transcriptomic analysis of the neurogenesis panel markers indicated reduced but continued neurogenesis in adults. Neurogenic abundance was also observed in a case with typical beta-amyloid plaques and Tau-positive neurofibrillary tangles in the hippocampal fields invading the neurogenic niche, however, without significant memory loss.

Conclusions: Continued hippocampal neurogenesis may be a natural mechanism for protecting against age-associated dementia and memory loss in Alzheimer's disease.

Targeting the Brain Renin-Angiotensin System for the treatment of diabetes-induced cognitive disorders

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Background: The Renin Angiotensin System (RAS) plays a vital role in glucose metabolism by regulating a complex hormonal cascade and maintaining blood pressure, water intake and electrolyte balance. However, it has been observed that the RAS is dysregulated under diabetic conditions. Brain RAS is a separate component of the RAS within the brain, and it has been implicated through recent studies in cognitive dysfunctions under diabetic conditions.

Purpose: To determine the involvement of brain RAS components in diabetes-induced amnesic conditions and to design suitable interventions for treating diabetes-induced cognitive disorders.

Methods: We used adult male SD rats and divided them into Vehicle, diabetic, amnesic, and diabetic+amnesic. Diabetes was induced by a single IP injection of Streptozotocin (STZ) at a dose of 55 mg/kg body weight. Amnesia was induced by an IP injection of Scopolamine at a dose of 1 mg/kg body weight dissolved in normal saline for 15 days. The brain-RAS components AT1 and AT2 expression levels were analyzed through qPCR in the hippocampus and pre-frontal cortex.

Results: Physiological data showed that diabetic groups had significant weight loss but increased food and water consumption compared to amnesic and Vehicle groups. As revealed from the behavioural, biochemical and molecular assays, we observed significant memory loss in the diabetic groups compared to the vehicle control group. For the brain-RAS components, the mRNA expression analysis showed that AT1 mRNA levels were elevated ($p<0.001$), but AT2 mRNA levels were decreased ($p<0.001$) in the diabetic and amnesic groups compared to the control group in both regions of the brain.

Conclusions: Our findings reveal that increased AT1 (with a simultaneous decrease in AT2) expression in the diabetic group might contribute to memory impairment, which can be targeted to ameliorate the diabetes-induced amnesic effects.

Targeting metabolic enzyme Pyruvate Kinase M2 provides cerebroprotection following ischemic stroke onset

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There is a critical need for cerebroprotective interventions to improve the suboptimal outcomes of patients with ischemic stroke treated with reperfusion strategies. We found that nuclear pyruvate kinase muscle 2 (PKM2), a modulator of systemic inflammation, was upregulated in neutrophils after the onset of ischemic stroke both in humans and in mice. Therefore, we determined the role of PKM2 in stroke pathogenesis utilizing murine models with preexisting comorbidities. We generated novel myeloid cell-specific $PKM2^{-/-}$ mice on wild-type ($PKM2^{fl/fl}LysMCre^{+}$) and hyperlipidemic background ($PKM2^{fl/fl}LysMCre^{+}Apoe^{-/-}$). Controls were littermate $PKM2^{fl/fl}LysMCre^{-}$ or $PKM2^{fl/fl}LysMCre^{-}Apoe^{-/-}$ mice. Genetic deletion of PKM2 in myeloid cells limited inflammatory response in peripheral neutrophils and reduced neutrophil extracellular traps following cerebral ischemia/reperfusion, suggesting PKM2 promotes neutrophil hyperactivation in the setting of stroke. In the filament and autologous clot/rtPA stroke models, irrespective of sex, deletion of PKM2 in myeloid cells either in wild-type or hyperlipidemic mice reduced infarcts and enhanced long-term sensorimotor recovery. Laser speckle imaging revealed improved regional cerebral blood flow in myeloid cell-specific PKM2-deficient mice that was concomitant with reduced post-ischemic cerebral thrombo-inflammation (intracerebral fibrin(ogen), platelet (CD41-positive) deposition, neutrophil infiltration, and inflammatory cytokines). Mechanistically, PKM2 regulates post-ischemic inflammation in peripheral neutrophils by promoting STAT3 phosphorylation. To enhance the translational significance, we inhibited PKM2 nuclear translocation using a small molecule and found significantly reduced neutrophil hyperactivation and improved short-term and long-term functional outcomes following stroke. Collectively, these findings identify PKM2 as a novel therapeutic target to improve brain salvage and recovery following reperfusion.

Targeting homeostatic plasticity through NMDA receptor modulation in the treatment of stress disorders

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Background and Purpose: The poor retention of extinction memory is a classical trait of psychiatric disorders, including post-traumatic stress disorder (PTSD) and N-methyl-D-aspartate receptors (NMDARs) activation facilitates the establishment and stimulation of alerted behaviour. However, the pathophysiological mechanisms underlying such vicissitudes remain unclear, resulting in non-availability of effective therapeutic interventions.

Methods: Single prolonged foot shock-(FS)-stress has been studied as an animal model of PTSD, in this study we assessed the ability of FS to evoke fear extinction and the effects of single dose administration of NMDARs antagonists (ketamine and memantine) on fear extinction, glutamate transmission and dendritic arborization in FS rats.

Results: We found the impaired fear extinction, whereas the treatment with ketamine (24 or 72 h before or 6 h after FS-stress) and memantine (1 h before and 6 h after FS-stress) alleviated the fear extinction during the one-week extinction training. FS induced the stress-dependent increase of spontaneous excitatory postsynaptic current (sEPSC) amplitude in prelimbic (PL)-PFC, which was reduced following treatment with ketamine 6 h post FS. At the same time, ketamine injection 6 h after FS was found to rescue apical dendritic retraction of pyramidal neurons induced by acute stress in PL-PFC. On the other side, treatment with memantine reduced the stressed dependent increase in the cortisol release in stressed rats.

Conclusion: These results show rapid effects of NMDAR antagonists in animals subjected to acute FS, in line with previous studies suggesting a therapeutic action of the drug in PTSD models. Likewise, the role of NMDAR antagonists regardless of their mechanistic involvement in facilitating fear extinction, might promote the re-establishment of synaptic homeostasis and blockage of NMDAR overstimulation.

Mitochondrial therapy to combat the metabolic dysfunctions in Alzheimer's disease

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Background: The intricate relationship between mitochondrial dysfunction and the pathogenesis of Alzheimer's disease (AD) has gained significant attention in recent years. It is well established that cognitive activity is highly reliant on mitochondrial function. Mitochondria fulfill the high energy demand of the neural tissue, while under stressful conditions, they are central participants in apoptotic and necrotic cell death. Thus even a modest mitochondrial bioenergetics failure render the neurons vulnerable to damage. Studies have shown that structural and functional abnormalities in mitochondria are one of the most significant features of AD and they manifest very early in AD, much before the amyloid-beta plaques deposition.

Purpose: Considering the crucial involvement of mitochondria in AD pathology, Mitotherapy which involves the transfer of healthy mitochondria into affected cells to restore their normal function and enhance cellular metabolism, has been proposed as a novel therapeutic strategy for slowing down or even reversing the progression of AD.

Methods: We have attempted mitochondrial transplantation in a rat model of AD. Mitochondria were sourced from the hippocampus of young healthy rats, their functional efficacy was ascertained and mitotracker tagging was done. Mitochondria were injected through the intra-cerebro-ventricular route.

Results: Incorporation of mitochondria into the host cells was ensured. Improvement in the neurobehavioral test scores as well as the mitochondrial functional parameters (mitochondrial membrane potential and levels of reactive oxygen species, calcium, Caspase 3 and Cytochrome C) was measured.

Conclusion: It is important to acknowledge that mitotherapy, though promising, is still an emerging field and requires extensive research to answer wide range of questions, such as, suitable source for healthy mitochondria, delivery protocols for maximum bio availability, immunogenic implications, long-term safety and efficacy.

Role of prenatal sleep in shaping the behavioural phenotypes of offspring: Complex modulation of heart-brain networks

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Sleep is an important component of our life as it plays a crucial role in modulation of daytime activities, physical performance and cognitive functioning in all the age groups. In recent years, concerns are raised on association between poor quality of sleep during pregnancy and the fetal outcomes. There are growing evidences that sleep during pregnancy plays an important role in shaping optimal neurocognitive development of offspring in human and other altricial species. Restriction of REM sleep during late pregnancy in a rodent model resulted in postnatal age-matched immature sleep networks in brain, reduction in crying (ultrasonic vocalizations obtained in isolation paradigm) patterns in neonates and depression like traits during adolescence. However, total sleep restriction during pregnancy also resulted in immature sleep networks but with increase in ultrasonic vocalizations in neonates, and hyperactivity and increased risk taking behavior in offspring. From the perspective of prenatal origin of adult diseases like depression, anxiety etc, it is utmost crucial to understand potential link and optimal tuning of state dependent changes i.e. sleep-wakefulness (S-W) networks with autonomic nervous system (ANS) for attaining emotional regulation of behavior. Since both these networks (S-W, ANS) are underdeveloped at birth making them vulnerable to any activation or perturbation during perinatal window thereby posing increasing risk of dysregulated emotions and cognitive decline in growing babies. In modern sleepless society, the role of prenatal sleep in shaping the health outcomes in offspring are discussed through a complex interaction of heart-brain in state dependent changes in heart rate variability during early postnatal development.

Electroencephalographic arousal is earlier than electromyographic arousal

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We all got up every morning after a goodnight's sleep. During the night we go through various stages of sleep. Also there are many spontaneous during the night from which we again go to sleep. During rapid eye movement (REM) sleep there is skeletal muscle atonia and EEG desynchronization. Early morning onwards there is final arousal. We studied the temporal relationship between EEG and electromyographic (EMG) changes during spontaneous and final arousal from sleep in 15 healthy young volunteers. The study was approved by institutional ethical committe. The spontaneous arousals, with associated EEG and EMG changes, occurred almost uniformly throughout non-rapid eye movement (NREM) sleep and REM sleep. EEG changes preceded EMG changes in majority of the events. There was a delay of more than a second in between EEG and EMG changes, in both spontaneous arousals and early morning awakenings. Compared to the pre-arousal values, there was a significant increase in the delta power and all the frequency bands during spontaneous arousals. Though similar changes in EEG happened during the early morning awakenings, there were significant differences in beta and sigma EEG powers and computed root mean square EMG during the early morning awakenings. The differences in the characteristic features of EEG and EMG changes during spontaneous arousal and early morning arousal indicated the probable role of these changes in facilitating the continuance of sleep in the former, and waking up from sleep in the case of the latter.

Randomness is characteristics of sleep-in meditators

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Background: Sleep is the most valuable essential behavior of life. Classical electroencephalography (EEG) analysis provides the pivotal scientific tool to quantitatively assess sleep state and underlying physiology. However, brain activity is a complex and dynamical non-linear system; therefore, nonlinear approaches are more appropriate for assessing the intrinsic dynamics of EEG and exploring the physiological mechanisms of brain activity during sleep. In the present study, assessment of non-linear approaches of EEG and exploration of neurovisceral integrative measures i.e heart beat evoked potential is carried out between controls and meditators.

Method: Healthy controls (n=21) and vipassana meditators (n=23) volunteered for two-day whole night polysomnography recordings. EEG (21 electrodes with mastoid as reference), chin EMG, EOG was recorded with Nihon Khoden and sleep was scored as per ASSM criteria. EEG power spectrum, non-linear and fractal measures were assessed for every 30 sec epochs across sleep stages and averaged and was compared between 2 groups with two-way ANOVA and post hoc corrections with $p < 0.05$ significant level. HEP is explored across sleep stages.

Results: Microsleep architecture showed reduced sleep spindles but the propensity to induce slow waves was higher. Both controls and meditators demonstrated more progressive decrease of fractal dimensions with increasing NREM sleep depth and increased during REM. However, Meditators showed lower lepulziv compressibility and higher entropy values across all measures when compared to controls. Exploration of heart beat evoked potential showed higher values during N3 in frontal electrodes in controls but such variations not observed in meditators.

Conclusion: Meditators demonstrated less coherent neural activity across all sleep stages when compared to controls and probably with reduced interoception.

Why does memory consolidation require sleep?

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Non-rapid Eye Movement (NREM) sleep and Rapid Eye Movement (REM) sleep, in both stages, together or individually, helps in memory consolidation. For example, short sleep deprivation (5-6 hours) soon after fear-conditioned training (cued and contextual fear conditioning) and appetitive-conditioned training (trace and delay appetitive conditioning) induced learning deficit in rodents. In addition, NREM sleep significantly increased at a specific window after fear-conditioning, whereas REM sleep significantly increased after learning appetitive-conditioning tasks. Further, we have observed that the changes in sleep architecture are an explicitly consolidation-dependent phenomenon. In addition, we have found that new learning augments sleep-associated brain oscillatory waves during NREM and REM sleep, which plays an essential role in the neural dialogue between circuitries. These findings suggest that sleep is necessary for neural optimization for memory consolidation.

Sleep may help in memory formation at the cellular and system consolidation levels. Short-term total sleep deprivation soon after fear-conditioning alters the expression of some memory candidate genes such as Gsk-3, NCDN, and Shank-3. In addition, short sleep deprivation alters the learning-induced changes in the expression level of protein kinases, cAMP, Arc protein, in the hippocampus. Short-term sleep deprivation soon after training alters the learning-induced increased adult neurogenesis in the dorsal hippocampus. In addition, sleep plays an essential role in inducing synaptic strength. We have shown that the cellular and molecular events involved in the induction of ocular dominance plasticity (ODP) in the visual cortex are triggered by sleep. Sleep consolidates ODP primarily by strengthening the cortical responses to the non-deprived eye through NMDA receptors and the protein kinase-A pathway. Consolidation is also associated with sleep-dependent increases in the activity of remodeling neurons and the phosphorylation of proteins required to potentiate glutamatergic synapses. Our findings demonstrate that sleep possibly helps in memory formation at cellular and systems consolidation levels.

Memory Encoding and Sleep in Older Adults: A Neurocognitive perspective

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Background: Aging is a well-established factor influencing sleep architecture and quality. Impaired sleep is increasingly recognized as an early marker of cognitive decline, particularly in the context of neurodegenerative diseases. The deterioration of sleep may precede observable cognitive deficits, making it an essential focus in studying age-related cognitive changes.

Purpose: This study aimed to evaluate the relationship between sleep quality and cognitive function, with a focus on memory encoding and consolidation, in older adults.

Methods: A cohort of 54 participants, aged 50-80 years, was recruited from both geriatric clinics and the community. Sleep quality was assessed using the Pittsburgh Sleep Quality Index. Cognitive performance across multiple domains, including episodic memory, attention, and executive function, was evaluated using the Indian Council of Medical Research-Neuro Cognitive Toolbox.

Results: 25 were good sleepers (PSQI score ≤5) and 29 were poor sleepers (PSQI score >5). PSQI was negatively correlated with episodic memory (immediate recall score) ($r=-0.38$, $p=0.004$) and delayed recall score ($r= -0.31$, $p=0.024$) and positively correlated with attention and executive function measured with trail making test-B (TMT-B) ($r=0.35$, $p=0.01$). There was a significant difference between good and poor sleepers in immediate recall score ($p=0.042$) and trail making test-B (TMT-B) ($p=0.002$). A significant decline in episodic memory performance was observed in participants with poor sleep quality, particularly affecting immediate recall. In contrast, delayed recall did not exhibit a statistically significant difference ($p=0.115$) between good and poor sleepers, suggesting that sleep quality may influence the encoding of new information rather than the long-term consolidation of memory.

Conclusion: Sleep quality is a factor in the immediate encoding of information in older adults, with potential implications for cognitive decline. Mechanistically, poor sleep may impair the brain's glymphatic system, reducing the clearance of neurotoxic waste and contributing to neuroinflammation and tissue atrophy.

Differential levels of post-cerebral ischemia recovery in males and females are mediated by sex-distinctive epigenetic modifications

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Background: A variety of risk factors, including a high body mass index, smoking, and lifestyle choices, could potentially have an impact on ischemic stroke, one of the main causes of neurovascularmorbidity and mortality. Even so, there is still a dearth of thorough research on the present and future burden of disease, especially as it relates to internal carotid artery occlusion (ICAO).

Purpose: Building on previous research that showed sex-specific responses to cerebaral stroke, our present work is designed to reveal if complex epigenetic regulatory pathways are responsible for these differences.

Methods: Using high-throughput illumina RNA sequencing, we want to clarify the sex-specific functions of histone methylases ezh1 and ezh2, as well as H3k27-specific demethylase kdm6b/jmjd3, in controlling neurogenesis. The other parameters were included behavioral assays, histological evaluations, immunoblotting, RT-qPCR and ChiP assay.

Results: This study identifies sex-specific roles of methyl transferases in neural stem cell proliferation and finds a new epigenetic modulator, kdm6b/jmjd3, targeting H3k27. Addressing the dearth of female stroke research and acknowledging the substantial influence of sex on ischemic stroke incidence, mortality, and functional outcomes are crucial components of this study. The results add to a complete framework that links neurogenesis, post-ICAO recovery, and gender-specific epigenetic regulation.

Conclusion: To sum up, this comprehensive method not only broadens our comprehension of ischemic stroke but also emphasizes how important it is for stroke researchers to take sex into account. The discovered epigenetic modulators and their functions in neurogenesis provide prospective targets for improved therapeutic approaches, highlighting the significance of personalized and gender-specific factors in stroke research.

Advancing Parkinson's Disease Modelling for Personalized Medicine: Insights from Patient-Derived iPSCs with the LRRK2 I1371V Mutation

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Background: LRRK2 mutations are critical in inherited Parkinson's disease, with variants displaying ethnic biases—G2019S in Caucasians and I1371V in East Asians. Beyond prevalence, LRRK2 variants show clinical heterogeneity, such as differences in age of onset, disease severity, brain pathology, clinical symptoms, drug response, and DBS efficacy. However, mechanisms underlying the I1371V mutation remain underexplored, necessitating further research.

Purpose: To investigate disease pathology in iPSC-derived dopaminergic neurons and astrocytes from LRRK2 I1371V PD patients.

Methods: Dopaminergic neurons and astrocytes differentiated from iPSCs derived from healthy controls and LRRK2 I1371V PD patients were analyzed for cell yield, function, and pathology. Key findings were validated in gain-of-function models using SH-SY5Y and U87 cells.

Results: LRRK2 I1371V PD iPSC-derived dopaminergic neurons had lower yield and displayed disease markers, such as increased phosphorylated α-synuclein, reduced vesicular dopamine release, altered Ca^{2+} responses, and shorter neurite length. Astrocyte yield was unaffected, but these cells showed elevated basal ROS and RNS levels and impaired functions, including reduced glutamate uptake, Nrf2-mediated glutathione response, lower α-synuclein clearance, altered neurotrophic factor secretion, and increased pro-inflammatory factor release. Mechanistically, membrane composition and fluidity were also disrupted due to elevated Rab8A and Rab10 phosphorylation, with gain-of-function studies confirming increased Rab8A phosphorylation, reduced membrane fluidity, and lower cholesterol content in I1371V.

Conclusion: iPSC-derived dopaminergic neurons and astrocytes from LRRK2 I1371V PD patients show distinct pathologies and intrinsic vulnerabilities, implicating this mutation variant in early disease onset, limited DBS efficacy, and Lewy body formation. These findings highlight the utility of iPSC platforms in identifying "predictive populations" for clinical trials, and emphasize the variant-specific effects of LRRK2 mutations on cellular function.

"Hitchhiking" on lysosomes: lysosome-dependent and independent mechanisms underlying axonal transport of TDP-43 RNP condensates

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Background: TDP-43, a highly conserved predominantly nuclear DNA/RNA-binding protein, regulates RNA stability, splicing and repression of cryptic exons. In the cytoplasm, TDP-43 is a component of neuronal ribonucleoprotein (RNP) granules, indispensable for axonal transport of mRNAs that maintain cytoskeletal and synaptic function. Axonal transport defects lead to neurodegeneration in Amyotrophic lateral sclerosis (ALS), a fatal disorder affecting motor neurons. We and others have shown that ALS-linked mutations of TDP-43's low complexity domain (LCD) impair RNP granule transport. The molecular mechanisms underlying this transport defect are still unknown.

Purpose: Recent studies showed that TDP-43 and other RNP granule proteins "hitchhike" on lysosomes. Hence, the aim of our study is to determine whether TDP-43 LCD mutations disrupt co-trafficking of TDP-43 RNP granules with lysosomes.

Methods: We performed live cell imaging of rodent primary cortical neurons expressing eGFP-tagged wild-type or mutant forms of TDP-43 and used lysotracker to visualize transport of TDP- 43 RNP granules and lysosomes in the axon 16hrs post-transfection. Kymographs were analyzed using the plugin Kymobutler in Fiji, and RNP granules were classified as motile (>10um net distance), oscillatory, or stationary.

Results: Approximately half of motile wild-type TDP-43 RNP granules co-traffic with lysosomes while the remaining TDP-43 granules travel independent of lysosomes. Consistent with our previous findings, ALS-linked TDP-43 RNP granules show markedly impaired motility. Importantly, we observed TDP-43 mutant RNP granules rarely co-traffick with lysosomes. The few TDP-43 mutant RNP granules showing net transport of >10um, appear to travel independent of lysosomes. Our preliminary data show that TDP-43 WT colocalizes with KIF5C motor protein, suggesting KIF5C is involved with anterograde axonal transport of TDP-43.

Conclusion: Our data suggest that transport defects of ALS-linked TDP-43 mutant RNP granules reflect an impaired ability of RNP granules to hitchhike on lysosomes. KIF5C motor and other organelles may also be involved in axonal transport of TDP-43 RNP granules.

Influence of europium doping on neuroprotective potential of polyacrylic acid functionalized cerium oxide nanoparticles

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Background: Cerium oxide nanoparticles (CeONPs) are known for their antioxidant properties, making them promising candidates for the treatment of neurodegenerative diseases. To further enhance these properties and add additional functionality, researchers are exploring the substitution of europium (Eu^{3+}) into CeONPs, which could also impart fluorescence to the nanoparticles.

Purpose: The study aimed to synthesize polyacrylic acid-conjugated cerium oxide nanoparticles (CeO NPs) and investigate the effect of substituting Eu^{3+} at various concentrations (5, 10, 15, and 20 mol%) on the neuroprotective properties and fluorescence of these nanoparticles.

Methods: CeONPs and Eu-doped CeONPs were synthesized, yielding nanoparticles with sizes ranging from 15 to 30 nm, stable at room temperature. The chemical states of the Eu and Ce components were analyzed using X-ray Photoelectron Spectroscopy (XPS), confirming the integration of Eu^{3+} into the cerium oxide lattice. The emission spectrum of the Eu-CeONPs was studied, focusing on the 7F0 → 5D1 and 7F0 → 5D2 transitions, indicative of Eu^{3+} acting as a luminescence center. The fluorescence of these nanoparticles was further demonstrated by depositing them on positively charged latex particles. The safety and neuroprotective efficacy of the nanoparticles were evaluated in human neuronal-like SH-SY5Y cells.

Results: Eu-doped CeONPs exhibited stable fluorescence and were safe for neuronal-like cells. Compared to pure CeONPs, the Eu-CeONPs demonstrated enhanced neuroprotection against 6-hydroxydopamine (6-OHDA). However, the neuroprotective trend of Eu-CeONPs against hydrogen peroxide (H_2O_2) was similar to that of the undoped CeONPs.

Conclusions: The study concludes that Eu-CeONPs offer enhanced neuroprotection and fluorescence, making them potential candidates for further investigation as theranostic probes in neurodegenerative disease treatment.

Monitoring age related factors influencing pharmacotherapy with anti-seizure medications [ASMs] among elderly persons with epilepsy [EPWE]: Challenges and solutions for corrective and preventive measures

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Background: Epilepsy a common neurological disorder is rapidly growing among elderly aged 60 or 65 years, a heterogenous population. The diagnosis, evaluation, clinical presentation of epilepsy, treatment and prognosis are complex among elderly.

Purpose: Factors like age-related physiological functions, multi-morbidities, polypharmacy influence pharmacokinetic profile of ASM/s and hence seizure control. Earlier study revealed 23.9% out of 49.21% persons with epilepsy[PWE] non-adherent to ASM/s due to adverse reactions which may affect optimal seizure control. However, considering complex treatment regimen no data is available among EPWE.

Methods: Data from two studies among PWE was considered for descriptive analysis of - demography, aetiology, seizure type, medications for common comorbidities and ASM/s. There were 5.36% [N=410] and 10.87% [322 PWE] EPWE during years 2006 and 2017 respectively. Anticipated age-related physiologic changes, factors influencing PK parameters of ASM/s and concomitant medication/s were evaluated by referencing standard text books and published papers.

Results: Seizure type was predominantly focal. Pattern of ASMs used was - phenytoin, oxcarbazepine, carbamazepine-CR, sodium valproate-CR during 2006; and clobazam, oxcarbazepine, levetiracetam, carbamazepine, sodium valproate, topiramate, phenobarbitone and lamotrigine in 2017. Possible challenges and criteria influencing age-related PK parameters, negative interactions of ASM combinations and polypharmacy for concomitant illnesses leading to antagonistic drug interactions likely to influence seizure control were identified and considered to formulate corrective and preventive measures and will be presented.

Conclusions: While there is steady increase in EPWE, studies identifying age-related PK parameters of ASM/s and comedications for concomitant illnesses anticipated to influence treatment outcomes are lacking. Therefore, more studies in larger numbers are warranted for appropriate and safe pharmacotherapy for optimal seizure control among EPWE.

Study of Neuropsychiatric Illness: A Journey

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The Brain and various aspects of the Mind are interlinked. This might seem quite obvious to a lay person, considering that the brain is the seat of the mind. However, in actual practice the actual aspects are often studied separately by different groups of researchers who are quite convinced that theirs is the most relevant. How related they can be, is seen in nature's experiments and also some analysis that we have carried out in our laboratory. I will share some of our findings over the years that have repeatedly confirmed this relatedness.

Epigenetic memories of stressful experiences and impact on Aggression

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Background: Early life traumatic experiences share a mysterious connection with later aberrant behavior and psychoses. In this regard, escalated and pathological aggressive behavior has emerged as a debilitating consequence of traumatic stress around puberty, spanning childhood and adolescence, though there is dearth of mechanistic evidences.

Purpose: The present study was designed to investigate the molecular basis of long term impact of early life stress on aggression.

Methods: We employed mouse model of peripubertal stress induced aggression, behavioral paradigms, brain region and sex specific transcriptome and epigenome analysis and stereotaxy based targeted gene manipulations.

Results: We deciphered role of hypothalamic thyroid hormone signaling in escalated male aggression. However, it is yet to be determined on how thyroid hormone levels regulate stress induced aggressive behavior. In parallel, we characterized few novel long non-coding RNAs derived from our transcriptome profiling that showed brain and germline enriched expression and abundant in chromatin fraction. Further, functional analyses of these candidate lncRNAs revealed lasting epigenetic marking of the genome and regulating genes including those of thyroid hormone signaling pathways indicating a potential pathway for stress induced long term behavioral outcomes.

Conclusion: We anticipate that our work might advance the fundamental molecular understanding of how childhood trauma might be connected with psychoses later in life. Our study might also allow development of new molecular tools for early prediction of aggressive disorders.

Understanding the contribution of immune factors to stress-responsive behaviour

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Background: Individuals in a population respond differently to stressful situations. While resilientindividuals recover efficiently, others are susceptible to the same stressors.

Purpose: It remains challenging to determine if resilience is established as a trait during development oracquired later in life. Further, the determinants of resilience are not well characterized.

Methods: We established a new 96-well plate based behavioural paradigm in zebrafish larvae whereby the dynamics of their recovery from intense stress was monitored. Using a statistical thresholding method, we were able to identify stress resilient and susceptible individuals in a population. We performed novel tank diving test on juvenile and adult zebrafish to test anxiety. We performed unbiased RNA-seq analysis on resilient and susceptible larvae and gene ontology analysis to understand the molecular changes.

Results: Using our novel behavioural paradigm, we show that resilience is determined and exhibited early in life. We also demonstrate that resilience to stress is a stable and heritable trait. Resilient larvae show a unique stress-induced transcriptional response, and resilient larvae downregulatemultiple factors of the innate immune complement cascade in response to stress. Perturbation of critical complement factors leads to an increase in resilience. Current experiments are focused on understanding the role of complement factors in the determination of other behaviours in addition to stress resilience.

Conclusion: Resilience is established during development as an early life behavioural trait and thecomplement pathway plays a negative role in determining resilience.

A cross ancestry genetic study of psychiatric disorders from India

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Background: Population-based analyses have been instrumental in identifying genetic contributions to the risk of psychiatric disorders. However, these studies are predominantly based on European populations, limiting the applicability of findings to other ethnic groups. Understanding how polygenic scores (PGS) derived from European samples perform in non-European populations, such as those from India, is essential for global psychiatric genetics.
Purpose: This study aims to estimate the extent of population stratification in Indian populations and assess the predictive accuracy of PGS derived from European genome-wide association studies (GWAS) when applied to an Indian dataset.
Methods: We analyzed 2,685 samples from two sources: a population neurodevelopmental study (cVEDA) and a hospital-based sample of individuals diagnosed with bipolar affective disorder (BD) and obsessive-compulsive disorder (OCD). Genotyping was conducted using Illumina's Global Screening Array. Population structure was examined using principal component analysis (PCA), uniform manifold approximation and projection (UMAP), support vector machine ancestry predictions, and admixture analysis. PGS were calculated for BD, OCD, and externalizing traits using the largest available European discovery GWAS summary statistics. Two Bayesian methods were employed—PGS-CS-auto, which incorporates local linkage disequilibrium structures, and SBayesRC, which includes functional genomic annotations.
Results: The global and continental PCA positions of the Indian samples overlapped with other South Asian populations. Admixture analysis revealed a north-south genetic axis within India ($F_{ST} = 1.6\%$). The UMAP partially reconstructed the geographic contours of the Indian subcontinent. Despite the cross-ancestry bias of the discovery GWAS datasets, Bayesian PGS analyses indicated moderate to high predictive power for BD but lower accuracy for OCD and externalizing traits. These findings confirm cross-population shared polygenic liability for the psychiatric phenotypes studied. The predictive accuracy was influenced by the sample size of the discovery GWAS and phenotypic heterogeneity across the examined syndromes and traits.
Conclusion: Our study highlights the accuracy and generalizability of newer PGS models that account for ancestry when applied to Indian populations. These results underscore the importance of ancestral diversity in genetic studies to enhance our understanding of the causal mechanisms underlying psychiatric syndromes and traits.

Dissecting Molecular Mechanisms of Neurodevelopmental Chromatinopathies

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Background: Neurodevelopmental disorders (NDDs) affect critical periods of brain development and plasticity. Chromatin-associated genes are frequently mutated in NDDs. The mutations affect chromatin structure and function, leading to disorders called chromatinopathies.

Purpose: Yet the mechanisms by which chromatinopathies disrupt brain assembly remain unclear.

Methods: My lab utilises an integrative approach, combining functional genomics with iPSC-derived cerebral organoid biology to unravel the molecular and cellular processes underlying chromatinopathies and NDDs.

Results: LSD1 is a conserved histone lysine-specific demethylase which functions in the demethylation of mono- and di- methylated H3K4 and H3K9. Mutations in LSD1 have been identified to be a putative cause of a rare genetic form of intellectual disability We have recently identified a human-specific, genomic control mechanism of LSD1 function in neuronal development (Channakkar et al., 2023, Stem Cells)
To study the underlying molecular mechanisms of bipolar disorder, a neuropsychiatric illness, we established cultures of cerebral organoids from patients from clinically dense families from the Indian population to identify disease-relevant, cellular neural development phenotypes and observed early cortical defects affecting the cellular topology in BD patient-derived organoids (Phalnikar et al., 2024, Oxford Open Neuroscience). We have also identified a rare genetic risk variant in SPEN, a transcriptional regulator, exclusively present in patients with 100% BD inheritance in the first generation.

Conclusion: Thus, we aim to uncover convergent and divergent disease pathways arising from mutations in related chromatin genes, leading to distinct NDDs. Our objective is to develop a molecular and cellular understanding of neurobiological pathways underlying neurodevelopmental and neuropsychiatric disorders to enhance diagnostics and therapies for patients.

Genetics of cognition in disease and well-being

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Background: Cognition *per se* encompasses all the activities and procedures related to acquiring, storing, retrieving, and processing information and then how it guides our behaviour. Cognition is constantly developing and adjusting to new information, regulating our behaviour throughout our lifespan, and is influenced by both hereditary and environmental variables. Understanding cognition is crucial not only for adequate cognitive development in maintaining well-being but also for a variety of neuropsychological disorders in which deficits occur. Wilson Disease (WD), caused by mutations in ATP7B, is a rare autosomal recessive disorder of copper metabolism, characterised by a wide-range of neurological symptoms including cognitive decline, psychiatric symptoms and behavioural changes. Patients even the siblings bearing same ATP7B mutations could produce varied clinical manifestations. We aimed to screen variants in *ATP7B* and other suspected modifier loci to correlate them with cognitive differences among WD patients. We also aim to assess the cognitive ability of the general population and asses their correlation with overall well-being followed by identifying the genes and variants regulating the interplay, if any.

Methods: The neurological symptoms of the WD patients were evaluated by expert neurologists; cognitive assessment was performed through ACEIII, VLT and FAB to comprehend the patients' orientation, attention, language, fluency, visuospatial skill, memory, and executive function skills; genotyping was done through PCR/RFLP/sequencing approach followed by statistical analysis, Multifactor Dimensionality Reduction Test (MDR), machine learning (CART Model) to correlate the genotype of carefully prioritized polymorphisms with the variable phenotype. Again, general cognitive ability and well-being of a total of 100 University level students (including post-graduation and PhD students; age group: 21-30) has been assessed through ACE-III Montreal Cognitive Assessment (MoCA) and SHS scales. The reliability of all the questionnaires have been assessed by checking their Cronbach's alpha value. The correlation between the well-being and cognition is being assessed paralleled by the prioritization of SNPs that may modulate their interplay.

Results: In case of WD, **a**nalysis of the 51 mutations and genotype data of 14 potential modifier polymorphisms of *APOE*, *PRNP, DBH*, *BDNF, DRD2, ATP7A, PNPLA3, HFE* revealed GG/AG genotype of *PRNP* rs1799990, *DBH* rs1108580 are associated with risk of cognitive impairment while *DBH* rs1611115 TT and *APOE* rs449647 AA act as a protective factor. Gene-gene interactions also had been found to modify the clinical traits among the patients when they presence independently or in combinations. Interestingly, using CART model we had identified that the patients having combination of *DBH* rs1108580 AG/GG and *BDNF* rs56164415 CC genotypes have lower ACE III score while patients with *DBH* rs1108580 AG/GG have lower FAB score. With respect to the cognition and well-being in the general population, we found a positive correlation between the two traits.

Conclusions: Cognitive decline among the WD patients may be attributed to the presence of different modifier genes implicated in copper metabolism and various neurological diseases having overlapping symptoms with WD. Concordant to our finding, variations in *PRNP, BDNF, DBH, APOE* have been associated with cognitive dysfunction and other neurological phenotypes in different neurological disorders. The study in general population aims to uncover common genetic determinants influencing cognition and overall well-being that are found to be positively correlated with each other.

Pannexin and P2X7 Receptor Crosstalk: A Key Determinant of Cell Fate

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Background: Pannexin 1 (Panx1) is a plasma membrane-localized ion channel that is ubiquitously expressed in many cell types, including astrocytes. In astrocytes, it functions as a major ATP channel and is believed to be predominantly activated under inflammatory conditions. ATP released through Panx1 activates the P2X7 receptor (P2X7R), allowing an influx of calcium ions, which in turn activates Panx1, amplifying the signaling through a positive feedback loop. However, the precise nature of the Panx1-P2X7R interaction and its impact on cell fate remains incompletely understood.

Purpose: The purpose of this study is to understand the regulatory mechanism of Panx1 on P2X7R and how this interaction influences cell survival and death.

Methods: The activities of Panx1 and P2X7R were measured using patch clamp and intracellular calcium imaging with Fura-2. The physical interaction between Panx1 and P2X7R was investigated via co-immunoprecipitation. Mitochondrial potential, reactive oxygen species (ROS), and caspase activation were assessed using appropriate fluorescent probes.

Results: Panx1 and P2X7R physically interact, as demonstrated by co-immunoprecipitation. Panx1 was found to attenuate P2X7R-mediated calcium ion flux through its carboxy terminus. During moderate activation of P2X7R, Panx1 acts as a physical brake to prevent excessive calcium entry, promoting cell survival. Conversely, overactivation of P2X7R triggers Panx1 activation via caspase cleavage of its C-terminus, contributing to cell death. Depending on the mode of Panx1-P2X7R interaction, Panx1 can be either pro-survival or pro-death.

Conclusions: Panx1 may play a dual role, being either pro-survival or pro-death, depending on the cellular context and the extent of P2X7R activation. We propose a novel mechanism that governs astrocyte fate under both physiological and pathological conditions.

Regulation of PPAR-γ and TLRs Expression in Ischemic Stroke Model Through PPAR-γ Agonist: A New Paradigm in Stroke Treatment

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Background: Exploration of Peroxisome proliferator-activated receptors-γ (PPAR-γ and Toll-like Receptor (TLRs) signaling pathways in ischemic stroke is a promising area of research, offering insights into potential therapeutic targets.

Purpose: This study evaluates the relationship between PPAR-γ, TLRs, and key molecular markers in *in vitro* ischemic stroke model.

Methods: To address the above purpose, the treatment of PPAR-γ agonist (pioglitazone) to both oxygen-glucose deprivation (OGD, ischemic conditions) and non-OGD SH-SY5Y cells was evaluated using the MTT assay for cell viability and flow cytometry to analyze the expression levels of PPAR-γ and TLRs (2, 3, 4) and, RT-PCR to quantify the expression of PPAR-γ, TLRs (2, 3, 4), and pro-inflammatory markers such as TNF-α, IL-12, and NF-kB. Further, molecular docking studies were carried out to evaluate the binding affinities of pioglitazone with PPAR-γ and TLRs.

Results: The results suggest that PPAR-γ agonist not only prevents ischemic injury in neuronal cells but also exhibits neuroprotective effects. Though not much is known about the cross-talk of PPAR-γ and TLRs in ischemic stroke, pioglitazone in this study regulated the PPAR-γ expression, TLRs 2, 3, 4 and pro-inflammatory markers (TNF-α, IL-12, NF-kB). Further, the PPAR-γ agonist increases the PPAR-γ expression and reduces the TLRs. Molecular interaction studies also suggest that there are strong interactions of pioglitazone with PPAR-γ as compared to TLRs. The agonist effect is also observed by regulating the expression of anti-apoptotic and apoptotic markers helpful in neuroprotection mediating through transcription factors.

Conclusion: The results suggest that PPAR-γ agonist (pioglitazone) regulates the PPAR-γ and TLRs pathways in ischemic stroke conditions, mediating through inflammatory cytokines, apoptotic and anti-apoptotic homeostasis, and transcription factors. Further evaluating the interplay between PPAR-γ and TLRs in modulating neuroprotection in the ischemic stroke condition regulating through PPAR-γ agonist might provide strong evidence in the stroke treatment.

Hypothalamus centered Pathogenesis of Heat Stroke Deaths- A Postmortem Study

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Background: Summer heat waves are widespread in tropical countries. Scores of people lose their lives every year globally due to excessive heat. Diagnosis of the cause of death is challenging during autopsy examination in such cases. The mechanism of heat stroke, which causes the death of the victim, is also required to be established.

Purpose: To establish the pathogenesis mechanism leading to death in heat stroke.

Methods: An autopsy examination was conducted in heat stroke cases to establish the cause of death. During the autopsy, tissue samples were preserved for histopathological and microscopic examination to understand disease pathogenesis.

Results: During the autopsy examination, we observed bleeding in two cases of death due to heat stroke in the anterior hypothalamus. The histological examination confirmed the bleeding in the preoptic area of the anterior hypothalamus. The bleeding was also noted in the other parts of the brain (brainstem, cerebellum), heart, lung, and kidney.

Conclusion: Bleeding from the preoptic area of the anterior hypothalamus, the body's temperature control center, associated with other brain parts and organs involved in hemodynamic circulation indicates a hypothalamus-centered pathogenesis in heat stroke.

Heavy metal Cadmium may induces potential brain tumour development by up-regulating mitogenic Shh-Gli1 (Sonic Hedgehog-Gli1) cell signaling pathway and stem cell marker BMI1 (B lymphoma Mo-MLV insertion region 1 homolog)

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Background: Heavy metal Cadmium is a toxic in nature that causes harmful effects on human health. However, its role in brain tumour development is not well explored.

Purpose: This study aims to determine the effect of cadmium on brain tumour development and behavioural changes.

Method: A total of thirty Wistar rats of 250-300g body weight range were classified into five different groups: Test groups 1 and 2 were orally administered with cadmium chloride in drinking water (30 mg/L, 60 mg/L). Positive controls 1 and 2 were orally administered with Zinc in drinking water (30 mg/L, 60 mg/L) and negative control group rats with double distilled water, for 28 days. Calculate the intake of water every week. Open Field Test (OFT) was performed in the 3rd and 4th week to observed behavioural changes after heavy metal dosing. Rats were sacrificed on day 29. Thereafter, the brain was isolated and performed the Shh-Gli1 cell signaling pathway target genes in the hindbrain by RT-PCR and Real Time RT-PCR.

Results: Intake of water decreased in both the test and positive control group. The OFT analysis showed significant behavioural changes in all parameters of both the test and positive control group compared to the negative control group, such as movement patterns, speed, travel distance, activity levels, and freezing behaviour. Gene expression analysis indicates increases in the expression of Shh, Gli1, BMI1, and P53 patterns in both the test and positive control group.

Conclusion: Cadmium exposure may initiate and promote brain tumour development by regulating Shh, Gli1, BMI1, and P53 expression and promote the mitogenic nature of Shh-Gli1 pathway in potential brain tumour development.

Rapamycin alleviates amyloid-beta-induced disruptions in redox balance and synaptic neurotransmission by activating autophagy and pro-survival signaling pathways

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Background: Autophagy is a catabolic process responsible for the continuous removal of toxic protein aggregates and cellular organelles to maintain proteostasis and cellular health. Studies have shown that autophagy provides neuroprotection, however, the detailed mechanism of autophagy-mediated neuroprotection is unclear.

Purpose: This study explores the role of rapamycin-induced autophagy and the PI3K/Akt1/mTOR/CREB signaling pathways in protecting hippocampal neurons from amyloid-beta (Aβ1-42)-induced damage in a rat model of Alzheimer's disease (AD).

Methods: In this study, stereotaxic injection of Aβ1-42 was given into the hippocampus of Wistar rats, and these animals were further treated with autophagy inducer (rapamycin) and inhibitor (wortmannin) for 4 weeks. Later, biochemical assays were done to measure oxidative stress parameters, and markers associated with autophagy, synaptic neurotransmission, and pro-survival pathways were studied by RT-PCR and western blotting in entire experimental groups.

Results: Aβ1-42 significantly impaired redox balance, synaptic neurotransmission dysfunction, and cognitive abilities, and suppressed pro-survival signaling in rats. Rapamycin treatment decreased mTOR complex 1 phosphorylation at Ser2481 and increased autophagy markers such as LC3, Beclin-1, sequestosome-1/p62, and ULK1. Next, rapamycin-induced autophagy stimulated the expression of p-PI3K, p-Akt1 (Ser473), and p-CREB (Ser183) in Aβ1-42-treated rats. Activation of autophagy also maintained redox balance by reducing the levels of ROS, intracellular Ca^{2+} flux and LPO, and increasing antioxidants like SOD, catalase, and GSH. Moreover, autophagy provides neuroprotection by increasing the expression of synapsin-I, synaptophysin, PSD95, CHRM2, DAD2 receptor, NMDA receptor, and AMPA receptor, and cognitive performance. On the contrary, wortmannin reduced autophagy and the neuroprotective effects provided by rapamycin.

Conclusion: Taken together, the data suggested that autophagy plays an important role in maintaining redox balance, synaptic neurotransmission, and pro-survival signaling pathways, and reducing neurodegeneration in the AD model.

Status of serum vitamin B12, homocysteine, folate and Hindi mental examination scale (HMSE) in older adults with psychiatric illness: A chart review from a tertiary care centre

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Clinicians face several challenges during evaluation and management of psychiatric disorders. These include definitive diagnosis, availability of reliable diagnostic tests and effective therapy. Diagnosis based on different cognitive scales such as Hindi Mental Status Examination (HMSE), Mini Mental Examination Scale (MMSE), Everyday Activity Scale of India, etc., is routinely employed by psychiatrists in India. However, specific diagnostic tests are not available for individual psychiatric disorders. For improved diagnosis, the clinicians usually request for specific biochemical tests such as serum vitamin B12 (B12), serum folate (FLT) and serum homocysteine (HCY) levels, since these parameters play critical roles in cognitive health. However, the direct correlation between these biochemical parameters and the cognitive status of the patient is not always conclusive, since these parameters could be influenced by several factors. Hence, we chose to examine the relationship between specific serum biomarkers (B12, FLT, and HCY) and cognitive performance, focusing on how these relationships vary between genders in geriatric psychiatric patients. We reviewed the clinical and biochemical data from the medical records of older adults (age 55 y and above), attending the geriatric clinical services at NIMHANS from 2019 to 2023. We assessed how these biomarkers correlate with cognitive health as measured by the HMSE. Our findings indicate a significant correlation between B12 levels and cognitive performance in female dementia patients and higher HCY and lower FLT levels linked to poorer cognitive outcomes, particularly in males. Our study suggests the need for multi-centric studies in different geographical locations of the country to draw meaningful conclusions that are applicable at the population level.

This research could help develop more precise diagnostic and treatment strategies, particularly for aging populations at risk of cognitive decline, by focusing on personalized nutritional interventions based on individual biomarker profiles.

Keywords: Cognitive performance, geriatric psychiatry, Vitamin B12, Homocysteine, Folate, Gender differences, Diagnostic Biomarkers.

Probing the *in-vitro* neuropathogenesis of SARS-CoV-2 to understand neurological complications of COVID-19

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Background: A significant proportion of all SARS-CoV-2 infected cases during the COVID-19 pandemic developed acute as well as long-term complications referred to as Long COVID. Neurological complications of Long COVID encompass stroke, sensorimotor difficulties, memory impairment, cognitive dysfunction, paraesthesia, dizziness, balance disturbances, sensitivity to light and noise, altered smell or taste perception, and autonomic dysfunction, often impeding daily functioning. Mass-spectrometry based quantitative proteomics have shown promise in unravelling host-pathogen interactions and affected pathways.

Purpose: Knowledge on infection biology of SARS-COV-2 in infected cells of central nervous system (CNS) origin, is important to understand the neuropathogenesis of this virus and identify affected host cellular pathways to guide research on development of therapeutic interventions for neurological complications of COVID-19.

Methods: The human neuroblastoma cell line, SHSY5Y, and human hepatic cell line, Huh7, were infected with SARS-CoV-2 virus isolate of lineage B.1.210. Mock-infected and virus-infected cell lysates were harvested at 4-, 8-, 24- and 48-hours post-infection. Quantitative proteomic analysis of the lysates was carried out using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS).

Results: Huh7 cells exhibited substantial increases in viral protein levels, whereas SHSY5Y cells displayed either decreased or similar levels of viral proteins. Tandem mass tag (TMT)-based quantitative proteomic analysis resulted in the identification of 4146 proteins in both the cell lines across the different timepoints. Principal component analysis (PCA) revealed a distinct proteomic profile for both the cell lines. Ribosomal and coronavirus disease pathways emerged among the top dysregulated pathways. Notably, the differential expression of complement proteins C3 and C9, as well as ubiquitin protein UBA52 in SHSY5Y cell line warrants attention in the context of SARS-CoV-2 infection.

Conclusion: The complement system has been implicated in the pathogenesis of COVID-19 contributing to inflammatory responses and tissue damage and may be involved in neurological complications of Long COVID.

Insights into SARS-CoV2 mediated Neuronal Damage - Possible Mechanisms of Brain Fog in Long COVID-19 cases

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Background: Neurological manifestations associated with the SARS-CoV-2 virus in COVID-19 survivors are a major concern worldwide in the post COVID pandemic.

Purpose: An understanding of detailed molecular mechanism of virus-mediated neuronal damage are warranted for designing potential therapies.

Methods: We screened the structural and non-structural SARS-CoV2 viral proteins for cell death, and found that Orf6 protein, an accessory protein of the virus known for inhibiting nuclear export and blocking host cell's interferon response, causes maximum cell death.

Results: We observed that in Orf6 expressing neurons, necroptotic cell death pathway was activated among other coronavirus-mediated cell death pathways (apoptosis, pyroptosis and autophagy). To validate this, we infected primary cultures of human neurons with the whole virus and determined cell death mechanisms. Further we used histological staining techniques for checking the expression of necroptotic cell death markers in the post mortem brain sections of COVID-19 patients. In addition to this, our studies revealed that the overexpression of Orf6 leads to mitochondrial perturbation and dysfunction in neurons via interaction with the host MTCH1 (Mitochondrial Carrier Homolog1) and opening of MPTP (Mitochondrial Permeability Transition Pore Complex). We further attempted to rescue the neuronal death and mitochondrial dysfunction by using specific inhibitors of necroptotic pathway markers and shRNA-mediated knockdown of host MTCH1 levels and have some interesting findings.

Conclusion: These findings reveal novel molecular mechanisms for neuronal death in COVID-19 patients, which may help us in better management of neurological manifestations.

Neuroinflammation to Neurodegeneration: Finding the roadmap for developing Anti-β Coronaviral therapeutics

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Background: Studying neuropathogenesis caused by murine β-coronavirus (Mouse Hepatitis Virus, MHV) offers insights into CNS pathobiology related to long-term COVID. Our studies focus on the cellular and molecular mechanisms of murine β-CoV-induced neuroinflammation, which mirrors aspects of multiple sclerosis.

Purpose: The innate and adaptive immune systems work hand in hand to ameliorate the neuroinflammation caused by β-coronaviruses. Hence, the consequence can be devastating if any critical immune checkpoint proteins or those that provide immunity are absent.

Methods: Intracranial inoculation of MHV-RSA59 at a standardized dosage, was administered to age-matched C57BL/6 wild-type (WT) and Ifit2-/-, CD4-/-, and CD40L-/- mice. The mice were sacrificed on different days post-infection for viral titer assessment, Western blotting, real-time PCR, histopathological examination, and flow cytometry analysis.

Results: In Ifit2-deficient mice infected with RSA59, disease severity and viral spread in the CNS were increased despite unaltered chemokine levels and reduced CNS inflammation. These mice showed impaired lymphocyte migration, particularly CD4+ T cells, and reduced CX3CR1 expression, leading to impaired microglial activation; even myelitis, and severe chronic demyelination was observed. To determine the importance of CD4+ T cells, CD4-/- mice were then studied, revealing a significant reduction in CD11b+ microglia/macrophages during the acute phase, alongside persistent viral RNA 30 days post-infection. These mice exhibited symptoms like poliomyelitis, bulbar vacuolation, and axonal degeneration, with greater susceptibility to chronic encephalitis and demyelination. However, CD11b+ phagocytic macrophages were observed during the chronic phase in inflamed brain and spinal cord regions. CD40L (T cell activation marker) deficiency further worsened disease severity by reducing microglia/macrophage activation in the acute phase, limiting T-cell infiltration in the CNS, and impairing T-cell priming in the cervical lymph nodes. In the chronic phase, extensive viral replication led to severe demyelination and axonopathy due to skewed populations of phagocytic microglia/macrophages caused by CD40L deficiency.

Conclusion: From the cellular and molecular aspect, Ifit2 and CD40-CD40L dyad provide antiviral and anti-inflammatory regimes in β-coronavirus- induced neuropathogenesis, which needs further attention.

Mechanisms underlying prescription opioid use post social defeat in HIV+ adolescents

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From a developmental milestone, adolescence is a very critical phase with changes occurring on different fronts: physical, cognitive, emotional, social, and behavioral. Any negative experiences at that stage can significantly impact the outcomes with serious ramifications that could persist into adulthood. This problem is further aggravated in HIV+ adolescents due to the associated stigma, negative attitudes, and prejudice in society. Social defeat (SD) employing a resident-intruder paradigm mimics bullying in humans and is considered a relevant animal model of psychosocial stress in defeated individuals. While previous literature has reported the experience of social stress to correlate with a higher incidence of stress-related psychiatric and addictive disorders, molecular mechanisms contributing to these outcomes remain unclear. As a step forward to fill this important knowledge gap, current works from our lab using a HIV transgenic (Tg) rat model, revealed significant increase in stress and inflammatory markers in adolescent Tg rats. Next, quantitative mass spectrometry proteomics on the purified synaptosomes from these animals identified key proteins associated with maintenance of cytoskeleton architecture, mitochondrial function to be significantly dysregulated in the Tg rats post SD. To further elucidate the role of dysregulated mitochondrial function post SD in the Tg rats, we are characterizing the role of a novel set of brain mitochondria vesicles extracellular (MEVs) in exacerbating synaptic function including identifying novel MEV protein cargo markers. Lastly, using the gold standard model of drug seeking, self-administration, we are examining how perturbed synaptic architecture eventually precipitates increased vulnerability to prescription opioid use during early adulthood in the SD animals. Such information gleaned from our holistic systems approach will further fuel mechanistic studies and eventually help develop future strategies to treat and improve neurological outcomes in this vulnerable population.

Glucuronoxylomannan from Cryptococcus *neoformans* preferentially targets neurons in immune-deficient human cerebral organoids

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Background: *Cryptococcus neoformans* cause lethal meningoencephalitis in humans, particularly in immunocompromised individuals. During this pathogenesis, cryptococcus extensively releases glucuronoxylomannan (GXM). This polysaccharide is the primary component of its capsule and the major virulent factor, that accumulates throughout the parenchyma in areas surrounding the infected tissues.

Purpose: To identify cellular and molecular targets of Glucuronoxylomannan from *Cryptococcus neoformans* in the brain

Methods: GXM is isolated from *Cryptococcus neoformans*. Human cerebral organoids lacking microglia are used to mimic immunocompromised conditions and 2-dimensional culturing of human neural stem cells and neurons. We used dual immunofluorescence, confocal microscopy, untargeted lipidomics, and 3D membrane modeling, etc to identify the targets.

Results: Capsular GXM from *Cryptococcus neoformans* induces cell death while progenitor cell proliferation is unaffected. Critically, capsular GXM preferentially targets neurons while neural stem cells and astrocytes are spared irrespective of their abundance in the organoids. A comparison of untargeted lipidomics data revealed higher membrane fluidity factors in neurons including higher abundance in phosphatidylcholine and reduced phosphatidylethanolamines along with higher unsaturation in fatty acids that could make them an easier target for GXM in the absence of phagocytic cells.

Conclusions: Since the high affinity of GXM for phosphatidylcholine in the present study along with facts from immunocompromised individuals having higher phosphatidylcholine in their subcortical regions, we hypothesize that GXM interacts with membrane lipids rather than specific receptors in *Cryptococcus. neoformans* infection under immune deficient conditions, suggestive of membrane modulation as a new avenue for reducing pathogenesis.

Elucidating the combinatorial effects of C9ALS/FTD-associated disease factors on RNA metabolism

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Background: C9orf72-associated Amyotrophic Lateral Sclerosis and Frontotemporal Dementia (C9- ALS/FTD) is a neurodegenerative disorder caused by a hexanucleotide G4C2 repeat expansion within the non-coding region of the C9orf72 gene. Pathogenesis of C9-ALS/FTD encompasses the loss-of-function of the C9orf72 gene product and the gain-of-function mechanisms by the expression of repeat expansion. C9-ALS/FTD is characterized by dysregulated RNA homeostasis and compromised autophagy with varied disease penetrance.

Purpose: We aim to study the physiological role of C9orf72 and how the loss-of-function of C9orf72 in combination with the expression of repeat-expansion leads to dysregulated RNA homeostasis.

Methods: We employed cryo-EM, biochemical and cellular assays to study the structure-function relationship of the C9orf72-SMCR8 protein complex. Thereafter, we have generated a cellular model system that allows controlled expression of repeat expansion in the absence and presence of C9orf72 protein. Presently, we employ single-molecule RNA imaging, next-generation sequencing and immunofluorescence to elucidate the combinatorial effects of C9ALS/FTD- associated disease factors on RNA metabolism.

Results: Our structure revealed the role C9orf72-SMCR8 protein complex as a GTPase activating protein complex for the Rab and Arf family of GTPases. Moreover, we identified a coiled-coil region within the catalytic domain of SMCR8 which could modulate the enzymatic activity of this complex by acting as a binding platform for other protein partners including RBPs. Single-molecule imaging of G4C2 repeat-RNA suggests that the loss of C9orf72 protein does not alter the expression, localization, and stability of repeat-RNAs. Intriguingly, transcriptome wide analysis suggests the loss of C9orf72 protein in combination with the expression of repeat expansion as a key driver of alteration in RNA metabolism, especially at the level of transcription. Strikingly, the genes that show altered expression in this context have an increased propensity to form R-loops their 3´ UTR.

Conclusion: Our results highlight that the combinatorial effects of C9ALS/FTD-associated disease factors on RNA metabolism is through the dysregulation of R-Loop homeostasis, however, further work is needed to elucidate the mechanistic basis of changes in the dynamics of R-loops.

Functionalized Nanomedicinal Strategies and Interventions for Neurodegenerative Disorders

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Background: Nanomedicinal strategies and ensuing interventions provide a unique and efficient way to overcome the various brain delivery related challenges, e.g., the low permeability through the blood brain barrier, which can be overcome by a rational choice of intelligent biomaterials and surface functionalization of the nanoplatforms with suitable ligands.

Purpose: The most effective neurotherapeutic approaches can be designed by incorporating the very complex neuroactive entities into nanostructures with directional cues and robust material characteristics for predetermined and site-specific release of the drugs.

Methods: This talk will present several methods and strategies developed over the last decade including pH-sensitive platforms for the delivery of interferon-β (multiple sclerosis), polymer coated cerium oxide nanoparticles as superantioxidant agents (Parkinson's disease), amantadine-loaded polylactide)-polymethacrylate nanospheres (amyotrophic lateral sclerosis), implantable nanoenabled multipolymeric scaffold (AIDS dementia complex), nanoliposomes functionalized with chelating ligands for neurotoxicity modulation of β-Amyloid aggregates (Alzheimer's disease), apo-lactoferrin–Galantamine proteo-alkaloid conjugate (Alzheimer's disease), nicotine-gelispheres compressed into polymeric matrix (Parkinson's disease), and interpolymeric blend/nanoenabled levodopa delivery systems, to name a few.

Results: The results obtained from the above platform systems provided important insights including the chelating ligand-bound nanosystems prevented CuAβ(1-42) or ZnAβ(1-42) aggregate buildup, increased intracellular uptake, bioactive combinations demonstrating iron and free radical scavenging ability, PLGA matrices incorporating gelispheres providing extended nicotine release for 50 days, and ease of entry into the brain tissue and interstitial fluid by small size range of the nanoparticles prepared and the negative potential.

Conclusion: The advanced nanoplatforms tested in these research initiatives demonstrated immense potential of nanointerventions in improving the neurological, neurochemical, and behavioral outcome inherent to effective and efficient neuro-protective, -regenerative, -reparative, and -restorative therapies.

Understanding Brain Diseases: Elucidation of Disease Mechanisms and Essentials of Drug Discovery Research

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Background: Neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD) and Parkinson's disease (PD) are fatal but clinically distinct. These diseases, in common, are pathologically characterized by the presence of abnormal assembly of one or many cellular proteins in different cell types, and exhibiting different patterns of neurodegeneration. For example, TDP-43 in ALS/FTLD and α-synuclein in PD are the proteins that undergo aberrant aggregation at the expense of losing their native functions.

Purpose: Tremendous efforts have been dedicated for exploring the structure and formation of these pathological aggregates *in vitro* and for the development of pre-clinical cellular/animal models. This pursuit aims to unravel the underlying disease mechanisms and, ultimately, to develop innovative strategies for diagnostic and therapeutic purposes.

Methods: During my post-doctoral work, we pursued on the objectives above, employing a range of multidisciplinary approaches, including protein engineering, structural biology, cell biology, and artificial intelligence.

Results: In the part of my ALS research, we gained knowledge on the sequence and structural determinants of TDP-43 aggregation and how its aberrant proteolytic events are the causal factors of TDP-43 pathology formation and disease progression. Secondly, we made collective efforts for the development of the methods and tools for advancing research and drug discovery efforts in PD and other synucleinopathies.

Conclusion: Though our work has provided novel insights on the disease mechanisms of ALS and PD, but we left with new questions. In my new group, I will follow-up with how our current findings raise important questions that set the basis for my future research objectives.

Gut bacteria-derived Imidazole Propionate elicits cerebrovascular dysfunction and reactive gliosis

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Background: Alzheimer's Disease (AD) and AD Related Dementias (ADRD) continue to present serious challenges in the aging population and there is a significant need to identify and reduce risk factors. Imidazole propionate (ImP) is a gut-bacteria derived metabolite of histidine, linked to type II diabetes, atherosclerosis, cardiac and renal failure. Higher levels of ImP were also associated with anxiety-like phenotype in mice. We have recently identified an association between ImP levels and longitudinal neurodegeneration as well as cognitive decline, among people with elevated risk for AD.

Methods: Human studies: We assessed abundance of bacterial taxa encoding urocanate reductase (*urdA*) in a metagenomic dataset from 180 individuals, including subjects with AD dementia, mild cognitive impairment and cognitively normal statuses. We performed linear regression between *urdA*+ taxa and reactive astrocyte biomarker (YKL40). We determined plasma ImP levels by uHPLC-MS/MS. These were then correlated with several AD biomarkers such as neurofilament light chain (NfL) that were quantified using Roche NeuroToolKit (NTK). Cognitive scores were assessed in a subset of the participants using verbal fluency and Boston naming test. Animal studies: Conventionally-raised wild type (WT) mice were fed with ImP for 8 weeks. Blood-brain barrier integrity was assessed using Evans blue extravasation assay. Conventionally raised WT, 5XFAD and PS19P301S were treated with ImP starting at weaning and maintained for the following 5 months. Brains were harvested post transcardiac perfusion and fixed in 4% paraformaldehyde (PFA) followed by 30% sucrose solution. 40µm thick coronal sections were performed on frozen, fixed brains to obtain sections equidistant from bregma for each sample. Coronal sections with visible hippocampus, retrosplenial and piriform cortices with matching physiological regions were stained for nuclei (TOPRO3), microglia (IBA-1), amyloid-beta (MethoxyX04), reactive astrocytes (GFAP), astrocyte end feet (AQP4), and astrocytes (ALDH1L1). Images were analyzed on Imaris using specialized MATLAB scripts.

Results: We found that participants with higher levels of YKL40 had increased abundance of bacterial taxa encoding the key enzyme involved in ImP production. Increased ImP levels were associated with NfL and cognitive in human subjects ($n=303$, $P<0.05$). ImP treatment increased extravasation of Evans blue in WT mice. ImP treated AD mice also show significantly higher glial reactivity which exacerbates AD associated neuropathology.

Conclusion: Our results suggest that elevated ImP may present an elevated risk potential for AD, further research is needed to establish a causal relationship.

Understanding Reserve and Resilience in Aging Through Social Cognitive Lens

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Background: Humans worldwide are living longer, and the global demographic is shifting towards an increasingly aged population. Normal aging is associated with alterations in emotional response and a decline in cognitive abilities, including executive functions and social processing. Weakened social networking during aging is associated with earlier mortality in humans.

Purpose: Research on cognitive aging is now expanding to include social cognition. Our current study investigates how social cognition is associated with direct determinants of capacity that deteriorate with aging in a Long-Evans rat model.

Methods: Young (6-7 months-old; n = 40) and aged (24-25 months-old; n = 75) male rats were behaviorally characterized based on their spatial memory performance in the Morris water maze, and then assessed for sociability and social novelty preference in a three-chambered social interaction test.

Results: In the sociability trial, both age groups exhibited preserved sociability. In the subsequent social novelty trial, when rats were given a choice between a familiar and a novel conspecific, young rats displayed a robust social novelty preference. Aged rats by comparison showed much wider individual differences, on average, distributing their exploration equally between the novel and familiar conspecifics. Strikingly, a substantial subset of aged rats spent more time interacting with the familiar animal, a social phenotype not observed in young rats. Further analysis revealed that the social and spatial learning indices were uncoupled, indicating that some features of social cognition are vulnerable to aging independent of memory changes. To explore the basis of the individual differences observed, we quantified oxytocin-immunoreactive neuron number in the hypothalamic paraventricular and supraoptic nuclei, i.e., a neuropeptide implicated in social cognition. Our results suggest that hypothalamic oxytocin cell number is preserved in aging, a finding previously reported in humans.

Conclusion: Ongoing work is exploring additional cell types, circuits, and interventions to interrogate the underlying networks of social cognition in aging.

Neurotoxic effect of nanoformulation of neonicotenoid pesticides in mice

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Background: The presence of pesticide residues in the food, water and environment is creating an alarming situation for adverse health effects in human. The continued monitoring and research work is going on to mitigate its toxic effect. In continuation to this, the nano formulations of these pesticides are also available in the market to claim better targeted action. However, non-targeted toxicity yet not explored and could be a high risk factor in the future.

Purpose: In view of the greater risk of toxicity of nano-formulations, the present work is aimed to assess the neurotoxic effects of nanoformulation of neonicotinoid pesticides in mice. The neurotoxic effect includes apoptosis, signaling proteins and altered gene expression in brain regions of mice.

Methods: Nano-formulations of neonicotinoid insecticides including acetamiprid and imidacloprid has been synthesized and their toxic effect was assessed in *in vitro* (L929 cell lines) and *in vivo* models. Male mice (30±2g) were divided into 4 groups and treated with nano-acetamiprid and nano-imidacloprid (both at the dose of 25mg/kg body weight p.o), combination of both the insecticides and control for 28 days. After last day of treatment, the mice were sacrificed, brains regions were dissected out and processed for analysis.

Results: The *in vitro* toxicity test for apoptosis was performed in L929 cell lines and observed an increased toxic effect of nano-formulations of pesticides as compared to normal neonicotinoid insecticides at various concentrations (0.01 to 50 μM) in different time points. Further, the alterations in gene expression of apoptotic and signaling proteins in brain regions of mice were also observed in various brain regions.

Conclusion: The result of the present study suggested that nano-formulations of acetamiprid and imidacloprid also caused significant toxicity in *in vitro* and *in vivo* models. Further studies are required to explore the detailed mechanism of action and molecular targets.

Nanoparticle Mediated Management of Dopaminergic Neurodegeneration

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Background & Purpose: Increased prevalence of conditions related to progressive irreversible dopaminergic loss in recent years requires newer approach for its management. An impaired dopaminergic system leads to lowered brain dopamine (DA)/irregular movements. Therapeutic management includes various approaches such a replenishment of DA through l-dopa DA antagonist, MAO inhibitors. Each of them shows limitations in the states of extensive damage with minimal behavioural relief. Considering this, we attempted nanoparticle (NPs) mediated delivery of dopamine and neurotrophins in 6-OHDA lesioned rat model of dopaminergic degeneration in order to achieve functional restoration. DA we thought would assist behavioural recovery while neurotrophins will support the dying neurons.

Method: Adult Wistar rats were stereotaxically lesioned in midbrain by 6-OHDA. Lesioned rats were treated with DA and neurotrophin NPs. Trans BBB delivery of NPs was checked. Restoration of dopaminergic system and linked neurobehavioral changes were recorded.

Results: The NPs crossed BBB, delivered the drug to the brain. A substantial neurobehavioral and neurochemical recovery was achieved.

Conclusion: This approach could be one of the valuable tool for achieving dopaminergic restoration.

Activation of EAAT2 impacts impulsive behaviour by reducing glutamate excitotoxicity in Parkinson's disease

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Background: Parkinson's disease (PD) is a systemic disease characterized by both motor and non-motor impairment. The loss of dopaminergic neurons in substantia nigra pars compacta region in PD disrupts dopamine-glutamate homeostasis in the corticostriatal circuit contributing to cognitive impairment. In addition, the excitatory amino acid transporter-2 (EAAT2) localized predominantly to the astrocytes and responsible for >80% of synaptic glutamate clearance is downregulated in PD causing glutamate spillover and excitotoxicity. This altered dopamine-glutamate homeostasis and excitotoxicity may have an impact on reward mediated and decision-making behaviors and promoting impulsive behaviors in PD.

Purpose: In this study, we hypothesized that GTS467, a small molecule activator of EAAT2 can effectively reduce excitotoxicity, treat cognitive impairment without promoting impulsive behaviors in PD.

Methods: Rats were unilaterally lesioned with 6-OHDA toxin to produce parkinsonian symptoms and are referred to as PD rats. PD rats were trained to baseline criteria in a 5-choice serial reaction time task and the chronic effect of GTS467 was assessed with a three-week treatment.

Results: Results from the study showed chronic treatment with GTS467 significantly improved correct responses, reduced premature impulsive responses and omissions compared to saline treatment. This improvement in performance correlated with reduction in glutamate levels, increase in EAAT2 expression and normalization of NMDA receptor subunits expression and signaling. Further, transcriptomics studies on prefrontal cortex tissue showed differential expression of genes involved in neuroprotection, neuroinflammation and learning and memory.

Conclusion: These results validate the role of glutamate excitotoxicity in promoting impulsive behaviors and that GTS467 can be developed as a therapeutic to reduce cognitive impairment and impulsive behaviors in PD.

Olfactory Bulb Shrinkage in Parkinson's Disease: Insights from a Meta-Analysis

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Background: Loss of smell is a common non-motor symptom of Parkinson's disease, affecting nearly 90% of patients. Interestingly, this olfactory impairment often occurs early in the course of the disease, sometimes months or even years before the onset of motor symptoms.

Purpose: This meta-analysis aimed to examine the differences in olfactory bulb (OB) volume between patients with Parkinson's disease (PD) and healthy individuals, a topic that has not been thoroughly investigated.

Methods: A comprehensive search of PubMed and Embase was conducted through April 2024 without language restrictions. Two independent reviewers identified relevant studies and collected data on study details and OB volumes. A systematic review and meta-analysis were performed using a random effects model. Publication bias was assessed by funnel plots and Begg and Egger tests. Subgroup analyzes were also performed to identify potential sources of variability.

Results: The analysis included 12 observational studies with a total of 370 Parkinson's patients and 313 healthy controls. The pooled weighted standardized mean difference (SMD) in OB volume was found to be- 0.90 SD[-1.36 to -0.43, 95%CI] for the right OB and -0.93SD[-1.43 to -0.43] for the left OB, indicating significantly smaller OB volumes in PD patients compared to healthy controls. There was no evidence of publication bias, as indicated by Egger's and Begg's -Mazumdaar tests. Sensitivity analyses confirmed the robustness of the results.

Conclusions: The study concluded that both left and right OB volumes are significantly reduced in PD patients compared to healthy controls. However, due to the significant heterogeneity, further research is required to confirm these results.

Cadmium and Movement Disorders: Molecular Insight to Preventive Intervention

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Background: Cadmium, a pervasive heavy metal, poses a significant health risk due to its insidious accumulation in the human body. Despite its slow clearance, with a half-life of 15-30 years, prolonged exposure to even low levels of Cd can have devastating consequences. One of the most vulnerable targets is the nervous system. Research carried out previously shows that excessive Cd exposure can exacerbate neurodegenerative disorder. Defining as a silent threat to brain, cadmium reported to cause motor alteration and deficits leading to development of Parkinson diseases.

Purpose: This study aims to uncover the specific molecular targets involved in cadmium-induced movement disorders by targeting the glial-mediated alterations in the TLR4/NF-κB signalling pathways.

Methods: The study utilized Wistar rats as an animal model to investigate the effects of cadmium exposure on movement disorders. Four treatment groups were established to assess different levels of cadmium exposure and potential interventions. To analyse molecular changes, western blotting, immunohistochemistry were employed. ELISA was used to quantify proinflammatory markers. Behavioural assessments, including locomotor activity, spatial working memory, motor coordination, and grip strength, were conducted using specialized apparatus.

Results: The rats treated with cadmium exhibit the significant upregulation in glial activation evident by IBA1 levels. Interestingly, a significant increase was observed in TLR 4 and Nfkb levels on cadmium exposure. The Proinflammatory molecules TNFα, IL-1B, Il-6 showing upregulation on cadmium treatment. Behaviour assessment showed a significant modulation in motor functions. Interestingly, quercetin, a flavonoid downregulated changes on simultaneous exposure with cadmium exhibiting its protective potential.

Conclusion: As a silent threat to brain, it is utmost important to understand and identify the molecular targets and mechanism associated with cadmium induced alteration in motor functions. The results of the present study highlight the importance of understanding these molecular mechanisms to develop effective strategies for preventing and treating cadmium-induced neurological impairments.

Retrograde death signaling in neurons by pan neurotrophin receptor p75NTR

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Assembly of the vertebrate nervous system is orchestrated by a balance between constructive andregressive events including neurogenesis and neuron death. Approximately half of the newly generated neurons undergo death during development indicating neuron death as an essential process for the constitution of a functional nervous system. It has been well established that during development, neurotrophins can activate retrograde pro-survival signaling in distal axons by binding to their specific receptor tyrosine kinases. I recently discovered that activation of the p75neurotrophin receptor (p75NTR) in distal axons by pro-apoptotic ligand binding or trophic factor deprivation initiates a retrograde death signal involving the intracellular domain (ICD) fragment of p75NTR. However, the mechanism for biogenesis and transport of such death signals is not known.

To investigate the retrograde transport of death signals, we utilized primary sympathetic neurons cultured in microfluidics devices. The results indicate local cleavage of p75NTR induced by trophic factor deprivation or pro-apoptotic stimulation by treatment with brain derived neurotrophic factor (BDNF) exclusively on distal axons. The released p75ICD is retrogradely transported to the cell bodies resulting in neuron death. In an effort to understand how the p75ICD would associate with retrogradely transported vesicle after losing its transmembrane domain, we found that post translational modification of p75NTR by palmitoylation at Cystine 279 residue isnecessary for its vesicular localization and neuronal apoptosis. Thus, palmitoylation represents anexcellent potential mechanism for attaching p75ICD to the retrograde transport vesicles and formation of degenerative signaling endosomes. To further explore the role of p75NTR palmitoylation *in vivo*, we also generated transgenic mice carrying a non palmitoylable mutant p75NTR by CRISPR. The mutant mice exhibited significant reduction in neuronal apoptosis in thesympathetic ganglia compared to wild type animals. In conclusion, these findings suggest that palmitoylation of p75NTR is essential for the normal apoptosis during development.

Small-molecule nutraceuticals, rescued the NADPH Metabolism in Glucose- 6-Phosphate Dehydrogenase deficient (G6PDd) microglia; thus suggested thenew-age neurotherapeutics for ASD

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Background: ASD has imposed a huge challenge for the global scientific society, clinicians and parents because of uncertainty in its origin for onset, unexplainable complex clinical heterogeneity with striking comorbidities. It is noteworthy that, nicotinamide adenine dinucleotide phosphate (NADPH) as one of major resource for maintenance cellular redox homeostasis. Glucose-6-Phosphate Dehydrogenase (G6PD) is reportedly the major contributor of cytosolic NADPH. Emerging clinical reports, including previous reports by ourteam have suggested the implication of G6PD deficiency on impeded cellular detoxificationof reactive oxygen species (ROS) linking to ASD. Microglia, the residential immune cells in the central nervous system (CNS) exhibits key roles in neurogenesis, myelination, synaptic transmission, immune surveillance, redox homeostasis and neuroinflammation.

Purpose: Thus, we aimed at understanding the importance G6PD-NADPH dysregulation in human microglia for development of new-age neurotherapeutics against neuropathology in ASD.

Methods: Towards this, we have used CRISPR-gene editing to develop G6PD-deficinet human microglia cells and studied NADPH-dependent redox pathways using several cell and molecular biology tools. Further we have screened the therapeutic potential of unique nutraceuticals in vitro.

Results: Our results demonstrated that nutraceuticals like citric and malic acid supplementation promoted NADPH production by the expression and activity of enzymes such as isocitrate dehydrogenase 1 (IDH1) and malic enzyme 1 (ME1) and reduced microglial oxidative stress. Additionally, the use of another group of small-molecule nutraceuticals, such as dieckol and resveratrol, enhanced the expression of IDH1 and ME1 enzymes to resolve the crisis of anti-oxidative support in G6PDd-microglia cells.

Conclusions: Combinatorial nutraceuticals increased NADPH production and restored redox homeostasis and lysosomal function in G6PD deficient microglia, indicating their further use as promising neurotherapeutics against G6PD deficiency linked to ASD and other neurological diseases.

Potential reversal of Alzheimer's Disease pathology by TB006 antibody targeting Galectin-3

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Background: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder caused by multiple pathogenic factors including Amyloid-β (Aβ), phospho-Tau, and Apolipoprotein E4 (ApoE4). It is widely accepted that Aβ intermediate forms (oilgomers)**,** rather than monomers or mature fibrils**,** are more neurotoxic. Galectin-3 (Gal-3) was reported to be involved in Aβ oligomerization and inflammatory processes.

Purpose: What leads the oligomerization of Aβ and is it possible to develop the alternative therapeutic modality for treating AD.

Methods: Here, we show that Gal-3 promotes oligomerization of Aβ and other pathogenic factors, and TB006**,** a monoclonal antibody targeting Gal-3**,** acts as a possible treatment for AD by degrading neurotoxic oligomers and reducing inflammation.

Results: In vitro, Gal-3 intrinsically and selectively promotes, while mTB001 and TB006 degrade, oligomerization of only the pathogenic protein forms like $A\beta_{42}$, phospho-Tau and ApoE4. Gal-3 enhances, while mTB001 blocks, $A\beta_{42}$-induced microglia activation and neuronal death. In three mouse models of AD, cognitive deficits are strongly attenuated after just two weeks of mTB001 treatment. Aβ deposition and neuroinflammation are reduced in AD mouse brains. Mechanistically, Gal-3 antibody blocked the initiating events in AD (Aβ aggregates), reduced inflammation and rescued neuronal damage. Furthermore, microhemorrhages, a potential safety liability seen with clinical stage drugs, are reduced.

Conclusion: Pre-clinical studies show that TB006 is an efficacious therapeutic entity through degradation of toxic oligomers and blocking or even reversing AD progression. Clinically, TB006 has shown a superior safety profile without any drug-related adverse events in a healthy volunteer trial.

Engineered Exosome-driven Therapy: Combatting Visual and CognitiveDecline with Anti-Inflammatory TSG-6

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Background: Traumatic brain injury (TBI) is projected to be a leading cause of death and disability, affecting vision and cognition, with military veterans at higher risk for Alzheimer's disease (AD) and related dementias.

Purpose: This study explores whether genetically engineered exosomes with surface TSG-6 can reduce inflammation and improve cognitive and visual functions in murine models of TBI and AD, building on previous findings that exosome-associated TSG-6 from mesenchymal stem cellsenhance these functions in mice.

Methods: HEK293 cells were used to overexpress human TSG-6, with or without a GPI-anchoredFc domain. Exosomes were purified through size exclusion chromatography and analyzed. DiI- labeled exosomes were injected into the eye or administered intranasally to monitor biodistribution. Mouse models of mild TBI or 5XFAD mice were treated with Control (Ctrl-Exo), human recombinant TSG-6 protein (hTSG-6), or TSG-6-Fc-GPI-Exo (TSG-6-Exo). Cognitive andvisual functions were assessed after one to three months using functional tests, and molecular histological analyses.

Results: Ctrl-Exo and TSG-6-Exo's were positive for CD9, CD63, and CD81, and negative for non-exosomal Calnexin. TSG-6 levels in exosomes were measured by ELISA. DiI-labeled TSG- 6-Exo primarily localized to retinal layers and the brain within 48 hours. TSG-6-Exo significantly improved visual acuity and a- and b-wave amplitudes in blast mice compared to Ctrl-Exo-treatedmice, with hTSG-6 showing a non-significant improvement trend. Increased GFAP and IBA1 in the Ctrl-Exo group post-TBI were reduced with TSG-6-Exo treatment. NOR test at ten weeks showed significant cognitive improvement in 5XFAD mice treated with TSG-6-Exo, with a marginally significant improvement in Ctrl-Exo, highlighting TSG-6-Exo's superior efficacy.

Conclusions: Exosomes are potential therapeutic delivery systems for cognitive and visual impairments in mouse models. TSG-6 linked to exosomes via a GPI anchor demonstrated greatertherapeutic benefits than soluble hTSG-6. Further research and development with non-MSC- derived TSG-6-expressing exosomes may advance clinical trials for neurodegenerative diseases.

Rodent model of small vessel dysfunction in understanding molecular aspects of dementia

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Background: Small vessel dysfunction due to vasoconstriction over a period can cause white matter hyper intensities (WMH) in many patients with dementia. Increased WMH are known to contribute to cognitive decline. However, we don't understand the underlying mechanisms triggering pathology in Blood Brain Barrier (BBB) to develop WMH.

Purpose: We developed mouse model of small vessel vasoconstriction to understand molecular underpinnings of BBB dysfunction leading to memory dysfunction.

Methods: ET-1(Endothelin- 1), a 21 amino acid vasoconstricting peptide was injected through guide cannula into the ventricle for a period of 9 weeks at an interval of 21 days in C57 mice along with pleiotrophin (PTN) two days earlier and 3 days after along with ET-1 injection. We also assessed the effect of vasoconstriction in AD mice.

Results: Recurrent vasoconstriction caused changes in BBB integrity triggering dendritic and neuronal loss leading to memory dysfunction.

Conclusion: Repeated vascular insult in small vessels triggers BBB dysfunction causing dendritic and neuron loss setting in cognitive decline. Maintaining BBB integrity with trophic factors helps in preserving cognitive function.

Synaptic actin cytoskeleton: Implications in Alzheimer's disease

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Background: Synaptic dysfunction is considered to happen much before the clinical manifestation of Alzheimer's disease (AD). Although AD recognizes dendritic spine loss as an early feature, the underlying mechanisms remain poorly understood. Filamentous actin (F-actin), the major cytoskeleton protein in dendritic spines, is important for defining spine structure and involved in memory.

Purpose: To explore how alterations in synaptic actin dynamics contribute to synaptic and cognitive deficits in AD.

Methods: We used APP/PS1 and controls mice for our experiments. Isolated highly enriched F-actin and G-actin fractions from synaptosomes from cortices of APP/PS1 and control mice. To assess the impact of restoring F-actin levels on synaptic and cognitive functions in APP/PS1 mice, we administered F-actin stabilizing agent, jasplakinolide. Behavioral deficits in the mice were evaluated using the contextual fear conditioning paradigm.

Results: We found a significant decrease in synaptic F-actin levels at presymptomatic age in male, but not female, AD mice. Interestingly, female AD mice began to decrease in synaptic F-actin levels at eight months of age. AD male mice showed deficits in memory recall at the age of two months, but female AD mice began to exhibit deficits in memory recall at eight months. We observed a significant reduction in PSD-95-actin association in synaptosomes of middle-aged AD compared to control mice. Using jasplakinolide to stabilize F-actin brought back memory loss, improved PSD-95-actin association, and raised synaptic F-actin levels in AD mice. Also, making actin more stable increased the levels of AMPA and NMDA receptors at synapses and increased the density of dendritic spines. This suggests that neurotransmission and synaptic strength might get better in primary cortical neurons from AD mice.

Conclusion: Our study shows that F-actin in the cytoskeleton changes at the dendritic spine and its connection with PSD-95 actin. This suggests a possible therapeutic target for treating AD.

Hippocampal Neurogenesis in STZ- Model of Alzheimer's Disease - Role of Pro-Proliferative and Neuronal Determination Factors

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Background: Synaptic dysfunction decreased hippocampal neurogenesis, neuro inflammation in key brain regions, may be a pivotal event leading to Alzheimer's dementia.

Purpose: Present study was designed to understand the molecular mechanism of decreased hippocampal neurogenesis in the early stage of insulin signaling impairment.

Methods: Insulin signaling impairment was induced in male Wistar rats (3months old) with intracerebroventricular (ICV) infusion of streptozotocin (STZ, 3mg/kg). Rats were sacrificed after 24hr, 48hr, 72hrs, 1week and 3weeks (n=12 for each time point). Rats in 3-weeks groups were subjected to water maze, novel object recognition, forced swim test, elevated plus maze behavioral tests during 3rd post infusion week. All experimental rats and control rats were either perfused with 4% paraformaldehyde or cold saline for morphological and biochemical studies respectively. Glial proliferation, neurogenesis, expression of BDNF, VEGF, pro-proliferative factor (Hes1) and neuronal determination markers (Mash1, Neurogenin1, NeuroD1) were studied in the hippocampal tissue. Data were analyzed with Two-way ANOVA followed by Bonferroni's multiple comparison test.

Results: The results showed compromised insulin function significantly increased neuro-inflammation [increased astroglia ($p<0.01$) and microglial ($p<0.01$)], significantly decreased neurogenesis, expression of BDNF, VEGF, pro-proliferative factor (Hes1) and neuronal determination markers at all time points ($p<0.05$-0.01), with a maximum effect at 72hrs post STZ infusion. Cognitive tests revealed a significant deficit in all behavioral tests ($p<0.05$-0.01). Biochemical and morphological changes in the hippocampus were significantly correlated with the impaired cognition of the animal ($p<0.05$).

Conclusions: Our data showed that impaired insulin signaling induces pathophysiologic changes as early as 24hrs after initiation, peaks by 72 hrs and continues for at least for three weeks. This suggests altered neurogenesis at the early stage of impaired insulin signaling may lead to AD later and hence therapy should be initiated at the earliest to prevent the neurogenesis deterioration.

Persistent DNA damage response drives neuroinflammation after traumatic brain injury in mice

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Background: Traumatic brain injury (TBI) is a leading cause of disability and death among children and adults. TBI can lead to long-term psychological, cognitive, and physical health deficiencies, in addition to increasing the risk of developing neurodegenerative diseases. Despite decades of research, there is no effective treatment that can provide relief to these patients suffering from the long-lasting symptoms of TBI. Thus, there is a critical need to improve our understanding of the molecular mechanisms underlying the neurodegenerative process in TB and to identify therapeutic targets for treatment.

Purpose: Recent studies provide clues on the pathogenic role of DNA damage in neurodegenerative diseases, but little is known about the molecular basis for DNA damage response in TBI. In this study, we showed that the accumulation of DNA double-strand break (DDSB), and/or DNA repair deficits, are key in the pathogenesis of TBI and triggers immune responses that precedes the onset of neuroinflammation and neurodegeneration in experimental model of TBI.

Methods: 3-month-old male wild-type (WT) mice were subjected to controlled cortical impact (CCI) injury or sham. 4-weeks after TBI, mice were tested for behavioral function and brain tissues were collected for further analysis.

Results: We found increased γ-H2A.X (Ser139) a biomarker of DNA DSB and altered expression levels of DNA repair proteins in the brain of TBI mice as compared to sham mice. This was positively correlated with upregulation of cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) immune regulatory pathway. Interestingly, modulation of DNA damage response limits inflammatory responses, and prevents functional deficits in mice.

Conclusion: Our data provide evidence that accumulation of DDSB and/or alteration in DNA repair proteins trigger inflammatory responses in the brain which may further influence neurodegeneration after TBI, and its regulation plays a critical role in alleviating the pathological consequences in TBI.

ICAM-1 reprograms microglia to ameliorate amyloid pathology and cognitive functions in a model of Alzheimer's disease

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Background: Alzheimer's disease (AD) is the most progressive neurodegenerative disease and it is estimated to affect 50 million people worldwide. Amyloid-β (Aβ) mediated neuroinflammation is one of the major causes of AD associated neurodegeneration and cognitive impairment. Microgliosis is one of the early hallmarks of AD that plays a crucial role in AD-associated neuroinflammation.

Purpose: We aim to harnessing microglial activation for long-term benefits in controlling disease pathogenesis in AD.

Methods: We performed cell viability assay, western blot, immunocytochemistry for using primary cultures. We did immunohistochemistry, TUNEL assay, behavioral assays such as novel object recognition, open filed, elevated plus maze, passive avoidance, contextual & cue dependent fear conditioning tests using 5xFAD mouse.

Results: We found that astrocyte secreted cytokine Intercellular adhesion molecule 1 (ICAM-1) improves memory and cognitive impairment in 5xFAD mice model of AD. Next, we investigated the possible mechanism of ICAM-1 that involves modification of microglial activation state and function. We found that ICAM-1 inhibits microglial inflammatory activation by inhibiting ERK-STAT3 pathway which is indispensable for microglial inflammation. Moreover, ICAM-1 was found to potentiate microglia to engulf and eliminate Aß in primary culture and reduced Aß plaque load and associated microglial activation in 5xFAD mice hippocampus. This reduced plaque levels and associated microgliosis in turn refurbished synaptic protein expressions and improved cognition and memory in these mice. Interestingly, ICAM-1 mediated microglial modification along with cognitive improvement was partially lost when ICAM-1-LFA-1 interaction was inhibited.

Conclusion: Our findings delineate the importance of ERK/STAT3 pathway in Aß mediated microglial inflammation and the modulatory role of ICAM-1 in microglial activation and phagocytosis to improve clearance of Aß and associated memory and cognitive impairments. We identify ICAM-1 as a multifunctional cytokine that reprogram microglia with long-term benefits and propose it as a promising therapeutic candidate in AD.

Deciphering the neuroprotective role of astrocytes in hypoxic brain injury by understanding glial cholesterol redistribution to sustain oligodendrocytes *in vitro*

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Background: In preterm infants, hypoxic injury to premyelinating oligodendrocytes leads to failure of oligodendroglial maturation causing long-term neuromotor disabilities.

Purpose: As astrocytes influence oligodendrocyte maturation, this study aimed to analyze the transcriptomic changes in astrocytes after hypoxic injury, to identify possible pathways influencing myelination.

Methods: Human fetal neural stem cell-derived astrocytes, expressing astrocyte-specific glial fibrillary-acidic protein (GFAP) and excitatory amino acid transporters (EAAT1 and EAAT2), were exposed to hypoxia (0.2% oxygen) and normoxia (20% oxygen) for 48 hours followed by RNA-sequencing.

Results: Transcriptomic analysis revealed the upregulation of cholesterol synthesis pathways in hypoxic astrocytes. Hypoxic astrocytes showed an increased expression of cholesterol synthetic and transport proteins HMG-coA reductase (HMGCR), squalene epoxidase (SQLE), apolipoprotein E and ABCA1 on western blot and qPCR (n=5). Astrocytic cell line SVG showed increased cell surface expression of ABCA1 on flow cytometry (n=3) and increased total cellular cholesterol content and efflux as measured by an enzyme-based assay (n=4). In contrast, premyelinating oligodendrocytes (Mo3.13) showed a decreased expression of HMGCR and SQLE on qPCR and western blot, and decreased cellular cholesterol on exposure to hypoxia (n=3). When SVG cells labelled with fluorescent BODIPY-cholesterol were cocultured with Mo3.13, SVG-derived cholesterol was seen in more Mo3.13 cells in hypoxic conditions as compared to normoxic controls (n=3). Moreover, treating Mo3.13 cells with exogenous cholesterol, increased their differentiation into mature oligodendrocytes (using PMA) as shown by increased myelin basic protein expression (n=3) on flow cytometry.

Conclusion: Increased astroglial cholesterol synthesis and transport can play a neuroprotective role in hypoxic injury by influencing oligodendrocyte maturation.

Exploring Non-Neuronal Therapeutic Targets for Epilepsy: A Novel Approach to Regulating Hyperexcitability

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Background: Recent advances in neuroscience have led to a shift in focus from purely neuronal mechanisms to the critical roles of non-neuronal cells in maintaining brain homeostasis and regulating neural activity. In cases of epilepsy where traditional treatments primarily target neuronal excitability, medicine-resistant cases remain a significant challenge. New evidence suggests that non-neuronal cells, particularly glial cells, may offer novel therapeutic strategies by regulating brain inflammation and hyperexcitability, opening new possibilities for treatment.

Purpose: This presentation explores the potential of targeting non-neuronal cells, particularly glial cells, as therapeutic avenues for managing epilepsy. By shifting the focus from neurons to the glial cells that modulate the brain's immune and inflammatory responses, this approach may provide new insights into managing epilepsy, especially in cases where conventional neuron-focused therapies fail.

Methods: The presentation will review recent studies using animal models of epilepsy, where glial cells have been shown to regulate neural excitability and protect against seizure-induced damage. Advanced imaging techniques and molecular studies have been employed to observe how these cells respond to heightened neuronal activity and influence synaptic plasticity and inflammatory responses during epileptic episodes.

Results: The findings demonstrate that glial cells, with their ability to modulate neuroinflammation and synaptic activity, play a crucial role in maintaining neural stability during hyperexcitability. In animal models, targeting glial pathways has shown promising results in reducing seizure severity, suggesting that these cells are critical players in seizure regulation and neuroprotection.

Conclusion: Targeting non-neuronal cells, such as glial cells, presents a promising yet underexplored therapeutic avenue for epilepsy management. By regulating inflammatory responses and synaptic activity, glial cells offer a potential alternative to traditional treatments focusing solely on neurons. This approach could lead to the development of more effective therapies for patients with refractory epilepsy and enhance our overall understanding of the disease mechanisms.

Unveiling Microglial Heterogeneity: Multifaceted Guardians of Brain Health and Disease

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Background: Microglial cells, which are the brain's resident immune cells, are now known for their diversity and important roles in maintaining brain health and contributing to disease processes. Recent research has identified various microglial phenotypes, each with unique functions. Understanding these diverse microglial subtypes has become a rapidly expanding field, as their distinct roles in neuroinflammation, synaptic regulation, and neuroprotection are now seen as crucial to brain health and disease.

Purpose: This presentation will explore the emerging field of microglial diversity, emphasizing the importance of studying these various phenotypes in both healthy and diseased brain states. The goal is to demonstrate how microglial diversity influences synaptic remodelling, neuronal health, and the neuroinflammatory response and to discuss the implications of this understanding for neurodegenerative diseases.

Methods: Different microglial phenotypes were studied using transmission electron microscopy to characterize structural features and in vivo two-photon imaging to observe real-time microglial interactions with neurons. These approaches provided insights into how microglia behave under normal conditions and in response to pathological stimuli, such as ageing and neurodegeneration.

Results: The findings reveal that microglial subtypes are highly responsive to changes in the brain environment, actively participating in synaptic pruning, inflammation regulation, and the maintenance of neural circuits. Their ability to adapt and respond to stressors such as ageing and disease suggests that distinct microglial phenotypes play a key role in both neuroprotection and neuroinflammation, with direct implications for diseases like Alzheimer’s and epilepsy.

Conclusion: Studying microglial diversity is crucial for understanding brain health and disease. Recognizing the diverse roles of microglial subtypes opens new therapeutic possibilities for targeting specific phenotypes involved in neurodegenerative diseases, potentially offering more precise interventions to modulate neuroinflammation and synaptic dysfunction.

Vitamin D signaling modulates human neural stem cell fate

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Background: Gestational vitamin D deficiency is associated with a decrease in fetal brain development and is correlated with reduced levels of the brain-derived neurotrophic factor. Animal studies suggest that maternal vitamin D depletion impairs recognition, long term memory and increases risk of neuropsychiatric and developmental disorder including schizophrenia and autism.

Purpose: Though findings in animal models suggest that early developmental vitamin D deficiency could substantially impact the neuronal development, whether vitamin D signaling impacts human neural stem cell (hNSC) fate remains largely unexplored. Therefore, we knock down vitamin D receptor (VDR) in our *in vitro* human hNSC model to investigate the vitamin D signaling in neuronal development.

Method: Induced pluripotent stem cells (iPSCs) were derived from human cord blood mononuclear cells using a mixture of Yamanaka factors. Differentiation of iPSCs in 2D led to the generation of hNSCs. We knock down VDR in hNSCs and assessed hNSCs' proliferation and differentiation.

Results: We observed increased expression of pluripotency markers such as OCT4 and SOX2 in iPSC colonies. After differentiation of iPSCs into hNSCs, almost 95% hNSCs were positive for Nestin and SOX2, indicating good quality of stem cells. Differentiation of hNSCs generated neurons, which were found to be positive for Tuj1 expression. We knock down VDR in hNSCs using siRNA, which resulted in suppressed proliferation of hNSCs as revealed by low expression of Ki67. Knock down of vitamin D receptor in hNSCs led to their accelerated differentiation into neurons as revealed by increased expression of DCX (early neurogenesis marker) and Tuj1 (early neuronal marker). RNA Seq is being performed to unravel the signaling pathways modulated by knock down of vitamin D receptor in hNSCs.

Conclusion: Our study provides human brain specific NSC model to investigate neural development and diseases. This study suggests that vitamin D signaling impacts human NSC fate.

Chymase and tryptase from mast cells mediate blood-brain barrier and neurobehavior dysfunction in a rodent model of anxious depression

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Background: Disorders related to anxiety and depression constitute majority of cases of neuropsychiatric disorders worldwide. Depression is often associated with neuroinflammation and blood-brain barrier dysfunction. The anxious depression, the comorbidity of anxiety and depression, is a common subtype of major depressive disorder and often resistant to standard treatments.

Purpose: Brain mast cells are one of the first responders before microglia and other mediators of neuroinflammation activate since mast cells can release prestored mediators. We hypothesized that chymase and tryptase produced by mast cells in anxious depression contribute to blood-brain barrier and neurobehavior dysfunction.

Methods: The experimental rats were subjected to chronic social defeat to induce anxious depression. Various pharmacological inhibitors were used to inhibit mast cells and its hydrolytic enzymes. The animals were subjected to elevated plus maze test, open field test, forced swimming test, light-dark test, social interaction test and fear conditioning test etc. to evaluate the anxiety and depression-like behavior.

Results: Our studies with rodent model of anxious depression showed the induction of mast cell degranulation and blood-brain barrier leakage in female rats more as compared to male rats. Mast cell inhibitors such as ketotifen, chromolyn sodium and methylene blue attenuated the blood-brain leakage, and anxiety and depression-like behaviour in rats. Inhibition of two dominant mast cell proteases i.e. chymase and tryptase improved the blood brain integrity, tight junction proteins and behaviour outcome in rodent model of anxious depression.

Conclusion: Our studies with the rodent model strongly indicate that mast cells are critical mediators of blood-brain barrier dysfunction following anxious depression. The induction of mast cells-derived chymase and tryptase contribute to degradation of blood-brain barrier and neuroinflammation in anxious depression. Further in-depth studies are required to explore the therapeutic potential of mast cells inhibitors in the treatment of anxious depression.

Neuro-protective Effects of Choline and DHA or Environmental Enrichment on Hippocampal Neural Cells in Early Life High Fat Diet Induced Obese Adult Rats

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Background: High dietary fat intake in early life disrupts adult hippocampal neurogenesis. Essential nutrients like Choline and Docosahexaenoic acid (DHA) or environmental enrichment attenuates obesity induced neural cell deficits.

Purpose: The present study assesses the neuroprotective role of essential brain nutrients and environmental enrichment in attenuating obesity induced neural cell deficits in hippocampal CA3 and outer dentate gyrus of adult rats.

Methods: 21day old male Sprague Dawley rats were divided into 4 groups (n=8 per group)- Normal control with normal chow diet (NC), Obesity-induced rats fed with high fat diet (OB), Obesity-induced rats fed with 150mg choline and DHA / kg / day (OB+CHO+DHA), and Obesity-induced rats fed high fat diet exposed to environmental enrichment for 1 hour/day (OB+EE). The duration of the experiment was for 3 months followed by normal pellet feeding for 5 months for all groups. Animals were euthanized, brains were excised and processed for cresyl violet staining. Neural cells of hippocampal CA3 region and outer dentate gyrus were quantified.

Results: Mean number of surviving CA3 neural cells were significantly reduced in OB group ($p<0.05$) and in outer dentate gyrus ($p<0.01$) as compared to that of NC group. Mean number of surviving neural cells were significantly restored in CA3 and in outer dentate gyrus ($p<0.05$) of OB+CHO+DHA and OB+EE groups as compared to that of OB group.

Conclusion: Supplements with nutrients like choline and DHA or environmental enrichment provide significant neuroprotection from high fat diet obesity induced hippocampal neural cell deficits even after the high fat diet is stopped for a period.

Neurophysiological correlates of dream recall: Insights from serial awakening paradigm in REM and NREM Sleep

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Background: Dream recall varies between REM (rapid eye movement) and NREM (non-rapid eye movement) sleep, influenced by distinct neurobiological mechanisms. Understanding these mechanisms is crucial for elucidating how dreams form and are remembered. Additionally, integrating learned experiences into dreams could modify their emotional impact, offering potential therapeutic benefits.

Purpose: The neuro-physiological mechanisms underlying dream recall are still unclear. To address this, the present study looked for specific features of dream recall during REM and NREM sleep. In addition, the current study also tested whether learned events can be incorporated into dreams.

Methods: We recruited 29 participants aged 20–35, equipping them with 64 EEG electrodes. The first night involved undisturbed sleep to establish baseline measurements. On the second night, participants were awakened at random intervals for dream reports. On the third night, after learning a specific audio-visual task, participants were exposed to the same audio cues during sleep and awakened for immediate dream recall.

Results: Preliminary findings indicate an increase in beta activity in both NREM and REM sleep preceding successful dream recall, with active beta in the medial frontal cortex observable via source reconstruction. Dream reports were obtained in 59.6% of N2 sleep awakenings and 78.7% from REM sleep. Additionally, 11.5% of the awakenings after audio cue presentations resulted in the incorporation of the learned video content into dreams.

Conclusion: These results suggest that dream recall is closely associated with beta activity across sleep stages. The ability to recall dreams and the failure to do so may be predicted by specific cortical EEG patterns. Furthermore, the successful integration of newly learned experiences into dreams may modify the emotional content of dreaming, offering potential therapeutic avenues for conditions like PTSD and nightmares. Further research is required to explore methods for positively influencing dream content to enhance emotional well-being.

Biochemical changes linked to altered social environment and its effect on social behavioral alterations related to neuropathology

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Background: Neurodevelopmental or neuropsychiatric conditions such as autism spectrum disorders (ASD) and schizophrenia (SZ) are complex and heterogeneous disorders, causes severe social behavioral deficits making it as one of the core symptoms of these mental health conditions. Along with the synaptic gene mutations or protein dysfunctions, social environment shown to be the causative of these neurological conditions, with no exact synaptic signaling being identified. A common possible mechanism often linked to these pathologies is GABAergic signaling perturbations, which makes it a target for drug ac3ons.

Purpose: This study aims to explore the biochemical changes linked to differential isolation induced social behavior alterations in mice.

Methods: We have employed C57BL6/J mice and exposed them to acute (2 hr) vs chronic (4 weeks) social isolation followed by biochemical analyses of protein expression in the brain tissue of group housed control mice and isolated mice. We have also performed the male-female interactions in a chronic isolated mice in comparison with the group housed mice.

Results: Our biochemical analysis indicate reduction in expression of hippocampal DRD2 in both acute and chronic isolated mice compared to group-housed controls. Further, the interaction partner of DRD2, the NCS1 expression also reduced in isolated mice at both the conditions. Further, the GABAergic transporter protein, VGAT expression is also reduced in both the acute and chronic isolated mice. However, except for trend towards decrease in social interaction, we did not find any other behavioral changes.

Conclusion: To conclude, our study identifies biochemical changes in synaptic proteins in hippocampus of mice upon different social isolation conditions, arguing for synaptic signaling as a potential therapeutic strategy in treating the social behavioral alterations linked to ASD and SZ.

Modulation of cortical excitability, plasticity and gut motility in hemiparetic cerebral palsy patients: Role of Probiotics

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Background: Cerebral palsy (CP) is the most prevalent neurodevelopmental disorder which compromises the posture and motor functions of the patients along with impaired cognition, sensory perception, behavioural abnormalities, epilepsy or other musculoskeletal abnormalities and dysbiosis. Gut-brain axis has a vital role in etiopathogenesis of neurodevelopmental disorders. Modulating the axis through interventions like probiotics could offer promising avenues for improving not only gastrointestinal health but also neurological and cognitive functions in CP children.

Purpose: The present research work is the first systematic study to evaluate the effect of probiotic administration on cortical excitability, plasticity and gut motility in hemiparetic CP patients.

Methods: Hemiparetic infantile CP patients with and without dysbiosis were recruited from Paediatrics OPD, AIIMS Delhi. A separate group of CP children with dysbiosis were given probiotics for 4 weeks. Before and after probiotic administration, after taking informed consent, resting and active motor threshold, motor evoked potential was recorded using Transcranial magnetic stimulation set up, gut mobility was recorded using Electrogastrography and Bristol stool scale for faeces characteristics. QUEST questionnaire was done to assess motor function in CP children.

Results: A significant increase in various domains of QUEST score (grasping, weight bearing, protective extension, dissociated movements) was evident following probiotic intervention as compared to sham. There was also an improvement in faecal characteristics along with an increase in EGG frequency, indicative of altered gut motility. A significant increase in cortical excitability was evident in resting and active motor thresholds following intervention.

Conclusion: Primary findings of the study suggest positive modulation of gut-brain axis by probiotic intervention in hemiparetic CP children.

Beyond the Gut: How Gut Microbiota Influence Neuropathic Pain Pathways

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Neuropathic pain, stemming from somatosensory nerve damage, remains challenging to treat due to limited therapeutic options and associated side effects. Emerging research indicates a role for the gut microbiome in pain modulation, though specific microbial species and mechanisms involved in chronic neuropathic pain are not yet well defined. This study examines how gut microbiota dysbiosis affects neuropathic pain by evaluating pain responses and inflammatory markers in pseudo-germ-free (PGF) rats subjected to chronic constriction injury (CCI) and subsequent fecal microbiota transplantation (FMT). In rats, gut microbiota depletion was achieved by administering broad-spectrum antibiotics before inducing chronic constriction injury (CCI). Microbial alterations were systematically monitored over 35 days, with pain responses assessed after fecal microbiota transplantation (FMT) from healthy (hFMT) and dysbiotic (dFMT) donor rats. Pain sensitivity was evaluated using mechanical, thermal, and cold hypersensitivity tests. CCI significantly decreased gut microbiota diversity, leading to notable increases in the phyla Proteobacteria and Fusobacteriota, while Actinobacteria levels were reduced considerably. LEfSe analysis revealed species-specific shifts, identifying increased levels of Pasteurellaceae bacterium, Megasphaera elsdenii, and Lactobacillus acidophilus in CCI rats. hFMT successfully mitigated hyperalgesia but did not fully reverse allodynia, whereas dFMT induced pain-like behaviors in healthy rats. FMT interventions resulted in distinct microbial shifts, correlating specific species such as Bifidobacterium adolescentis with heightened pain sensitivity, and Bifidobacterium animalis with healthier gut states. Notably, hFMT led to increased spinal expression of claudin-5 and anti-inflammatory markers, including TGF-β and IL-10, while concurrently downregulating pain-related ion channels such as TRPM8, Nav1.8, Nav1.7, and TRPA1. Conversely, dFMT was associated with elevated levels of pro-inflammatory cytokines TNF-α, IL-1β, and IBA1, indicative of spinal microglial activation and a subsequent inflammatory response. In conclusion, these findings highlight a bidirectional relationship between gut microbiota and neuropathic pain, where the microbiota not only plays a significant role in pain modulation but may also contribute to the development of pain-like behaviors following nerve injury-induced dysbiosis. These results suggest that microbiota-targeted therapies may offer a promising strategy for the effective management of neuropathic pain.

Gut Microbiome Patterns: Assessing Clinical Relevance in Schizophrenia

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Emerging studies have highlighted the potential role of gut microbiome in the pathophysiology of Schizophrenia (SCZ), a severe neuropsychiatric disorder. Schizophrenia's complex etiology, encompassing genetic, environmental, and neurobiological factors, has expanded to include the gut-brain axis, with growing evidence linking gut microbiota alterations to neuropsychiatric outcomes. Studies indicate that individuals with schizophrenia often exhibit reduced microbial diversity, an imbalance in beneficial and pathogenic bacterial species, and increased intestinal permeability. Specific microbial taxa, including Firmicutes, Bacteroidetes, and Actinobacteria, have been implicated in symptom severity and cognitive dysfunction. These microbiota alterations may influence neurotransmitter pathways, particularly those involving glutamate, GABA, and serotonin, thereby contributing to the neurodevelopmental and neurodegenerative aspects of schizophrenia. Additionally, inflammatory responses and altered immune functioning, often observed in schizophrenia, may be mediated through microbial mechanisms, further exacerbating the disorder's course. Our recent study examined the patterns of gut microbiome dysbiosis in schizophrenia, exploring their clinical relevance. Understanding these gut microbiome patterns offers new avenues for potential diagnostic biomarkers and therapeutic interventions, such as probiotics, prebiotics, and fecal microbiota transplantation. However, current studies are limited by small sample sizes, heterogeneity in patient populations, and varying methodologies, necessitating further large-scale, longitudinal research. Integrating gut microbiome assessments into clinical practice could improve individualized treatment strategies, potentially alleviating symptoms and improving quality of life for patients with schizophrenia. This underscores the need for a multidisciplinary approach to unravel the gut-brain interactions that may play a pivotal role in the onset and progression of schizophrenia.

Computational system biology approaches to understand the gut-brain connections in neurodegenerative diseases

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Background: Neurodegenerative diseases that cause motor, cognitive and autonomic dysfunction over time refer to incurable and debilitating conditions resulting progressive degeneration of nerve cells or neurons in the brain like Parkinson's disease (PD). The binding of hazardous chemical compounds such as polycyclic aromatic hydrocarbons (PAHs) into the ligand binding site of AhR may cause oxidative stress leading to PD.

Purpose: The present study aimed to unravel the complex interactions of the microbiota-gut-brain-axis to pave a better understanding of microbiota-mediated neurodegenerative disorders. The objective was to know the mechanism of molecular activation and nuclear translocation of Aryl hydrocarbon receptor (AhR upon binding of several exogenous and endogenous ligands that regulates expression of several downstream genes of Cytochrome P450s (CYPs) super family.

Methods: The present study was performed through selection of suitable natural compounds having ameliorative effect by modifying the gut microbiota population. The *in silico* study for phytochemicals were first screened to identify suitable agonists of human AhR protein which further validated through Molecular docking, ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis, Molecular dynamics (MD) simulation and Pharmacophoric study.

Results: *In silico* study findings showed the phytochemicals of *Withania somnifera* with potential ligands showing protein-protein interaction to trigger AhR activity. To its support, *in vivo* study findings also conducted in a mouse model, which showed the amelioration of CYP over expression when exogenous retinoic acid (RA) and *W. somnifera* leaf extract were co supplemented to benzo[a]pyrene (B[a]P) administration.

Conclusions: Current study suggested that withanolide B of *W. somnifera* plant as a strong agonist of AhR which may ameliorate the effect of environmental toxicants. The study advocated for the neuroprotective role of exogenous retinoic acid (RA) and phytochemicals of *W. somnifera* to alter the adverse effects of B[a]P in brain which may throw light upon alternative management of neurodegeneration in PD.

Diving into Microbiome Gut-Brain Axis to Predict Biomarkers Through Artificial Intelligence

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Background: Microbiome-gut-brain axis represents a complex, bidirectional communication network connecting the gastrointestinal tract and its microbial populations with the central nervous system (CNS). This complex system is important for maintaining physiological homeostasis and has significant implications for mental health. The human gut has trillions of microorganisms, collectively termed gut microbiota, which play important roles in digestion, immune function, and production of various metabolites.

Purpose: The present study aims to investigate the communication between gut microbiota and the brain that can occur via multiple pathways: neural (e.g., vagus nerve), endocrine (e.g., hormone production), immune (e.g., inflammation modulation), and metabolic (e.g., production of short-chain fatty acids).

Methods: Artificial Intelligence (AI) has emerged as a powerful tool in interpreting the complexities of the microbiome-gut-brain axis. AI techniques, such as machine learning and deep learning, enable the integration and analysis of large, multifaceted datasets, uncovering patterns and correlations that can be avoided by traditional methods. These techniques enable predictive modelling, biomarker discovery, and understanding of underlying biological mechanisms, enhancing research efficiency and covering the way for personalised therapeutic approaches.

Result: Dysbiosis, or imbalance of gut microbiota, has been linked to mental health disorders such as anxiety, depression, multiple sclerosis, autism spectrum disorders, etc, offering new perspectives on their etiology and potential therapeutic interventions.

Conclusion: The application of AI in microbiome research has provided valuable insights into mental health conditions. AI models have identified specific gut bacteria linked to disease, offered predictive models, and discovered distinct microbiome signatures associated with specific diseases. Integrating AI with microbiome research holds promise for revolutionizing.

Number of hUCB-derived Lin-ve stem cells is crucial for effective amelioration of retinal injury and improvement in associated memory

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Background: Damage in the retinal layer causes visual field defects such as cognition decline and memory loss. Although, various research investigations have attempted to reverse the damage using therapeutic interventions, however, these have not been successfully translated.

Purpose: The study aims to evaluate the efficacy of lineage negative (Lin-ve) stem cells derived from hUCB in reversing the retinal injury and visual memory by sub-retinal transplantation in laser injury mice model.

Methods: Retinal injury was introduced in C57BL/6J male mice (24-28g) by using laser photocoagulation around the optic disc that disrupted the RPE layer of the retina. The 2 laser spots (2L) and 8 laser spots (8L) were created in each eye of the mice. The Fundus Fluorescein Angiography was used to confirm the establishment of varying degree of retinal injury. Around 50,000 stem cells were transplanted in each eye after 24 hours of laser injury. After 1 month, neurobehavioral assessments were carried out to estimate the visual-spatial memory using Morris Water Maze (MWM) and Passive Avoidance. Subsequently, the molecular assessment including RT-PCR and immunohistochemistry were done.

Results: Fundus angiography confirmed presence of retinal vein leakage in the injury model in comparison to healthy control. The neurobehavioral tests show learning and cognitive improvement in the stem cell group in comparison to the injury group which was better in 2L group. Further, gene expression of neurotrophic factors, proliferative and apoptotic factors showed upregulated neuronal activity and possible neuroprotective role in rescue of retinal injury in both stem cell groups. However, the rescue was pronounced in mild injury i.e. 2L than severe injury i.e. 8L.

Conclusion: The Lin –ve stem cells rescued the injury and reversed the visual memory and retinal injury. The study shows that, with degree of injury, the number of lin –ve stem cells should be increased.

Influence of glycation modification on alpha-synuclein structure and pathology

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Parkinson's disease (PD) is an age-associated neurodegenerative disease. Aberrant misfolding and aggregation of α-Syn protein drives disease pathogenesis. Several factors influence its aggregation propensity and pathogenicity including post-translational modifications (PTM). Glycation is a non-enzymatic PTM elevated during hyperglycemia. Glycation of biomolecules drives aging and Type 2 Diabetes (T2D), both risk factors for PD. We observed that glycation of human α-Syn using MGO, causes a distinct deviation from its ability to form beta-sheet rich aggregates. Glycated α-Syn formed heterogeneously sized assemblies distinct from the long fibrils structure formed by its non-glycated counterpart under similar conditions. Upon injection of these assemblies in the mouse brain, we observed deterioration of neuromuscular grip strength in mice that received glycated α-Syn assemblies. The latter also encountered a similar extent of TH cell loss at SN despite lacking amyloid fibrillar structure. Glycation clearly enhances the toxicity of α-Syn towards dopaminergic neurodegeneration. Glycation of α-Syn due to hyperglycemia might be a reason channeling the increased risk of PD in diabetic population. These findings provide a novel insight on linking α-Syn pathology with conditions of elevated glycation potential such as T2D.

Heterogeneity of molecular organization at single synapses drives onset of Alzheimer's disease

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Despite intuitive insights into differential proteolysis of amyloid precursor protein (APP), the stochasticity behind local product formation through amyloidogenic pathway at individual synapses remain unclear. Here, we show that the major components of amyloidogenic machinery namely, APP and secretases are discretely organized into nanodomains of high local concentration compared to their immediate environment in functional zones of the synapse. Additionally, with the aid of multiple models of Alzheimer's disease (AD), we confirm that this discrete nanoscale chemical map of amyloidogenic machinery is altered at excitatory synapses. Furthermore, we provide realistic models of amyloidogenic processing in unitary vesicles originating from the endocytic zone of excitatory synapses. Thus, we show how an alteration in the stochasticity of synaptic nanoscale organization contributes to the dynamic range of C-terminal fragments beta (CTFb) production, defining the heterogeneity of amyloidogenic processing at individual synapses, leading to long-term synaptic deficits as seen in AD.

Modulation of amyloid assembly by chaperone-like proteins

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Soluble proteins have an inherent propensity to undergo altered protein folding, forming cross-β sheet-rich structures called amyloids. Amyloid fibrils have gained significant attention due to their involvement in neurodegenerative disorders. Parkinson's disease (PD) is one of the most common movement disorders and the fastest-growing age-related neurological disorder. It is characterized by progressive loss of dopaminergic neurons in substantia nigra due to the accumulation of α-synuclein amyloid fibrils leading to the formation of Lewy bodies. Co-aggregation of α-synuclein with other amyloidogenic proteins such as amyloid-β, Tau, and IAPP contributes to the pathophysiology and severity of PD, suggesting that PD progression is associated with other neurological disorders such as Alzheimer's and Huntington's and non-neurological diseases such as Type 2 diabetes and systemic diseases where amyloid deposits can be found in multiple organs including liver, kidney, and heart. An intricate machinery of chaperones and chaperone-like proteins keeps a check on protein aggregation and amyloid formation. However, these guardians lose their properties with age, and proteins such as α-synuclein accumulate in cells. Understanding the role of chaperone-like proteins as amyloid modulators will help in the early diagnosis of disease and present a novel approach to mitigate amyloid burden in neurodegenerative disease. Using bioinformatics tools, we have rationally identified human β-sheet rich proteins that have the potential to act as chaperone-like proteins to inhibit amyloid assembly. These proteins possess remarkable structural similarity, with 50-60% of the structure contributed by β-sheets. We speculated that the β-sheet-rich regions in the proteins may present a scaffold to the growing chain of aggregates, which is incompetent for maturing into amyloid fibrils. We have taken a multi-disciplinary approach involving microbiology, biochemistry, biophysics, and molecular and cellular biology tools to decipher the mechanism of amyloid inhibition by chaperone-like proteins. We demonstrated that sub-stoichiometric ratios of CLP drive α-synuclein into soluble off-pathway aggregates incompetent of making amyloids under *in vitro* conditions. We believe that unravelling the potential of chaperone-like proteins to alleviate amyloid burden will pave the way for future therapeutics to treat neurodegenerative diseases.

LC-3-associated phagocytosis facilitates extracellular Tau internalization and degradation in microglia

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Microglia, the brain resident phagocytic cells, are involved in the active clearance of microbes, misfolded proteins, cell debris, etc. In Alzheimer's disease, microglia play a pivotal role in clearing extracellular Amyloid-β plaques and intracellular Tau aggregates in the brain environment. Microglial cells have several mechanisms of Tau internalization, such as macropinocytosis, HSPGs, dynamin dependent endocytosis, and receptor-mediated endocytosis. Internalized Tau seeds either undergo proteosomal or lysosomal degradation or exocytosed to extracellular space via exosomes. LC-3-associated phagocytosis (LAP) is a recently discovered microglial mechanism for an effective clearance of apoptotic cells and microbes via lysosomal degradation. LC3-associated endocytosis promotes Amyloid-β clearance and alleviates neurodegeneration in murine Alzheimer's disease. In this study, we report LC3-associated phagocytosis of Tau monomer and aggregate by murine microglial cells, which are further degraded by lysosomal fusion. We have analyzed microglial activation by ionized calcium-binding receptor (Iba-1) levels by immunofluorescence and western blot assay. LC3-associated phagocytosis of human full-length Tau species, where LC-3 colocalizes with phagocytosed Tau followed by lysosomal degradation of internalized Tau are shown in this study. Accumulation of internalized Tau at the perinuclear region of the cell in the presence of chloroquine supports phagolysosomal fusion and degradation. Hence, we conclude that microglia phagocytose extracellular Tau species by LAP which further undergoes degradation by lysosomal pathway.

Key findings

- Microglia phagocytose full-length Tau (hTau40wt) oligomers via actin remodelling.
- LC3-associated phagocytosis of extracellular Tau by microglia
- Microglia localizes internalized Tau monomer and aggregate at different cytosolic locations
- Lysosomal degradation of extracellular Tau species by microglia

Chloroquine impairs autophagosome-lysosomal fusion and promotes accumulation of autophagosome in microglia

Pax6 regulates genes associated with motor and non-motor function in brain of MPTP-treated mouse model of Parkinson's disease

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Background: Parkinson's disease (PD), is one of the most common neurodegenerative disorder characterized by range of motor and non -motor symptoms. Identification and evaluation of early molecular markers and targets are of current scientific concern. In this report it is intended to present, a transcriptional regulator and multifunctional protein, Pax6- regulated genes and proteins as putative early and late markers using a mouse model of PD.

Purpose: It would be useful because patients having mutation of PAX6 show several motor and non-motor symptoms and phenotypes like microcephaly, autism, mental retardation, aniridia, glucose intolerance and aging associated disorders.

Methods: Parkinson's disease model was developed by injecting MPTP (1mg/kg) intraperitoneal for 21 days in adult mice of AKR strain and equal volume of saline in vehicle control group, was used. Brains were used for differential evaluation of transcriptomes, proteomes, ChIP and ChIP-sequencing.

Results: Significant alterations of novel transcripts, proteins and Pax6-binding to promoter sequences, UTR, distal Intergenic and Introns of several genes of early non-motor symptoms like REM sleep disorder (Snca, Tau), depression (Slc25a12, Ctnnd1), anxiety (Cntn1) to late symptoms like dementia (Stx12), visual halluucinations (Gabarap11, Gabarap12), .cytokines, growth factors, neurotrophic factors, synaptic functions, cell junction assembly and inflammatory processes were observed.

Conclusion: Periodic tests on the levels of Pax6 may serve as a transcription factor based biomarker for differential diagnosis and better management of Parkinson's disease because most of genes involved in motor and non-motor functions of Parkinson's disease are regulated by the Pax6.

Third-generation antiseizure medication: Effects on excitatory and inhibitory currents and synaptic plasticity in the hippocampus.

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Epilepsy is a neurological disorder that affects 1% of India's population. Antiseizure medications (ASMs) are drugs to control seizures and help in the well-being of patients. Patients with epilepsy often suffer from various comorbidities, including memory and cognitive problems. It has been observed that the use of anti-seizure medications (ASMs) sometimes worsens the conditions. Here we investigated the ASM eslicarbazepine's (ESL) action on excitatory and inhibitory synaptic transmission in the hippocampal synapses. Moreover, we also studied the effect of ESL on the cellular model of memory long-term potentiation (LTP) in the hippocampal synapses. We used single-cell patch clamp and field recording experiments to understand the effect of ESL on hippocampal CA1 neurons. We studied the intrinsic properties, synaptic transmission, and synaptic plasticity of CA1 hippocampal neurons in the rat brain slices. We found that at a clinically relevant concentration (100 μM) ESL reduced the amplitude of spontaneous AMPA and GABA-A receptor currents and increased the inter-event interval of spontaneous GABA-A receptor currents. In evoked excitatory postsynaptic field potentials (fEPSPs), ESL 50-100 μM increased the amplitude of fEPSPs. This increase in fEPSPs was due to the antagonistic effect of ESL on adenosine A1 receptors. We also studied the effect of ESL on synaptic plasticity and found that the application of 100 μM ESL impaired the LTP in hippocampal synapses. In conclusion, at clinically relevant concentrations ESL not only target the voltage gated sodium channels, but also affects the AMPA, GABA A and adenosine A1 receptor currents.

Biology of the Blood-Brain Barrier

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Background: Though blood-brain barrier (BBB) was discovered in the 1880s, only in 1981 was the initial understanding of the uniqueness of BBB tight junction and its physiology explained. The BBB in adults comprises a complex cellular network, brain endothelial cells, a highly specialized basal membrane, plenty of pericytes embedded in the basal membrane, and astrocytic end-feet. It offers a natural defense mechanism that protects the neural tissue from germs, toxins, and some chemicals in the circulating blood from reaching the brain. The BBB's unique guarding features are highly specialized and any breakdown of this multicellular structure, subsequently promoting neuroinflammation and neurodegeneration.

Purpose: The brain is considered the most delicate organ of the human body, and several diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, stroke, and tumors affect brain function irrevocably. In recent times, there has been a marked increase in the incidence of CNS diseases because of a surge in the aging population and the growing prevalence of brain cancers and infections, but there is no effective treatment for almost all brain diseases. In most cases, the primary cause is the presence of the BBB, which has long been posing a significant challenge in delivering drugs to the brain.

Methods: While the barrier typically hinders the influx of toxins and bacterial infections, it also makes many drugs incapable of reaching the patient's brain. Even the impaired and more permeable BBB in several pathologies such as stroke, AD, and PD can pose severe challenges to drug delivery into the brain. To overcome this limitation, neuroscientists are developing new in vitro BBB models and therapeutic approaches to enhance drug entry into the brain.

Conclusion: In this lecture, we will talk about BBB composition and characteristics in normal physiology and in pathologies, and novel therapeutic approaches with promising outcomes.

Insights into the molecular signature of neurodegeneration in WNIN/Ob rat

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Background: The cause for neurodegeneration is diverse. It could be a defect in any of the molecular machineries used for cellular metabolism. Such molecular defect can manifest multiple phenotypes in various tissues. A spontaneous mutant rat (WNIN/Ob) shows such multiple phenotypes like retinal degeneration, obesity and diabetes. Obesity and diabetes are serious health menace and are major risk factor for non-communicable diseases that account for >70% of early deaths in the world. These NCDs have multifactorial aetiology though disruption of leptin signaling is the major pathway implicated in obesity but it cannot account for the diabetes in the mutant animal. Similarly, mutation in leptin pathway cannot account for the retinal degeneration in mutant. It indicates an elusive molecule linking these various phenotypes.

Purpose: We aim to identify this elusive putative molecule.

Methods: We employed whole genome sequenced (WGS) to identify the mutant. Further, western blot was used to characterize the molecular signaling pathway implicated in obesity. RNAseq was used to identify the molecular pathway affected in degenerating retina.

Results: Our analysis identified a set of putative mutant genes by analysis of single nucleotide polymorphisms (SNPs). We also analysed the gene expression profile of the degenerative retinal tissue in the mutant rat to identify the putative signaling networks involved in the onset of retinal degeneration.

Conclusion: This multi-pronged approach is providing novel insight on a putative cellular pathways affected in the mutant. These new finding will be discussed.

Blood-based molecular signals and psychopathology of schizophrenia: A proteomic exploration study using various stages of psychosis patients

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Background: Our previous research have noticed the relationship between complement pathway proteins with psychopathology in clinical high-risk population (CHR). Based on these observations, we investigated the blood samples from cohorts of early psychosis and found that baseline complement pathway proteins not only associate with worsening of clinical symptoms in CHR but also useful in identifying responders to anti-psychotic treatment in first episode of psychosis (FEP) [doi: 10.1016/j.bbi.2021.09.018, doi:10.1016/j.bbi.2022.03.013 & DOI: 10.1093/schbul/sbac201]. Since these findings have high clinical value in early intervention of psychosis, in the current study we validated our previous observations in a different clinical cohort of CHR and drug naïve FEP patients.
Hypothesis: The current study hypothesizes that high levels of baseline complement pathway proteins in the blood predicts the worsening of functioning in CHR patients and predict the good clinical response to antipsychotics in FEP patients. To test these hypotheses, first we explored the relationship between complement pathway proteins at baseline and functional scores at follow-up in CHR population; Second in FEP patients, we tested whether the baseline complement proteins associate with change in functioning or change in psychotic symptom severity before and after treatment.
Methodology: Our team performed protein quantification of the blood samples from two clinically unique cohorts namely the STEP (n~175) clinical trial of UHR patients from Australia and the Gapi (n~85) clinical trial of FEP patients from Brazil. The complement pathway proteins were quantified using immune-assays and state of the art Mass-Spectrometry (MS) approaches. Linear regression models were used to investigate the relationship between protein levels and clinical symptom scores for the analyses. These models were adjusted for potential covariates.
Study results: First, discovery based mass spectrometry study revealed that in UHR population (STEP study) showed a positive association of C4a with psychotic symptoms and inverse association with functional status. Second, in the GAPi clinical trial, we noticed a similar cross sectional association for complement proteins with psychopathology at baseline. Above all, these baseline complement proteins demonstrated a significant relationship with improvement in psychotic symptoms and functioning after 2 months of risperidone. Overall, these findings strongly validated our previous observations in both CHR and FEP patients.
Conclusion: We for the first time identified the relationship of complement proteins with functional deterioration in CHR subjects and with functional improvement after anti-psychotics. We have now replicated in three independent cohorts of psychosis patients by showing the relationship of complement proteins especially C4a with psychotic symptoms and functioning. These findings suggest that complement protein levels could be a strong markers for predicting the course of the disease in high-risk state. Furthermore, in FEP patients, these baseline complement protein levels could be clinically useful to identify the responders from non-responders to anti-psychotics. Since anti-psychotics are effective only in 50-60% of the patients, these markers of treatment response would be novel to modify the early intervention strategies to maximize the treatment response in psychosis. Further validation studies are underway which are funded by HRB, ORYGEN and Future Neuro-2.

Development of optogenetic tools for delineating neural signaling and associated diseases

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Background: Sensory photoreceptors have been utilized to control intracellular ion fluxes (action potential), secondary messenger (cAMP and cGMP), protein-protein interaction, gene expression process of the human neural cells simply by illumination (Optogenetic Methods). Photoactivated adenylate cyclase (PAC) was utilized as optogenetic tools for controlling cAMP level in neural cells and in whole animals (Mammals, Drosophila and Nematodes etc.).

Purpose: Smaller bacterial PAC (bPAC) were needed for harnessing their full potential in optobiology and the same were also characterized for the blue light activated adenylate cyclase activity and bPAC was used as optogenetic tool for manipulating cAMP *in vivo* settings.

Methods: This simple bPAC was engineered and converted for photoactivated guanylate cyclase (bPGC) activity, recombinant bPGC protein showed guanylate cyclase activity *in vitro* system. Standard biochemical assays for measuring cAMP and cGMP, molecular biology, cell biology methods were adapted.

Results: Newly characterized PACs from protozoa *N. gruberi* (renamed NgPACs), which are consist of cyclase homology domain (CHD) and BLUF domain, respectively. Functional characterization of these PACs exhibits light regulated cyclase activity. These PACs were used as optogenetic tools to modulate the human cellular physiology and cAMP-modulated gene expression of the HEK293T cells. Elevated cAMP level in a light dependent manner, activated the CREB transcription factor associated expression of associated genes (e.g., Cox-2 and cIAP2). Recently, we have characterized several other modular photoreceptors and established their optogenetic application for controlling various cellular process across the biological systems.

Conclusions: Molecular characteristics of the diverse multi-domain light-sensitive proteins had been deciphered using array of spectroscopic methods. The mechanistic basis of optical regulation of the associated effector module is highly evolved. Optobiotechnological applications of the native and engineered photoactivated modular proteins for modulating human cell signaling, neural physiology, neural gene expression and ciliogenesis simply by illumination will be presented in detail.

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Dr. Sourav Banerjee, Scientist V, Cells and Molecules Systems and Behavior, National Brain Research Centre, Manesar; his area of interest includes RNA and memory.

Alterations is cortical processing of context specific vocalization sequences in a mouse model of autism spectrum disorders

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Background: Preclinical studies of autism spectrum disorders (ASDs) extensively use mouse ultrasonic vocalizations (USVs) as a means of communication. Auditory cortical (ACX) representation of whole natural USVs sequences and not their components show social experience based plasticity. We investigate altered ACX representation of USVs sequences in-utero valproate-exposure based mouse model of ASDs (VPA).
Methods: Single-unit recordings and 2-photon Ca^{2+} imaging were performed in the ACX of typically developed (TD) and VPA mice. Neural responses to random (SR) and predictive USV courtship sequences (natural, SN) of male mice were obtained before and after a particular social experience. The USV sequences consisted of five syllable types: noisy (N), single-pitch (S), pitch-jump (J), harmonic (H) and multiple pitch-jumps (O).

Results: Spike-rate based differential representation of single syllables by TD ACX singleunits and excitatory neurons in different sequence types is absent in VPA. Rate responses of syllable-syllable transitions of SR and SN, were not different in VPA, unlike TD. Average selectivity to single syllables in SN and SR showed preference for syllables in SN but no preference was observed in transitions. Lack of differential selectivity to transitions in SN over SR suggests absence of selectivity to the entire SNs over SRs as observed in TD. Surprisingly we find that neurons in VPA showed higher selectivity to SNs. Comparison with selectivity to whole SNs and SRs in TD, however, showed 20-30% reduction in selectivity in VPA.

Conclusion: Reduced auditory cortical selectivity to natural sound sequences suggests an alteration in sensory processing of social communication based sequences in VPA ASDs model mice. Thus mechanistic understanding of deficits in ASDs may be studied in the above framework.

Etiopathogenesis of Autism Spectrum Disorder: A Multifactorial Approach based on genetics and epigenetics

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Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction and behavior. The etiopathogenesis of ASD is multifactorial, involving both genetic and environmental factors.

Purpose: This review aims to explore the multifactorial causes of ASD, focusing on the contributions of genetic and environmental factors, as well as the role of epigenetic changes in linking these factors to ASD symptomatology.

Methods: Key areas of investigation include – (i) genetic factors contributing to ASD, ranging from genetic syndromes, microdeletions/microduplications, mutations in single genes, and single nucleotide polymorphisms (SNPs) affecting neurodevelopmental processes such as neuronal formation, axon guidance, synaptogenesis, and synaptic plasticity; (ii) environmental factors, including fetal microenvironment, micronutrient deficiencies, air pollution, toxic metal exposure, and psychological factors; (iii) the role of epigenetic mechanisms, particularly altered DNA methylation and histone modifications, as a common link between genetic and environmental factors in ASD.

Results: Both genetic and environmental factors contribute to ASD, with genetic causes ranging from large-scale chromosomal alterations to single-gene mutations. Environmental influences, including prenatal exposures and nutritional deficiencies, further complicate the etiopathogenesis. Epigenetic changes, such as DNA methylation and histone modifications, serve as a bridge between these factors, influencing gene expression and contributing to ASD symptomatology.

Conclusion: ASD results from a complex interplay of genetic, environmental, and epigenetic factors. Understanding these multifactorial causes can provide insights into the development of more targeted interventions and therapies for individuals with ASD.

Using Zebra finches as a model system to study Vocal Deficits in Neurodevelopmental Disorders

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Background: One of the hallmarks of autism spectrum disorders (ASD) is the presence of various deficits in speech and language. Songbirds such as male zebra finches are excellent models systems to study these deficits, since they learn their songs from their fathers during a sensitive period, much as humans learn speech. Singing and song learning are controlled by different sets of neural circuits, whose organization is similar to those important for human speech and hearing.

Purpose: Recent findings suggest that some of the genes linked to ASD, including those associated with the endogenous opioid system which code for μ- and δ-opioid receptors (ORs), are present in the song control regions of zebra finches.

Methods: Juvenile males were systemically injected with CTAP or naltrindole, which blocked μ- and δ-ORs, respectively, for a 10-day period during the sensitive period for vocal learning. The female-directed (FD) songs of these birds were recorded and analyzed when birds attained adulthood. Following naltrindole treatment, immunohistochemistry was performed to detect dopaminoceptive neurons and excitatory synapses in extracted brains.

Results: Whereas blocking μ-ORs led to an increase in the motivation to sing FD songs, there was no change when δ-ORs were blocked systemically. The quality of songs was altered after blocking either μ- or δ-ORs during development. Furthermore, blocking δ-ORs led to an increase in the number of medium spiny neurons (MSNs) and synapses in a striatal nucleus involved in singing.

Conclusion: Our results suggest that OR neuromodulation during the sensitive period for song learning can have long-term effects on vocalization, since it alters the neural circuits underlying this behaviour. Given the similarities between neural circuits involved in song control and speech, our results suggest that altering opioid neuromodulation in the striatum of songbirds could be used to model deficits in speech and language associated with ASD.

Autism spectrum disorder and epilepsy -A complex interplay!

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Background: Autism spectrum disorder (ASD) can coexist with intellectual disability (ID), attention deficit hyperactivity disorder (ADHD), epilepsy and sleep disturbances, and adversely affect behavioural and cognitive outcomes. Epilepsy is reported in 4% to 38% of patients with ASD and is more prevalent in older children and those with ID. ASD and epilepsy have shared neurobiology and are a common presentation in various genetic disorders such as Rett syndrome and Angelman syndrome.

Purpose: Limited literature exists on the differentiating features of ASD with (ASD-E) and without epilepsy (ASD) phenotypes. Hence, we aimed to describe the clinical, electrophysiological and radiological profiles of children with ASD alone and ASD with epilepsy (ASD-E).

Methodology: This is a retrospective descriptive study of ASD patients who attended our hospital between 2011 and 2021. The demographic, clinical, developmental, electroencephalography (EEG) and neuroimaging parameters were compared between ASD-E and ASD groups. Logistic regression analysis was performed to identify factors associated with epilepsy in ASD.

Results: Among 441 ASD patients, the mean age was 7.3 ±4.6 years, and 319 (72%) were males. ASD- E phenotype was present in 191 (43.3%) patients. Global developmental delay (GDD) (78% vs 22%, $p< 0.001$), psychomotor regression (34.3% vs 10.3%, $p<0.001$), background activity (BGA) slowing in EEG (62% vs 17%, $p<0.001$), interictal epileptiform discharges (IEDs) (81% vs 35%, $p< 0.001$) and structural abnormality in neuroimaging (48% vs 32%, p 0.013) were higher in ASD-E than in ASD group. ASD children who have a history of global developmental delay and abnormal EEG had higher odds of developing epilepsy.

Conclusion: The propensity for developing seizures in children with ASD could arrive from clinical, EEG and neuroimaging data, which will help us to prognosticate.

Neural basis of real-world vision

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Background: Monkeys are widely used to study the neural basis of vision and cognition. Real-world vision involves extensive exploration of objects as well as our surroundings, but most studies are conducted in highly artificial settings where images are shown on a monitor with animals restrained to obtain stable eye signals and neural recordings.

Purpose: Our goal was to investigate the neural basis of real-world vision by performing wireless recordings from the high-level visual and motor regions in freely moving monkeys.

Methods: Here, we implanted two monkeys with 256 electrodes into high-level visual and motor areas (IT, PMv, vlPFC) to simultaneously record brain activity wirelessly while the animals engaged in a variety of real-world natural behaviors as well as touchscreen-based tasks. We propose that such wireless recordings in naturalistic environments can reveal the neural basis of real-world vision and cognition.

Results: We validate and demonstrate the utility of this approach through the following findings: (1) We demonstrate characteristic neural responses to visual images in IT, and to eye and hand movements in PMv and vLPFC; (2) We demonstrate that object identity can be decoded from neural activity while monkeys interact with real objects; (3) We demonstrate that hand movements can be decoded from neural activity while monkeys engage in natural behaviors; (4) We demonstrate common neural signatures during sleep; and (5) We demonstrate simultaneous brain recordings from both monkeys engaged in social interactions.

Conclusion: We propose that such wireless recordings in naturalistic environments can reveal the neural basis of real-world vision and cognition.

A presynaptic autophagic dysregulation that underlies photoreceptor cell vulnerability in aging human retina

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Background: Autophagy is common in aging, pathological alterations, and many diseases. In the retina, a dysfunctional autophagy is implicated in the pathogenesis of age-related macular degeneration, characterised by the loss of central vision. Human retina with aging shows mitochondrial alterations in photoreceptor cells. However, information on the status of autophagy in aging human photoreceptor cells is rather limited.

Purpose: Because aging human photoreceptor cells show significant mitochondrial alterations, it is imperative to known the fate of damaged mitochondria in photoreceptors with aging.

Methods: This study examined human retinas (donor age: 56-94 years; N=12) by transmission electron microscopy to assess mitochondrial dynamics (fission versus fusion) and status of autophagy, and immunolabelling for ATPase (involved in ATP synthesis) in macular photoreceptor cells. The findings were analysed in the light of overall changes in autophagy status between the lower aged-(56-75 years) and advanced aged retinas (80-94 years).

Results: Mitochondrial fusion is predominant in photoreceptor inner segments than in presynaptic terminals. However, unlike photoreceptor inner segments, the aged photoreceptor presynaptic mitochondria alter significantly, showing loss of cristae and swelling and a decreased ATPase labelling, compared to that in lower age group. In advanced aged retinas, the presynaptic terminals contain large autophagosomes, each with many damaged mitochondria. However, autolysosomes are rare, and thus the aged presynaptic terminals harbour many autophagosomes, indicating dysfunctional autophagy (lack of fusion of autophagosomes with lysosomes).

Conclusion: The accumulation of large autophagosomes, rather than sporadic autolysosomes in the presynaptic photoreceptor cell compartments in advanced aging, may indicate dysregulation of autophagy. It is likely that an altered mitochondrial population and defective autophagy in presynaptic terminals may influence photoreceptor survival in late aging.

In silico analysis of phytoconstituents targeting N-methyl-D-aspartate, acetylcholine, γ-aminobutyric acid, and dopamine receptors for therapeutic use in learning and memory

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Background: Learning and memory are cognitive functions mediated by a complex array of receptor subtypes such as N-methyl-D-aspartate **(**NMDA), nicotinic acetylcholine (nAChR), gamma aminobutyric acid B ($GABA_B$) and dopamine D_1 .

Purpose: Phytoconstituents from medicinal plants have been found to be effective memory enhancers by virtue of regulating these receptors' subtypes. This study aims to compare the interactions of selected phytoconstituents from the ethanolic bark extract of *Holarrhena pubescens* Wall. ex.G.Don with these receptors' subtypes in order to determine their potential use as learning and memory enhancers.

Methods: The phytoconstituents of the ethanolic bark extract of *H. pubescens* were analyzed using GC-MS. The identified compounds were then evaluated for pharmacokinetic properties using SwissADME and toxicity profiling via ProTox 3. Molecular docking studies were performed using AutoDock Vina to analyze the binding affinity of the phytoconstituents with NMDA, nAChR, $GABA_B$, and dopamine D_1 receptors' subtypes obtained from the RCSB PDB database. *In vivo* behavioral study in albino mice was performed to validate the *in silico* findings.

Results: The GC-MS analysis of *H. pubescens'* ethanolic bark extract revealed the presence of bioactive phytocomponents. *In silico* pharmacokinetic and toxicity profiling indicated that the majority of these phytocomponents showed positive drug-like properties and were low in toxicity. Molecular docking experiments demonstrated that certain phytoconstituents have high binding affinity to the targeted receptors' subtypes. *In vivo* behavioral tests confirmed these findings, with the extract causing a significant dose-dependent enhancement in spatial learning and memory in treated mice.

Conclusion: The study underlines the potential of *H. pubescens*' phytoconstituents as learning and memory enhancers. It is anticipated that the use of herbal treatments may lead to the discovery of novel chemicals in the drug development process for enhancing learning and memory.

The penguin brain: a morphological and magnetic resonance imaging study

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Background: Penguins are have unique morphological, physiological, and behavioral features. These adaptations have allowed the penguins to colonize at some of the most extreme conditions of Antarctica. The pallium of the cerebrum is responsible for cognition and control of functions. Till today no study is available on penguin brain.

Purpose: To study the gross morphological and microscopic features of the of the cerebral and cerebellar neurons and compare with magnetic resonance imaging.

Methods: Adélie penguin heads were collected from Svennar Island, Antarctica according to the prescribed protocols.

The penguin heads were placed in a lucite container and positioned in a 7 tesla MR scanner (Biospec 70/20, Bruker Biospin GmBH) inside a volumetric coil (72/112 1H volume coil). 3D T1 weighted imaging sequences with isovoxel resolution were acquired and diffuser tensor imaging with 0.8mm slice thickness were also acquired.

After imaging, the brain was dissected out and immersion-fixed in 4% paraformaldehyde, embedded in 30% sucrose and cryo-sectioned at 8 μm thickness. These sections were cresyl violet, mounted and examined under a microscope.

Results: The dorsal surface of each hemisphere was smooth and delimited from the rest of the brain by a shallow groove (vallecula). It had large midbrain and cerebellum with welldeveloped folia. The MR images of the brain could differentiate the cerebrum, brainstem and cerebellum. The grey and white matter could be differentiated.

On cresyl violet stained sections, the pallium and cerebellum contained well-preserved multipolar neurons and glial cells identified by their characteristic features. However, it had numerous irregular to linear artifacts of freezing.

Conclusion: The penguin brain is very similar to the other avian brains containing forebrain, midbrain, and hindbrain with large cerebellum, pons and medulla. During long migration birds change their neuronal structure. It will be interesting to study the neuroplasticity in penguin brain during various phases of their life cycle.

Identification, Localization and significance of neuropeptides in non-mammalian vertebrates

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Background: Neuropeptides are small proteinaceous substances produced and released by neurons through the regulated secretory route and acting on neural substrates. They are mainly suited to comparative and evolutionary studies, as they have been highly conserved during evolution. On the basis of primary amino acid structure, neuropeptides can be arranged in to families and synthesized as multiple molecular variants. These neuropeptides play different functional roles in different organs and tissues of the same species/or among species or classes.

Purpose: Considering teleost as a non-mammalian vertebrate,in the present study our objective was to identify, localise key neuropeptides in the brain of catfish *Heteropneustes fossilis* with its functional significance.

Methods: By using Immunohistochemistry (IHC), In situ hybridization (ISH) and mRNA expression (qRT-PCR) techniques, identification, localization and significance study was conducted with various neuropeptides proteins and mRNA in tissues and cells of non-mammalian vertebrate (teleost model system).

Results: In the present study, from catfish brain cloning, characterization and identification, localization of oxytocin, vasotocin, novel isotocin analog, gonadotropins, kisspeptins, secretogranin (secretoneurin), tachykinins (neurokinin) were documented. Further, functional significance was studied with respect to exposure of environmental contaminants (mainly Endocrine Disruptors) and reproductive cycle. Our study shows that in catfish *H. fossilis,* neuropeptides are modulated by various endocrine disrupting chemicals and change in seasonal breeding phases/cycle.

Conclusion: Thus, with present study we can conclude that neuropeptides exert differential function with respect to their presence in various tissues and organs of organisms and establish its importance in neurotoxicity and regulation of reproduction.

Circadian Misalignment in Aging and Neurodegeneration: Therapeutic Interventions

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Background: Aging is associated with significant changes in the basic parameters of the circadian timing system (CTS), leading to circadian dysfunction. The interplay between the core circadian machinery and a network of interconnected transcriptional and translational feedback loops enables the SCN to maintain daily 24-hour rhythms including the sleep-wake cycle.

Purpose: To understand clock dynamics, we have extensively investigated various behavioural, histological, biochemical, and molecular parameters in aging and Neurodegeneration. Furthermore, we have studied the therapeutic effects of melatonin and herbal nutraceuticals towards developing novel treatments for circadian dysfunction, promoting good health, and increasing longevity.

Methods: Male Wistar rats of various age groups and animal models for Parkinson and Alzheimer Disease were used. Tissue samples were collected at various time points Zeitgeber time (ZT) such as 0/24, 6,12 and 18. Various techniques behavioural, histological, biochemical, and molecular such as enzyme assays, RP-HPLC, qRT-PCR, 2-D protein profiling etc. along with statistical tools such as R-program Pearson correlation, one way ANOVA were used for data analysis.

Results: We observed alterations in daily locomotor rhythms, clock gene expression, serotonin metabolism, protein profiles, antioxidant enzyme activity, immune gene expression, and molecular markers of inflammation, learning, and memory.

Discussion: Our findings suggested differential alterations in the various parameters in aging, PD and AD. Therapeutic interventions used helped restore the functional integrity of the CTS differentially. This work has implications for developing novel treatments for circadian dysfunction, promoting good health, and increasing longevity.

Parkinson's Disease Risk Classification: A Deep Learning-based Artificial Intelligence Approach

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Background: Parkinson's disease (PD) is a progressive disorder affecting movement due to dopamine neuron degeneration, causing tremors, stiffness, and balance issues. Genetic and environmental factors contribute; treatments manage symptoms, but there's no cure.

Purpose: There is an early need for a non-invasive and early diagnosis of PD risk and its risk stratification, to minimize the adverse effects of PD and proper preventive measures can be assured.

Method: Our approach utilizes deep learning (DL) algorithms with attention to the dataset having 188 subjects with Parkinson’s disease. The dataset has 107 men and 81 women ages ranging from 33 to 87 (65.1Â±10.9). The attention-based recurrent neural network (RNN), gated recurrent unit (GRU), and long short-term memory (LSTM) were compared to the conventional models. Five-fold (K5) cross-validation was used for performance evaluation. The reliability and statistical tests were conducted using three methods for attention-based models. Area-under-the-curve (AUC) was obtained using the receiver operating characteristics (ROC) curve along with p-value significance, as part of the performance evaluation.

Results: The attention-based DL models showed a mean improvement of 5.12% over the conventional DL system. As part of systems reliability, the p-value significance for attention-based DL models was < 0.001 when compared to the conventional methods, complying with the regulatory standards.

Conclusion: The hypothesis designed for attention-based DL models was scientifically validated and tested for reliability, stability, and further adaptability clinically.

Identifying connectivity markers of brain aging and cognitive decline with deep learning models

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Background: Neuroimaging-based biomarkers of brain health enable early diagnosis of cognitive decline in the aging population.

Purpose: While many recent studies have investigated whether an individual's "brain age" can be accurately predicted based on anatomical or functional brain biomarkers, comparatively few studies have sought to predict brain age with anatomical connectivity alone.

Methods: We analyzed 23 standardized cognitive test scores obtained from these participants. Next, using diffusion magnetic resonance imaging (dMRI) and state-of-the-art tractography algorithms, we estimated the structural brain connectome in the same set of individuals

Results: All test score variations could be explained with just 3 independent cognitive factors, each of which declined markedly with age. Deep learning models trained with structural connectivity features robustly predicted chronological age and inter-individual variations in cognitive factor scores. Moreover, they identified hemispheric asymmetries in fronto-parietal connections whose strength most strongly predicted each of these variables.

Conclusion: In ongoing work, we seek to augment these deep learning architectures with recent "transfer learning" approaches, utilizing large, public domain datasets with thousands of scans to enable more accurate brain age prediction in smaller, locally sourced datasets.

Risk Stratification for Cardiovascular and Stroke Events in Parkinson's Disease Patients Using Atherosclerosis Pathways and an Artificial Intelligence Framework

Background: Parkinson's disease (PD) is a serious, incurable, and costly condition that often leads to heart failure. However, the association between PD and cardiovascular disease (CVD) remains unclear, resulting in conflicting evidence and poor patient outcomes. While Artificial Intelligence (AI) has shown potential in risk stratification for CVD and stroke, existing studies have been limited by small sample sizes, comorbidities, insufficient validation, clinical variability, and a lack of big data frameworks. Consequently, no comprehensive, unbiased AI studies have established clear CVD/stroke risk stratification in the context of PD.

Purpose: This study aims to (i) establish a definitive link between PD and CVD/stroke and (ii) leverage AI to develop a robust framework for CVD/stroke risk stratification in PD.

Methods: Using the PRISMA method, we identified 223 relevant studies on CVD/stroke risk. Of these, 54 and 44 studies examined the PD-CVD and PD-stroke connections, respectively; 59 studies explored a combined PD-CVD-stroke framework; and 66 studies focused on early PD diagnosis without reference to CVD/stroke. Sequential biological pathways were analyzed to substantiate our hypothesis. For the AI model, PD-related risk factors were used as predictors, with CVD/stroke outcomes as the gold standard for risk prediction.

Results and Conclusion: Our findings indicate that the primary mechanism linking PD to CVD/stroke risk is cardiac autonomic dysfunction resulting from neurodegeneration, which contributes to heart failure and related complications, validating our hypothesis. We present novel AI-based approaches for predicting CVD/stroke risk in patients with PD and propose strategies to minimize bias in AI-driven CVD/stroke risk models in this context.

An Integrated Radiomics-Attention-Graph Network for Prognostic Prediction in IDH-Wildtype Glioblastoma Multiforme (GBM) Patients

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Background: IDH-wildtype Glioblastoma Multiforme (GBM) is a highly aggressive brain tumor with poor prognosis. Accurate prediction of overall survival (OS) is crucial for personalized treatment. This study introduces, an innovative Radiomics-Attention-Graph Analysis Network, designed to predict OS in IDH-wildtype GBM patients using multiparametric MRI scans into two categories short(≤ 12 Months) and long(> 12 Months) survivors.

Purpose: The primary purpose of this study is to develop and validate an innovative prognostic model to predict OS in IDH-wildtype GBM patients. By leveraging multiparametric MRI scans, the model aimed to accurately classify patients into short-term and long-term survivors. The ultimate goal is to provide a tool that enhances clinical decision-making by offering precise, individualized predictions for GBM patients, thus contributing to more effective and personalized treatment strategies.

Method: The model combined radiomic features from T1, T2, FLAIR, and T1GD MRI scans with graph-based features to capture spatial and physiological relationships in tumor regions and selected 200 relevant features. Feature selection process included a two-step process: removing low-variance features followed by Recursive Feature Elimination (RFE). An attention mechanism focused on key regions of interest (ROIs) to enhance predictive accuracy, filtering noise and irrelevant data.

Results: This novel model was validated on a replication cohort of 99 IDH-wildtype GBM patients, achieving accuracy - 87.78%, precision - 88.03%, recall - 90.25%. The model demonstrated the cross validated ROC-AUC value of 0.94 ± 0.04 (Standard Deviation) for discovery cohort, and 0.84 AUC in the replication cohort. Kaplan-Meier analysis showed significant predictive power (p-value < 0.0001) to categorize short and long survivors, which offers valuable insights for clinical decision-making.

Conclusion: This novel integrated model represented a significant advancement in predicting OS in GBM patients, leveraging the strengths of radiomics, graph analysis, and attention mechanisms.

Radiomics and RadioGenomics in Aging Associated Disorders and Gliomas

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Background: 'Brain Health' is a multifactorial phenomenon, so is 'Brain Disorders'. However, quantifying the clinically relevant genetic, epigenetic and biochemical underpinning of brain disorders is complicated, given the challenges associated with surgical interventions in the brain to obtain the tissue biopsies. Advanced neuroimaging methods combined with Artificial intelligence provides a quantitative highly precise platform to sneak into molecular underpinning of brain health and disorders.

Purpose: To establish Brain Segmentations, Neuroanatomic volumetry and Geometry measurements as determinant of Brain Age in Aging subjects and establish tumor geometry as determinant of molecular subtype of gliomas.

Methods: In order to obtain optimal number of brain features as determinant of Brain Age, we have quantified WMH load, neuroanatomic-volume, and thickness in cognitively normal, MCI, and AD subjects in a large aging cohort from NACC and ADNI. Longitudinal T1w and T2-Flair from NACC subjects (CN=528, MCI=146, AD=276) were segmented for 178 neuroanatomic features and Periventricular WMH (PVWMH) and Deep WMH (DWMH) using an in-house optimized pipeline. A Brain Age model was established to predict Brain Age and Brain Age Gap (BAG) using the following equation. **BAG = Chronological Age – Estimated Brain Age** To establish Radiomic features; tumor geometry, shape and size of tumor as determinant of molecular subtypes of Gliomas, we segmented brain tumors across enhancing, nonenhancing and edema subcomponents of gliomas. Bounding box and Gliding box methods were used to determine Fractality and Lacunarity of the subcomponents of the gliomas. The AI model was trained and tested on the Geometry measurements of glioma subcomponents as determinants of IDH and MGMT status of Gliomas.

Results: The cognitively normal subjects who had high WMH volume (5-10ml) were estimated to have a significantly higher Brain Age Gap ranging from +2.4 to +3.5 years at the early age group and 3-6 years at the intermediate age groups compared to the subjects with NO detectable WMH. Permutation importance analyses for the top ten brain volumetry contributors towards Brain age estimation for the subjects with no WMH revealed that the volume of 3rd-ventricle is the topmost feature with an importance factor of 0.14 while, for the subjects with high WMH, PVWMH was the most important feature, with an importance factor of 0.083.A combination of fractality of enhancing and non-enhancing subcomponents wrapped in the SVM-model was able to discriminate the IDH-mutant and wildtype status accurately with an accuracy of 89% and ROC-AUC of 0.92.

Conclusion(s): 'Brain Age' of an individual differs from the chronological age as a function of Neuroanatomic volume and WMH load at the given chronological Age. Brain age may potentially serve as a clinical scale of evaluating Brain Health.

Serotonergic Neuroreceptor manipulation ameliorates ADHD Symptoms in rats-Role of Dopamine DA1 and DA2 Neuroreceptors in the Prefrontal cortex and the Striatum

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Background: The pathophysiology of attention deficit hyperactivity disorder (ADHD) primarily involves hypofunction of the adrenergic (NE) and dopamine (DA) systems in the prefrontal cortex and striatum. When stimulant medications fail to alleviate ADHD symptoms, second-generation antipsychotics are sometimes employed, which target the serotonergic system (5-HT) in addition to NE and DA systems, achieving some degree of success. The mechanism by which 5-HT receptors mitigate ADHD symptoms remains unclear, but it is believed to involve modulation of the brain's DA system.

Purpose: Therefore, the present study investigates the role of 5-HT receptors in addressing core ADHD symptoms and the involvement of DA receptors in relevant brain regions.

Methods: Male spontaneously hypertensive rats (SHR) at fifteen days old (n=8 per group) received either a 5-HT1A agonist (Ipsapirone) or a 5-HT2A antagonist (MDL100907) intraperitoneally from postnatal day 15 to 42, alongside age-matched Wistar Kyoto rats (WKY). ADHD-like behaviors were assessed using a battery of behavioral tests from postnatal day 105 to 126 for long term effects. Subsequently, rat brains were analyzed to estimate the density of DA-D1 and DA-D2 neuroreceptors in the prefrontal cortex and striatum.

Results: Both the 5-HT1A agonist and 5-HT2A antagonist effectively mitigated core ADHD symptoms in SHR. This beneficial effect was associated with downregulation of DA-D1 receptor expression in both prefrontal cortex and the striatum while upregulating DA-D2 receptor expression in the striatum but not in the prefrontal cortex.

Conclusions: The study thus demonstrates that monotherapy with either a 5-HT1A agonist or a 5-HT2A antagonist can reduce ADHD behaviors even after discontinuing therapy through modulation of DA receptors.

Hyperexcitability in early stages of Alzheimer's Disease causes aberrant expression of two pore domain leak potassium channels

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Background: Alzheimer's Disease (AD) patients exhibit hyperactivity of brain cells at early stages of the disease caused partly by toxic amyloid β (Aβ) peptide species. There is mounting evidence that E/I imbalance and neuronal hyperexcitability at early stages of the disease lead to rapid progression of the disease eventually causing cognitive decline. Interestingly, two pore domain leak potassium channels (K2P) decrease neuronal hyperactivity and protect brain cells in several neurological disorders like cerebral ischemia and epilepsy where the major pathophysiological signature is excitotoxicity.

Purpose: However, it is unknown if and how Aβ affects neuroprotective K2P channel expression and function in neurons. Therefore, we studied whether pathological Aβ peptide species (Aβ 42) disrupt the expression of K2P channels like TREK1 and TASK3 leading to the modulation of their function.

Method: We used P0-P1 rat hippocampal/cortical neuron astrocyte primary cultures and 3month-old transgenic APP/PS1 hippocampal/cortical brain cryosections to study the expression pattern of K2P channels TREK1 and TASK3 using immunostaining methods and calcium imaging.

Results: We observed increased TREK1 and TASK3 expression in the presence of Aβ42 oligomers in cortical and hippocampal neurons. Mechanistically, hyperexcitability and intracellular calcium increase due to Aβ42 oligomers led to activation of downstream signaling pathways which in turn caused an increase in TREK1 and TASK3 expression. Additionally, we found that AD transgenic models like APP/PS1 mice also showed increased expression of TREK1 and TASK3 in early stages of AD.

Conclusion: The results suggested that Aβ mediated hyperexcitability at early stages of AD can lead to dysregulated expression of K2P.

Unravelling Depression: A Molecular Meta-Analysis of Blood Biomarkers in MDD

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Background: Advances in molecular diagnostics, mainly from human blood samples, have significantly improved early disease detection through biomarkers. However, Major Depressive Disorder (MDD)—a multifaceted condition influenced by genetic, environmental, and psychological factors—lacks a standardized molecular diagnostic method, leading to inconsistent treatment outcomes. MDD triggers various biochemical changes in the brain, affecting gene, protein, and metabolite signalling.

Purpose: This study aims to identify potential biomarkers for MDD diagnosis and treatment by integrating data on genes, proteins, and metabolites using meta-analysis and bioinformatics approaches.

Methods: A comprehensive search of PubMed, Web of Science, ProMENDA, and PsycNet databases was conducted, focusing on clinical trials. Studies were screened using Rayyan, and bias was assessed with the RoB 2.0 tool. Extracted data included study ID, biological samples, control and case statistics, marker levels, and effect sizes. Meta-analysis was performed using R, evaluating effect sizes, heterogeneity, and publication bias, with visualization through forest and funnel plots. Subgroup analysis focused on age-related demographic differences. Bioinformatics analysis involved gene and protein enrichment using String, Cytoscape, and ShinyGO, along with metabolite analysis via MetaboAnalyst 6.0.

Results: From 18,651 studies identified, 17 were included: 7 genomic, 5 proteomic, and 5 metabolomic. Effect sizes were calculated for genomic (SMD 2.63, 95% CI [2.22; 3.05]), proteomic (SMD -0.13, 95% CI [-0.15; -0.10]), and metabolomic (SMD 5.64, 95% CI [5.26; 6.02]) markers, with high heterogeneity observed. Subgroup analysis revealed significant age-related differences. Bioinformatics highlighted fundamental interactions and functions, particularly involving TNFα, IL6, LEPTIN, BDNF, CRP, PRL, and IL8.

Conclusion: This study identifies potential MDD biomarkers, such as COMT, CRP, IL6, IL8, folic acid, and homocysteine, which could enhance diagnostic and therapeutic strategies. Future research should focus on gender-specific expressions and neuropsychological correlations to improve biomarker accuracy.

Resting-State Brain Networks and Graph Theory: Unlocking Signatures to Differentiate Adolescent Mood Disorders

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Background: Adolescence is a critical period for the onset of mood disorders such as Major Depressive Disorder (MDD) and Bipolar Disorder, which are often difficult to differentiate clinically. Emerging evidence suggests that brain network efficiency, as measured by graph theory analysis of restingstate fMRI data, may provide distinct neural markers for these disorders. This study aims to determine whether graph theory-based brain network analysis, combined with behavioral and demographic data, can effectively differentiate between adolescents with MDD, bipolar disorder, and healthy controls.

Methods: Resting-state fMRI data were collected using a 3T MRI scanner from 20 adolescents with MDD, 20 with bipolar disorder, and 20 healthy controls, all aged between 12 to 16 years. All participants were recruited from the Child Psychiatry Unit of the Department of Psychiatry at King George Medical University, Lucknow. Graph theory metrics, including global and local efficiency, average path length, and degree centrality, were calculated to assess brain network topological properties. These metrics were then correlated with behavioral assessments and demographic data to explore their potential in differentiating the disorders.

Results: Significant differences in brain network metrics were observed across the three groups. Adolescents with bipolar disorder exhibited lower global efficiency compared to both MDD and healthy controls, while those with MDD showed reduced local efficiency in specific brain regions. These network disruptions correlated with behavioral symptoms and demographic variables, enhancing the differentiation between MDD and bipolar disorder when combined with graph theory metrics.

Discussion: The study demonstrates that graph theory-based network analysis of resting-state fMRI data, combined with behavioral and demographic information, can provide distinct neural signatures for MDD and bipolar disorder.

Conclusion: This integrated approach could improve the clinical differentiation and management of mood disorders in adolescents, offering a promising tool for more accurate diagnosis and personalized treatment strategies.

Lipid metabolism predictive analysis: Implying in finding genetic commonality between Alzheimer's disease and metabolic syndrome

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Background: Alzheimer's disease (AD) is an age-associated neurodegenerative disorder characterized by progressive cognitive waning. AD, lipid metabolism (LM), and metabolic syndrome (MTS) are intricately interconnected, reflecting a complex interplay of metabolic and neurodegenerative processes. Dyslipidemia is a common feature of both MTS and AD.

Purpose: Understanding and predicting the interrelationship between AD, LM, and MTS, especially at the genetic strata is crucial for early detection and developing integrated therapeuticstrategies against AD through metabolic and lifestyle interventions.

Methods: NCBI and HGNC databases were mined to enlist the genes. Later primary genes, secondary genes, and intersecting genes were obtained. STRING, an online tool was used to makethe network. Cytoscape-associated plug-ins such as cluster-viz, cytoHubba, and merge network analyzer were employed to analyze STRING-generated networks. Topological analysis of intersecting genes was performed which was functionally annotated using DAVID online. ClueGOand CluePedia tools were also used to investigate the contribution of genes to key diseases.

Results: 1706,1338, and 569 primary genes were mined and later 31, 25, and 43 clusters were formed of AD, LM, and MTS respectively using STRING and Cytoscape. 248, 248, and 546 secondary common genes were found between AD-LM, AD-MTS, and LM-MTS. Further 246 intersecting genes were established. The topological analysis generated 5 hub-bottleneck genes i.e., INS, GAPDH, AKT, TNF, and IL-6, which were functionally annotated by the DAVID onlinetool. KEGG and DisGeNET analysis results showed their involvement in AD, diabetes mellitus, etc.

Conclusion: The proposed study entails the commonality at the genetic level between AD and MTS based onLM suggesting a shared pathophysiological foundation. The functional analysis of these genes will also pave the way for future studies to understand the mechanism behind each gene and identify potential biomarkers for early AD detection.

Investigation for Anticancerous agents with Lithium and Turmeric extract on specific activity of β-galactosidase and Acid Phosphatase in glioblastoma (LN229) cell lines

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Background: Multiforme (GBM) are tumours arising from astrocytes, which are transformed, and the supportive cells of neurons. These tumours are highly malignant due to high proliferation capacity, angiogenesis, activation of oncogenes, high expression of cancer proteins and enzymes such as kinases.

Purpose: Therefore, it is essential to study the effect of inhibition of various proteins, enzymes and their expression levels in cell lines. β-galactosidase and acid phosphatase lysosomal hydrolytic enzymes when expressed in abnormal levels have major impact in cancer progression. Higher expression of β-galactosidase has been reported in glioblastoma tissue, which promotes the degradation of glycol-conjugates present in the ECM and promotes tumor infiltration and metastasis. Signalling pathways such as MAPK/ERK, PI3K involves kinases, which phosphorylate cancer proteins and activates certain transcription factors required for cancer activation. Therefore, it is necessary to dephosphorylate cancerous protein where the phosphatases play a very important role in the inhibition of cancer.

Method: It was aimed to study the effect of chemical modulator (Lithium) and indigenous modulator (*Curcuma longa* extract) on β-galactosidase and Acid Phosphatase in LN229 cell lines.

Results: Total protein content (Lowry's assay) significantly reduced with an increase in concentration of both the modulators (Li-1µM,2µM,5µM,10µM), Curcuminoid-2.5ppm,5ppm,10ppm,25ppm) in cell line and spent media. β-Galactosidase content and specific activity in cells were found to be downregulated in cells and upregulated in spent media. However, acid phosphatase concentration and specific activity was increased with an increase in the concentration of both the modulators in the cells and was found to decrease in spent media.

Conclusion: Hence, it was concluded that both the modulators Lithium and Turmeric extract were positive for acid phosphatase and negative for β-galactosidase dealing with lysosomal activity and failure of membrane permeability. These results pave way for its use as conjugates with anti-cancer drugs.

Mechanistic investigation of Trigonelline hydrochloride for alleviating the oxidative stress, neuroinflammation and functional disabilities in rat model of traumatic brain injury

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Background: Traumatic brain injury (TBI) involves impact, penetration, or rapid brain movement within the skull, leading to neurological dysfunction. The myeloperoxidase (MPO) enzyme, present in infiltrating neutrophils, worsens neuroinflammation after TBI. Trigonelline hydrochloride (TG), a plant alkaloid, has shown neuroprotective effects in stroke by reducing MPO levels, indicating its potential for treating TBI.

Purpose: This study investigates TG effects on weight drop-induced TBI in rats

Methods: Male Wistar Rats were assigned into six groups with six animals in each group. Normal control, TBI-induced-disease control, three TG treatment groups (25, 50, and 100 mg/kg), and one standard group treated with 4-Aminobenzoic acid hydrazide (4ABAH) (100 mg/kg) were assigned. Trauma was induced in rats by Marmarou's weight drop method. In addition to the histopathological and behavioural studies (beam walking test, rearing test and rotarod test), biochemical parameters such as brain oedema, MPO activity, levels of malondialdehyde, nitrite, superoxide dismutase, catalase, reduced glutathione and tumour necrosis factor-alpha in brain tissue were also estimated.

Result: This study shows that TG is a promising neuroprotective agent for TBI. Low dose (25 mg/kg) showed no significant effects, medium (50 mg/kg) and high doses (100 mg/kg) of TG significantly improved locomotor and motor coordination altered due to TBI. Additionally, it mitigated the altered levels of MPO, malondialdehyde, nitrite, TNF-α levels, glutathione and catalase in brain due to trauma. Histopathology revealed reduced vasogenic oedema and fewer lesions in TG-treated groups compared to TBI group.

Conclusion: Our results indicate that TG effectively mitigates behavioural, biochemical, and histopathological consequence of brain injury through MPO inhibition, positioning it as a promising therapeutic for TBI.

Efficacy of *Spondias pinnata* bark extract as an adjuvant for the management of chemobrain by alleviation of oxidative stress in etoposide administered *Wistar* rats

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Background: chemotherapy-induced cognitive impairment (CICI) or chemobrain is one of the common adverse effects of chemotherapy. It is characterized by impairment of memory, attention and executive functions that may adversely affect the patient's daily function and quality of life.

Purpose: the aim of the present study was to investigate the efficacy of *spondias pinnata* (sp) bark extract on chemobrain in etoposide administered adult male Wistar rats. The objectives were to estimate the levels of superoxide dismutase (SOD), nitric oxide (NO) and protein carbonyl (PC) in the brain tissue homogenates of etoposide administered as well as SP bark extract treated rats and compare them with each other.

Methods: The study was carried out on six groups of adult Wistar rats (n=6), which included normal control, etoposide (45mg/kg body weight) administered, etoposide along with 3 different dosages of SP (200, 300, and 400 mg/kg body weight) and SP control (400 mg/kg body weight).

Results: The etoposide group showed significantly increased PC and SOD when compared with that of normal control and the NO was decreased ($p<0.01$). Whereas the 300 & 400mg of SP treatment showed a significant decrease in the PC and SOD levels and increase in the NO when compared with that of the etoposide group ($p<0.01$).

Conclusion: Elevated PC and reduced NO in etoposide group indicates oxidative stress in the rats and the SOD was elevated as a normal cellular response attempting to overcome the oxidative stress developed by exposure to etoposide. However, these levels were reversed in the SP bark treated groups. Hence, it can be elucidated that SP bark extract helps in decreasing the oxidative stress induced by etoposide. The result of the current study might help in the development of future therapeutic adjuvants for chemotherapy to minimise the challenges associated with chemobrain.

Multi-omics & Systems Biology Approach reveals mitochondrial associated proteins in Alzheimer's disease progression

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Background: Alzheimer's disease is the most common form of dementia and the sixth-leading cause of death in the US, affecting more than 5 million Americans with a healthcare cost of $236 billion. By 2050, AD patients are projected to reach 13.8 million in the US and 100 million worldwide.

Purpose: Currently, AD diagnosis is based on patient's symptoms, memory and behavior tests, brain imaging, as well as post-mortem brain pathological assays. The requirements for a biomarker include the ability to measure a pathologic process, predict outcome, distinguish disease, or measure a pharmacological response to a drug treatment or therapeutic intervention. Here we present an unbiased proteomic profiling of these human samples has been initiated to identify many novel AD biomarker candidates and revealing consistent mitochondrial protein changes between control and AD samples.

Methods: We present a comprehensive strategy to identify biomarker candidates of high confidence by integrating multiple proteomes in AD, including cortex, CSF, and serum. The proteomes were analyzed by the multiplexed tandem-mass-tag (TMT) method, extensive liquid chromatography (LC) fractionation and high-resolution tandem mass spectrometry (MS/MS) for ultradeep coverage. A systems biology approach was used to prioritize the most promising AD signature proteins from all proteomic datasets. Finally, candidate biomarkers identified by the MS discovery were validated by the enzyme-linked immunosorbent (ELISA) and TOMAHAQ targeted MS assays.

Results: We quantified 13,833, 5941, and 4826 proteins from human cortex, CSF and serum, respectively. In summary, 37 proteins emerged as potential AD signatures across cortex, CSF and serum, and strikingly, 59% of these were mitochondria proteins, emphasizing mitochondrial dysfunction in AD.

Conclusions: Our results demonstrate that novel AD biomarker candidates are identified and confirmed by proteomic studies of brain tissue and biofluids, providing a rich resource for largescale biomarker validation for the AD community.

Natural Nutraceutical restores Motor Function and Increases Tyrosine Hydroxylase in Parkinson's Disease Models

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting the basal ganglia, where neuroinflammation plays a crucial role in its pathophysiology. Due to the lack of effective treatments, novel therapies with minimal side effects are being explored. Plant-based nutraceuticals, enriched with free fatty acids and polyphenols, are typically derived from natural sources such as palm oil, coconut oil, and other plant-based fats through processes like cold pressing or solvent extraction.

Purpose: We investigated a fatty acid-based nutraceutical's potential in mitigating PD through a preclinical study using a rotenone-induced PD model.

Methods: Our study employed a multi-tiered approach combining in-silico analysis, in vitro experiments, and in vivo studies to explore the potential therapeutic effects of the natural nutraceutical in Parkinson's disease (PD).

Result: Our *in-silico* analysis revealed that it could interact with key molecular targets involved in PD pathology. *In vitro* experiments demonstrated the treatment with this significantly improved the viability of neurons, reduced cell death (MTT assay), and enhanced the production of neurotransmitters (TNF-α, IL-1β, IL-6). Additionally, *in vivo* studies showed improvements in motor function and neurotransmitter levels in mice with PD.

Conclusion: These findings suggest that it may offer a novel therapeutic approach for PD by targeting specific molecular pathways. Further research is needed to fully understand its mechanisms of action and explore its potential for clinical use. We conducted ELISA and Western blot analyses to assess biomarkers associated with oxidative stress (SOD, GPx, GSH, PGC-1α, Nrf2) and neuroinflammation. The anti-inflammatory effects of this natural neutraceutical are crucial in downregulating inflammatory gene expressions such as Cox-2, iNOS, TNF-α, and IL-6. Our findings suggest that it may improve progression of PD, with underlying mechanisms involving antioxidant and anti-inflammatory pathways. Our findings suggest that this natural nutraceutical may offer a novel therapeutic approach for PD, but further studies are needed to fully understand its mechanisms and establish optimal dosing.

Downregulation of Pten ameliorates Huntington's disease in Drosophila model

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Background: Huntington's disease (HD) is a progressive neurodegenerative disorder that affects 8-9 per 100,000 individuals worldwide. The abnormal expansion of CAG in the first exon of the Huntingtin gene (HTT) causes the formation of poly(Q) aggregates that are toxic to the neurons. In a normal person, the CAG repeats range from 10-35. When the repeat length is above 40, it becomes pathogenic, and the repeat length is inversely correlated with the onset of the disease.

Purpose: The current pharmaceutical intervention for HD focuses on symptom reduction, with no cure available to halt the progression of neurodegeneration. However, our understanding of HD has significantly advanced. Several studies have shown that HD affects the Receptor Tyrosine kinase (TrkB) and antagonizes Epidermal growth factor signaling. This study aimed to investigate whether the downregulation of Pten, a negative Pi3k/Akt signaling regulator, could not just ameliorate the HD phenotype in the Drosophila disease models.

Method: We used the UAS-Gal4 system to express mutant HTT with 93 and 138 poly(Q) repeats in a tissue-specific manner.

Result: Overexpression of HTT.Q138 and HTT.Q93 in the entire brain and PNS caused climbing defects and reduced the survivability of these flies. The expression of HTT.Q138 and HTT.Q93 induced progressive loss of brain tissue and motor neurons in Drosophila thoracic muscles. We observed that the Knockdown of Pten in the disease background significantly improved the climbing and lifespan. Moreover, the loss of neuronal tissue was suppressed by the downregulation of Pten expression. Subsequently, the administration of Pten inhibitor improved the climbing ability of HTT-expressing flies and reduced the level of poly(Q) aggregates and cell death.

Conclusion: Our study significantly contributes to the growing knowledge of HD. It illuminates that inhibiting Pten activity is a potential therapeutic application for HD intervention.

Quercetin role in tackling endothelial cell degeneration of retinal capillaries in DR

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Background: Diabetic Retinopathy (DR) is a condition caused by hyperglycemia-induced blindness, resulting from retina damage due to oxidative damage, blood vessel leakage, ROS overproduction, endothelial cell degeneration, and pericyte death. Quercetin, an antioxidant, may help mitigate this damage by scavenging reactive oxygen species.

Purpose: To assess how well quercetin protects retinal capillary's endothelial cells from oxidative stress brought on by hyperglycemia.

Methods: Rats induced with streptozotocin (45 mg/kg BW) and having blood glucose levels of 300 mg/dL were thought to have diabetes. Quercetin (50 mg/kg BW) was given once a week for 16 weeks. Fundoscopy was used to examine physiological changes in retina. Pro-inflammatory cytokines, VEGF, and antioxidants levels estimated using ELISA. For the qualitative and quantitative analyses of selectin and integrin IHC and western blot were performed.

Results: ELISA findings showed significant increase in VEGF-A ($p \leq 0.001$) , IL-1β($p \leq 0.001$) and TNFα ($p \leq 0.01$), while significant reduction in glutathione ($p \leq 0.001$), SOD (DR+control $p \leq 0.001$ and DR+Qctn $p \leq 0.01$) and catalase ($p \leq 0.001$) levels in diabetic retina as compared to control and quercetin treated. IHC and western blot analysis showed significant increase in level of selectin (DR+control $p \leq 0.0002$ and DR+Qctn $p \leq 0.001$) and integrin (DR+control $p \leq 0.0002$ and DR+Qctn $p \leq 0.001$).

Conclusions: The study reveals that diabetes-related oxidative stress increases pro-inflammatory cytokine levels and lowers antioxidant levels. Elevated VEGF and Integrin β1 expression in diabetic retinopathy (DR) indicates neovascularization, while elevated E-selectin levels indicate inflammation. Quercetin therapy helps manage DR issues, but further research is needed to understand its effectiveness.

Changes in the primary visual cortex (V1) during retinal degeneration in rd1 mice model

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Background: Humans rely on their eyesight to provide information about the outside world and is a dominant sensory modality. Retinal degeneration (RD) is the leading cause of blindness around the globe and patients suffering from inherited RD undergo loss of photoreceptors such as rods and cones. The progression of degeneration affects the primary visual cortex manifesting in abnormal cortical activity.

Purpose: Cortical networks are composed of glutamatergic and diverse types of local GABAergic inhibitory neurons that regulate signal flow and network dynamics. We investigated if the disbalance in cortical activity is linked to changes in GABAergic population of neurons and glutamatergic thalamocortical afferents in V1.

Methods: We performed toluidine staining on the retina of C3H/HeJ (rd1), mice to check the morphology and compared with C57BL6 mice (wt) at P40. Tissue sections from V1 region was used for immunofluorescence to detect the total neuronal population, GABA+, PV+ and SST neurons. We analyzed the changes in excitatory neurotransmission using vesicular glutamate transporter 2 (VGLUt2) and quantified its levels using Western Blotting. Images were taken with confocal microscope and estimation of neuronal density in each layer of cortex was done with ImageJ.

Results: The general morphology of the retina showed absence of the photoreceptor layer in the rd1 retina while the bipolar and the retinal ganglion cells were intact. We observed reduced immunolabeling and marked decrease in the levels of VGLUt2 in degenerated mice. The total neuronal population (NeuN+) as well as GABA+ neurons exhibited no changes. Quantitative analysis of PV+ neurons showed no differences in the overall density between the rd1 and wt mice whereas SST+ neurons showed a significant reduction in all layers of V1.

Conclusion: Our results demonstrate the implications of RD on GABA inhibitory neurons and glutamatergic thalamic afferents that eventually lead to physiological alterations in the V1.

Regulation of Vascular Endothelial Growth Factor is significant in the pathology of Ocular diseases

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Background: Vascular endothelial growth factor (VEGF), a signalling molecule of the endothelial cells is intricately involved in the pathology of glaucoma, diabetic retinopathy (DR), and retinoblastoma. PI-3K pathway gets activated in ocular conditions of hyperglycemia, glutamate excitotoxicity and proangiogenic conditions which increases the expression of VEGF/VEGFR molecules.

Purpose: Dopamine (DA), Coenzyme Q10 and trolox and IGF-1 have proven to be effective therapeutic molecules to regulate the VEGF/VEGFR expressions and attenuating symptoms of DR, glaucoma and retinoblastoma respectively.

Method: DA alone at 10mg/kg body weight and DA + IGF-1 (2µgm/eye) was administered in animal models of DR maintained for a period of 12 as well as 16 weeks characterizing non proliferative and proliferative stages of DR. Glaucoma was induced by causing glutamate excitotoxicity of the NMDA receptors by intravitreal administration of NMDA. Coenzyme Q10 and Trolox given at concentrations of 10mg/kg BW and 1 µgm/µl for a period of 7 days. Retinoblastoma model was setup by growing Y79 cells in vitro. The mRNA transcript levels of VEGFR1, VEGFR2, IGF-1R, Drd1,2 and 4, Grin2A and Grin2B are determined. Protein expressions of pVEGFR2, ERK, pERK, Akt and pAkt observed through western blotting and immunohistochemistry.

Result: VEGFR1, VEGFR2 expressions suppressed but Drd2 and IGF-1R enhanced in DR. VEGFR1, VEGFR2 and Grin2A expressions enhanced but diminished Grin2B expression in glutamate excitotoxicity model of glaucoma. Suppressed VEGFR1, VEGFR2 and IGF-1R expressions in Y79 model of retinoblastoma.

Conclusion: Regulation of VEGFR2 and VEGFR1 as downstream targets of Pi-3K/ERK/ Akt signalling pathways is crucial in the therapeutics of DR, glaucoma and retinoblastoma.

Dysregulation of lysosomal pH and cathepsin processing contribute to the pathogenesis of infantile Batten disease

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Background: Infantile Batten disease (IBD), a subtype of neuronal ceroid lipofuscinosis, is a fatal neurodegenerative disorder characterized by the accumulation of autofluorescent storage material in neurons and other cells. This accumulation is primarily caused by mutations in the gene encoding palmitoyl-protein thioesterase 1 (PPT1), an enzyme crucial for the degradation of lipid-modified proteins within lysosomes. The resulting deficit in lysosomal proteolysis impairs the clearance of damaged or misfolded proteins, leading to progressive cellular dysfunction and neurodegeneration.

Purpose: However, the precise substrates of PPT1 are still not known and the mechanism of neurodegeneration remains obscure.The objective of this study is to identify the proteins that participate in the neurodegenerative process

Methods: Using cells from IBD patients and PPT1-KO animals, we have identified several proteins with increased *in vivo* palmitoylation which might play role in the disease pathogenesis.

Results: These proteins include vATPase subunit V0A1, Rab7, cathepsin D etc lack of depalmitoylation of which impair endomembrane trafficking and endolysosomal homeostasis, disrupting lysosomal pH and autophagy. Our findings also reveal that impaired lysosomal function triggers a cascade of pathogenic events, including oxidative stress, mitochondrial dysfunction, and neuronal apoptosis.

Conclusion: Understanding these mechanisms provides critical insights into the molecular underpinnings of PPT1 and highlights potential therapeutic targets aimed at enhancing lysosomal proteolysis to ameliorate disease progression. This study emphasizes the need for strategies that restore lysosomal function as a therapeutic avenue in infantile Batten disease.

When does object familiarity lead to a task advantage?

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Background: While it is well known that humans quickly become familiar with items that are repeatedly viewed, it is unclear whether this familiarity confers any task advantage. With extreme familiarity, such as in the case of reading, readers discriminate between letters of their own scripts better than those of unknown scripts. However, it is unclear at what time scales such effects develop, and whether these effects are dependent on the nature of experience with letters.

Purpose: Here, we investigated whether short-term familiarity with novel shapes can lead to improved shape discrimination.

Methods: We performed five experiments. In each experiment, we trained two groups of naïve participants on letters or bigrams of two novel scripts. We also conducted familiarity tests with varying difficulty, at various time points, to assess their familiarity to the viewed items.

Results: All participants were highly accurate on the familiarity test (with even as few as 100 exposures), even when they had to identify a familiar letter compared to a slight modification of the letter, and even when tested two months after training. Thus, familiarity was quick, robust, and long-lasting.
However, does this familiarization produce a task advantage? In Experiments 1 & 2, participants discriminated familiar letters faster only on hard trials of a visual search task. By contrast, in Experiments 3 & 4, when letters were dissimilar to each other, familiarizing them did not produce such a task advantage. In Experiment 5, when we created hard visual search trials by embedding familiarized letters against slightly modified distractors, participants were more accurate on familiar compared to unfamiliar letters both in a visual search task as well as a same-different task.

Conclusions: Taken together, our results show that, while the effects of familiarity are fast and robust, this familiarity leads to a task advantage only for highly similar shapes.

Chronic mitochondrial disruption leads to lysosomal deficit through parkin-sorting nexin 9 axis of mitochondrial quality control: Relevance in Parkinson's disease

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Background: Mitochondrial dysfunctions are recognized as the most significant pathological hallmark for the development of Parkinson's disease (PD). While lysosomal dysregulations are emerging risk factors for PD, the specific mechanism(s) by which mitochondrial disruption leads to lysosomal dysfunction remains unclear.

Purpose: The primary objective of this study is to investigate how mitochondrial disruption induces endolysosomal dysfunction in a PD cellular model.

Methods: To achieve this, mitochondrial disruption was induced using 1-methyl-4-phenylpyridinium (MPP^+) in differentiated SH-SY5Y cells. Significant mitochondrial fragmentation and the generation of mitochondrial reactive oxygen species (ROS) were characterized using MitoTracker and MitoSox, respectively. The cells were further assessed for endolysosomal abnormalities using Lysosensor DND-198, LAMP1 immunostaining and subcellular fractionation.

Results: We uncovered temporal changes in endolysosomal machinery including changes in lysosomal pH, cathepsin processing and proteolysis in MPP^+-treated SH-SY5Y neurons. Although, acute MPP^+-induced mitochondrial disruption caused no effect lysosomal homeostasis, chronic treatment of the neurotoxin led to lysosomal dysfunction. Mitochondria-derived vesicles (MDVs) as revealed by TOMM20 immunostaining, in cells chronically treated with MPP^+, were seen colocalized with mitochondrial ROS, as demonstrated by combined MitoTracker Green and MitoSox Red staining. Chronic MPP^+-treatment resulted in the downregulation of Parkin, leading to the accumulation of its substrate sorting nexin 9 (SNX9), which mediates the generation of MDVs. Overexpression of TFEB (transcription factor EB), a master regulator of autophagy and lysosome biogenesis, protected these cells from MPP^+-induced neurotoxicity.

Conclusion: Overall, our findings indicate that mitochondrial disruption in MPP^+-treated cells may adversely affect endolysosomal function by promoting the formation of MDVs carrying ROS to lysosomes and impairing proteostasis in PD. Understanding these interplays between mitochondrial- lysosomal quality control mechanisms would provide valuable insights into the molecular basis of PD and could lead to novel therapeutic targets aimed at restoring cellular homeostasis in PD.

Alterations in Excitatory Neurotransmitters may Underlie the Inhibitory Shifts During Epileptogenesis in a Lithium -Pilocarpine model of Temporal Lobe Epilepsy

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Background: Amino acid neurotransmitters, such as glutamate and GABA, are crucial in maintaining neuronal balance and synaptic transmission. Imbalances in these neurotransmitters are central to epilepsy development with GABA hypoactivity and glutamate hyperactivity being prominent features.

Purpose: Excitatory synaptic transmission, excitation cell death, and reduced inhibitory synaptic transmission further culminate in synaptic reorganization and spontaneous recurrent seizures during the chronic phase. Hence, longitudinal assessment of excitatory-inhibitory network dynamics during epileptogenesis is crucial.

Method: Experimental animals — adult male Wistar rats were administered with the muscarinic receptor agonist pilocarpine. 17-24 h before induction (day 1), animals were pretreated with lithium chloride (127 mg/kg b.w., i.p.) to reduce the pilocarpine dose (30 mg/kg b.w., i.p.) required to induce seizures. Methylscopolamine (1 mg/kg b.w., i.p.) was administered to minimize the peripheral effects of pilocarpine. Following this, the rats were subsequently (if required) injected with 20 mg/kg b.w., for 3-4 times at 20–30 min intervals till stage 5 seizures of Racine scale appear, following which status epilepticus (SE) was allowed to persist for 120 minutes, then terminated by administration of a single dose of diazepam (10 mg/kg b.w.). Following this, micro-dissection of different brain regions was done for time-course assessment of aminoacid neurotransmitter levels using high-performance liquid chromatography (HPLC) analysis.

Results: Our findings reveal distinct, region-specific changes in neurotransmitter levels: the frontal cortex shows early alterations in glutamate, glycine, and taurine, followed by GABA changes, whereas the hippocampus exhibits initial changes in glutamine shortly after seizure induction and later shifts in glycine and GABA levels. These results suggest that epilepsy's pathophysiological mechanisms may vary both temporally and regionally within the brain.

Conclusions: These investigations illuminate the role of the excitatory-inhibitory network dynamics in epileptogenesis and offer a comprehensive insight into neurochemical alterations and mechanistic underpinnings of temporal lobe epilepsy progression.

Prediction of Stroke Risk by using an Attention-based Deep Learning Paradigm

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Background: Stroke occurs when blood flow to the brain is interrupted, leading to brain cell damage. It causes sudden symptoms like paralysis, and speech difficulties, and can be life-threatening, requiring urgent treatment. It is the 2nd leading cause of death globally, responsible for approximately **11%** of total deaths.

Purpose: There is an early need for a non-invasive and early diagnosis of stroke risk and its risk stratification, to minimize the deaths resulting from stroke by assuring proper preventive measures.

Method: Our method makes use of deep learning (DL) algorithms, paying particular attention to the Stroke dataset, which has 5110 observations with 12 attributes. There are 3015 women and 2095 males in the dataset, with ages ranging from 10 to 87. The traditional models were contrasted with the attention-based recurrent neural network (RNN), gated recurrent unit (GRU), and long short-term memory (LSTM). Performance evaluation was conducted using five-fold (K5) cross-validation. Three techniques were employed to conduct statistical testing and reliability assessments for attention-based models. As part of the performance evaluation, the receiver operating characteristics (ROC) curve and p-value significance were used to calculate the area-under-the-curve (AUC).

Results: The best performing model is attention-based LSTM showing **94%** accuracy along with AUC **0.902** in prediction. Compared to the traditional DL system, the attention-based DL models demonstrated a mean improvement of **7.20%** in accuracy. The performance evaluation parameters used were sensitivity, specificity, and F1 score. The attention-based DL models' p-value significance for systems reliability was **<0.001** when compared to traditional approaches, meeting regulatory requirements.

Conclusion: The theory behind attention-based deep learning models was verified by science and put to the test in real-world settings for consistency, stability, and additional clinical adaptability.

Dysregulated HPA axis and Metabolic Changes: At the Crossroads of Injury Progression Post Blast Exposure and Blunt Impact TBI

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Background: Traumatic brain injury (TBI) leads to progressive and silent effects on health with long-term consequences on endocrine, neurological, and psychiatric function resulting in chronic health disease.

Purpose: TBI is a lifelong process, with an accelerative impact on brain and multiple organ systems. Therefore, it is important to identify factors that facilitate progression of injury.

Methods: To understand the accelerative nature of TBI, two different models of injury, blast neurotrauma (diffuse) and blunt impact (focal) were observed throughout the study**.** HPA axis was assessed using quantitative measurement of ACTH and CORT hormones from acute to chronic stages of injury. The metabolic alterations were evaluated at the systemic (serum metabolomics using 1H-NMR spectroscopy) and neuronal level (*in vivo* metabolic changes through MRS at 7T- Animal MRI). Along with this, mitochondria respiration using pyruvate, glutamate and succinate were evaluated by a clark-type oxygen electrode in the hypothalamus and hippocampus. The functional outcomes of these alterations on memory and anxiety were assessed using behavioral paradigms.

Results: TBI results in a time, region and injury type specific alterations in the brain, where *in vivo* metabolic studies (MRS) showed altered TCA cycle after both the injuries. State V mitochondrial respiration with glutamate and succinate was increased in the hippocampus of blunt impact injury, while in blast exposed rats' mitochondrial respiration was decreased in both the regions.
Serum metabolism was also altered, where, PCA and PLS-DA plots showed segregation between the acute stage and control group after blast exposure. On the other hand, blunt impact had a clear segregation between the control group and other stages of injury. A persistent HPA dysregulation was observed after both injuries with dysfunction in memory and anxiety like behavior after blunt impact.

Conclusion: The study provides an overview of HPA axis and metabolic alterations at the systemic and neuronal levels from acute to chronic stages of TBI. The study also highlights heterogenous response post blast exposed and blunt impact injury in rats, with endocrine and metabolic alterations as the central drivers in injury progression.

Antibiotic-induced maternal dysbiosis during pregnancy leads to anxiety and depression-like behaviour in offspring

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Background: Anxiety and depression, the most common mental health disorders, affect millions worldwide. Anxiety impacts 4% of the global population, while depression, afflicting 280 million people, is a leading cause of disability. Aaron T. Beck, the father of Cognitive Therapy, aptly described depression as 'a prison where you are both the suffering prisoner and the cruel jailer,' capturing the profound internal struggle faced by those affected. The gut's resident microbiota is critical in mental well-being and mood through the gut-brain axis, a complex communication network. Changes in the microbiota can directly influence mental health, contributing to conditions like anxiety and depression. Despite this, the impact of maternal microbiota changes, such as dysbiosis during pregnancy, on offspring's long-term mental health is not well understood.

Purpose: How antibiotic-induced maternal dysbiosis during pregnancy affects the offspring's anxiety and depression-like behaviour.

Methods: To address this, we conducted a study using pregnant mice who were administered an antibiotic cocktail to induce gut dysbiosis. The offspring underwent behavioural tests to evaluate anxiety and depression-like behaviours, including the Open Field Test (OFT) and Elevated Plus Maze (EPM) for anxiety and the Forced Swim Test (FST) and Tail Suspension Test (TST) for depression. Systemic inflammation was assessed through blood parameter profiling, measuring white blood cell (WBC) counts and inflammatory markers like IL-1β and TNF-α.

Results: Our results showed that offspring exhibited decreased struggling time in the FST, which reflected increased despair, and displayed anxiety-like behaviours in the EPM. Additionally, there was a significant rise in WBC count, absolute neutrophils, and MID cell levels, indicating systemic inflammation.

Conclusion: These findings highlight that maternal gut microbiota disruption can significantly affect offspring behaviour, underscoring the importance of maternal microbiome health in influencing the emotional and psychological outcomes of the offspring.

Female chronic social defeat stress: A novel model for investigating female depression

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Background: Female depression is a multifaceted and pervasive disorder affecting millions of women globally, yet the underlying mechanisms remain inadequately understood due to the gender bias in preclinical models predominantly focused on males. To address this gap, in this study, we introduce a novel female Chronic Social Defeat Stress (fCSDS) rodent model to investigate depression in females.

Purpose: To characterize a female-specific model of depression that accurately reflects the unique biological, behavioral and molecular aspects of depression in female mice.

Methods: We employed a carefully designed protocol which involved inducing aggression in parous CD1 females through prolonged cohabitation with castrated male partners. Adult female C57BL/6J mice were subjected to repeated exposure to aggressive CD1 females over 10 consecutive days, mimicking chronic social defeat stress without male influences. We further conducted label free Quantitative MS-MS analysis of nucleus accumbens, a region thought to have a key role in reward and motivation.

Results: Behavioral assays, including the sucrose preference test, forced swim test, elevated plus maze, and social interaction test displayed significant stress-induced depressive-like behaviors in the experimental group. Molecular analyses revealed dysregulation in estrogen receptors (ESR1 and ESR2), histone modifications (H3K9me3 and H3K27ac), and synaptic markers (SYP and PSD-95) across the brain regions implicated in depression. Further analyses revealed significant reductions in EAAT1 l and increased glutamate levels in the caudate putamen, indicative of glutamate excitotoxicity, along with increased serum cortisol indicating an amplified stress response. Notably, our mass spectrometric analysis of nucleus accumbens identified disruptions in synaptogenesis signaling pathways and mitochondrial cytopathy-associated pathways.

Conclusion: Our findings demonstrate that the fCSDS model effectively recapitulates key aspects of female depression. This model not only fills a critical gap in depression research but also provides a foundation for developing targeted therapeutic strategies for women.

Progesterone restores aging-induced impaired cognitive function and gut health

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Background: Aging is a progressive biological process that develops many pathological conditions. During aging the endogenous progesterone level deteriorates and found to be associated with many age-related pathophysiology. Progesterone is an ever-ignored male hormone which need to be studied.

Purpose: Present study deals with the aging related cognitive function, histological marker of neuronal plasticity, gut microbe (*Bifidobacterium longum*) and intestinal motility and the role of exogenous administration of progesterone (5mg/Kg, s.c.; for 21 consecutive days).

Methods: The male albino Wistar strain rats were used as experimental animals. Cognitive function was measured by radial 8-arm maze and novel object recognition (NOR), dendritic spine density was measured with Golgi Cox stain under the compound microscope, intestinal motility by kymograph, and *Bifidobacterium longum* from the faeces sample using RT-PCR.

Results: The results indicate that the cognitive function was reduced during aging with the reduction in the brain regional dendritic spine density and intestinal motility. The gut bacteria, specifically the *Bifidobacterium longum* was reduced in the aged rats. The treatment of progesterone to the aged rats attenuated the aging-induced reduction of cognitive function, dendritic spine density, intestinal motility, even the gut-microbe pool. But the treatment of progesterone in young rats reduced the intestinal motility, without any significant alteration in other studied parameters.

Conclusion:It may be concluded for the present investigation that progesterone supplementation restores the aging-induced impairment of cognitive function, histological marker of neuronal plasticity, gut-microbiota and intestinal motility towards those observed in young rats, indicating its (progesterone) beneficial role for the aged rats, but reduced the intestinal motility in the young rats. This crucial observation may open up a new avenue of therapeutics for the elderly population worldwide to promote healthy aging in near future.

Intermittent theta burst stimulation revamping mobility in complete Spinal Cord Injury

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Background: Spinal cord injury (SCI) is a debilitating condition that causes damage to the ascending and descending tracts leading to the destruction of neurons and resulting in motor and sensory dysfunction. Unfortunately, there is a lack of potential interventional tools to regain locomotion in paraplegic and quadriplegic complete SCI patients (cSCI). Intermittent theta burst stimulation (iTBS) is an upcoming therapeutic technique that augments plasticity and alters the excitability of neurons.

Purpose: The present study aims to assess the efficacy of iTBS on motor and sensory function recovery, cortical excitability, plasticity, and SCI-associated biomarkers and neurotransmitters in cSCI patients.

Methods: In this study, 30 ASIA-A spinal cord injury patients (aged 18-60) were randomly assigned to five groups and received 10 sessions of intermittent theta burst stimulation (iTBS) twice daily over 5 days. Neurological outcomes were measured with the ASIA scale, functional outcomes with the Spinal Cord Independence Measure (SCIM), and the Walking Index for Spinal Cord Injury (WISCI). Electrophysiological parameters were assessed using single-pulse TMS, and biomarker levels in plasma and serum were quantified via ELISA.

Results: The study showed notable improvements in ASIA motor and sensory scores, advancing from A to B and C, alongside increased WISCI and SCIM mobility domain scores. Significant reductions in resting motor threshold (RMT) and cortical silent period (cSP) suggest modulation in cortical excitability and corticospinal circuitry. Additionally, the first follow-up revealed decreased levels of interleukin-6 and phosphorylated neurofilament (pNF), signifying reduced inflammation and axonal damage. Elevated neurotrophin-3 (NT-3) levels post-intervention further indicate enhanced neuron survival, growth, and differentiation. These findings suggest that the intervention effectively promotes mobility, and augments plasticity, thus facilitating mobility in cSCI patients.

Conclusion: Our novel findings provide evidence for the modulation of neural inhibitory-excitatory networks by iTBS in SCI patients, that induced ambulation in complete SCI patients.

Therapeutic Role of Connexin 43 in Restricting Murine-β-Coronavirus Spread and Virus-Induced Demyelination in the Central Nervous System

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Background: Mouse hepatitis virus (MHV), a murine β-coronavirus, serves as an experimental model to study virus-induced encephalitis during the acute stage, followed by central nervous system (CNS) demyelination in the chronic stage. This demyelination mirrors pathological features observed in human CNS demyelinating diseases, such as multiple sclerosis (MS). Previous studies in this model, as well as analyses of human MS patient tissues, have implicated changes in the expression of astroglial Connexin 43 (Cx43) as a key factor underlying the observed pathology. Cx43 is one of the most abundant gap junction proteins in astrocytes, crucial for metabolic coupling with other CNS cells to maintain homeostasis. MHV infection in mice leads to a significant decrease in Cx43 expression during the acute stage (days 5-6) of infection. In vitro studies suggest that maintaining steady-state Cx43 expression through pharmacological agents or molecular chaperones restricts the spread and infectivity of MHVA59.

Purpose: This study aims to establish the therapeutic effect of maintaining stable Cx43 expression in the mouse CNS on restricting acute stage MHV-A59 spread and infectivity, thereby reducing chronic stage demyelination.

Methods: We utilised 4-phenyl butyric acid(4-PBA) to maintain steady levels of Cx43 in the mouse CNS. Through histopathological analysis, as well as RNA and protein studies, we assessed the effect of 4-PBA on viral spread, infectivity, and virus-induced demyelination to understand the underlying mechanisms.

Results: Our study demonstrates that stable Cx43 expression significantly reduces MHV-A59 infectivity and spread in the CNS of infected mice. Furthermore, stabilised Cx43 expression also preserves the expression of its coupling partner Connexin 47 in oligodendrocytes, thereby mitigating chronic stage demyelination.

Conclusion: Maintaining stable Connexin 43 expression in the mouse CNS significantly reduces MHV-A59 spread and infectivity and reduces chronic demyelination. These findings highlight Cx43 as a promising therapeutic target for preventing virus-induced CNS damage.

Sertad1 interference using RNAi rescues cognitive and synaptic loss in Alzheimer's disease models

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Background: There is massive accumulation of undigested autophagosomes in the Alzheimer's disease (AD) brain due to impaired autophagy. However, mechanism of autophagic dysfunction in AD remains elusive. Sertad1, a transcriptional coregulator is activated in neurodegeneration and plays an important role in autophagy-lysosomal pathway in cancer, but its pertinence in AD pathogenesis remains elusive.

Purpose: Our aim was to study autophagy progression at different stages of AD pathogenesis. We hypothesized that since Sertad1, a multimodal transcriptional coregulator is elevated in AD, its downregulation could be neuroprotective and play an important role in cognitive function in AD. To study the role of Sertad1 in AD pathogenesis, we downregulated Sertad1 in AD mice using lentiviral particles.

Methods: We prepared protein lysates from cortex and hippocampus of 5xFAD or wild-type (WT) mice of different ages for biochemical analysis. We prepared lentiviral particles expressing shSertad1 or empty vector (EV) and injected them in 5xFAD or WT hippocampus by bilateral stereotaxic surgery. After 14 days, we performed cognitive tests for assessment of memory followed by biochemical analysis.

Results: We found robust progressive accumulation of autophagy markers in 5xFAD mice. We identified Sertad1, as a crucial regulator of impaired autophagy in AD. We found that Sertad1 increases progressively in 5xFAD mice relative to WT. Knockdown of Sertad1 in 5xFAD reduced levels of autophagosome and lysosome markers in 5xFAD brain. FoxO3a is an important regulator of the autophagy network. In Sertad1 knockdown cells, inactive FoxO3a was exclusively retained in the cytoplasm and Akt activity was restored. Further, we found that Sertad1 knockdown mice performed significantly better than WT mice in cognitive tests along with a restoration in synaptic health.

Conclusion: Taken together, our results show that autophagy pathology progressively increased in the AD brain. Sertad1 knockdown reduced plaque burden, ameliorated autophagy deficits, improved synapse health and cognitive functions in 5xFAD mice.

Neural mechanisms of social-fear in animal models of autism and post-traumatic stress disorder

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Background: An appropriate response to social cues with either approach (if a friend) or avoidance (if a foe) is impaired in several neuropsychiatric conditions like autism-spectrum disorder (ASD) and post-traumatic stress disorder (PTSD). While non-aversive social interactions have been extensively studied (e.g., three chambered test), we focused on identifying neuronal circuits of aversive social cognition.

Purpose: ASD individuals routinely face aversive social-encounters (bullying, social discrimination), and social trauma-exposure can also cause PTSD (witnessing domestic violence as a victim, experiencing emergencies as first responders). We aimed to (i) discover circuits involved in social-fear cognition, and (ii) identify novel therapeutic approaches to reduce social-fear in both ASD and PTSD.

Methods: We used social-fear conditioning and observational fear conditioning as two models of socially acquired fear learning and recall in ASD (*Magel2* knockout mice, model of Prader-Willi syndrome) and PTSD, respectively. Key brain areas were identified with cFos mapping, and neuronal activity was imaged *in vivo* using fiber photometry. Circuits were functionally dissected *in vivo* using optogenetics (ASD) and chemogenetics (PTSD) with Cre-reporter mouse lines targeting specific neuronal ensembles.

Results: We identified the lateral septum (LS) as a crucial hub involved in socially acquired fear in both ASD and PTSD. First, *Magel2* KO mice showed impaired extinction of social-fear memory. This was associated with hyperactive somatostatin neurons in the LS, due to weakened hypothalamic oxytocin neurons lying upstream. Next, we also identified LS as a critical hub in the observational fear model of PTSD. Using engram-trapping strategies, we propose a novel approach as an alternative to the widely used extinction protocols to reduce social-fear in PTSD.

Conclusion: This work establishes a crucial mechanistic framework to understand the neurobiology of social trauma across two disease models. It proposes new clinically relevant strategies for improving social aversive cognition that have strong translational potential.

Differentiation and lineage commitment of Peripheral blood mononuclear cells (PBMNCs) isolated from human buffy coat into neurons

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Background: The regenerative potential of the neural tissue is very limited but they undergo degeneration due to aging, pathological conditions or accidents. There is a need to supplement the degenerated tissue with new cells so that they aid in regaining tissue functionality. PBMNC that is found in the blood can be used as an easily accessible cell source for differentiation into neurons. They have very limited differentiation potential but it is possible to achieve neuronal differentiation with the right culture conditions having growth factors. Differentiated neuronal cells can then be encapsulated in a fibrin matrix and eventually stereotaxically transplanted into damaged neuronal tissue in animal models.

Purpose: To find the differentiation potential of PBMNC into neurons in the fibrin matrix and then study its regenerative potential in the rat model of parkinson disease.

Methods: Human buffy coat was obtained from the blood donors. PBMNCs was isolated from it using density gradient centrifugation. It was then cultured in DMEM F12 media having FBS and combination of growth factors. Serum concentration in the media was altered to find the minimal amount required for the cells to survive and differentiate. Gene expression of neuronal markers such as TUJ1 and MAP2 was checked by RT-PCR. Protein level expression was analyzed using anti-TUJ1,anti-MAP2 and anti-Th antibody by immunocytochemistry.

Results: The cells had neuronal morphology and the control PBMNC are round in shape. The gene level and protein level expression shows that the cells have indeed moved to neuronal differentiation state.

Conclusion: These findings show that PBMNC can be a useful source for obtaining differentiated neurons for use in various tissue engineering applications. It can be easily collected and also autologously transplanted into patients having neurodegenerative disorders.

A novel approach to investigate neuroprotection and the impact of sex differences in ischemic preconditioning mouse model

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Background: Ischemic stroke is a major cause of death and disability worldwide, driven by acute disruptions in cerebral blood flow. While the instant effects on the brain are often severe, studies suggest that chronic subthreshold hypoxic exposure may prime the brain for enhanced resilience, potentially reducing the impact of subsequent acute ischemic events. However, the mechanisms by which chronic cerebral hypoperfusion (CCH) provides neuroprotection remains poorly understood, partly due to limitations in existing animal models.

Purpose: This study aimed to investigate the neuroprotective effects of ischemic preconditioning and to explore the underlying mechanisms with special reference to the sex differences through a novel approach of ischemic preconditioning in permanent unilateral common carotid artery occlusion mice model (UCCAo).

Methods: A novel approach of utilizing a preexisting mouse model, permanent unilateral common carotid artery occlusion on the right side (rUCCAo) was taken taken into account followed by an acute occlusion of contralateral carotid artery (left) after 12-16 weeks. Behavioral assessments were conducted on male and female CD1 mice on 1st and 7th day post-ischemia using rotarod, grip strength, and open field tests. Molecular analyses were performed in striatal tissues to assess neuroinflammation, synaptic plasticity and autophagy dysregulation.

Results: Preconditioned animals displayed improved functional outcomes, especially female mice showed notably faster recovery. Molecular analysis revealed an initial reduction in neuroinflammatory markers in both sexes, however there was an increment observed only in females at day 7 post-stroke. This differential neuroinflammatory response may be associated with faster recovery mechanisms in females, together with improved synaptic plasticity and autophagy.

Conclusion: The findings suggest that ischemic preconditioning modulates neuroprotection through a differentially regulated inflammatory response that may play a crucial role in sexspecific dynamics of recovery and repair processes. The overall study highlights the importance of sex-specific mechanisms underlying the neuroprotection through chronic hypoxia preconditioning.

Finding the target underlying ttherapeutic Potential of IM-1725-RS-109 in treating chronic peripheral nervous system injury using mouse model: a proteomic approach

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Background: Peripheral Nervous system Injury (PNI) has emerged as one of the leading causes of disability in the world in recent years. Traumatic injuries to peripheral nerves like sciatic nerve, facial nerve, radial nerve, etc. has profound and debilitating impacts on the patient's quality of life (QOL) including severe motor disability and shortening of life expectancy, often leading to psychiatric disorders thereby burdening the social economy.

Purpose: Therapeutic interventions to minimize PNI-induced neuropathy and neuropathic pain are inadequate due to poor understanding of the underlying molecular mechanisms involved in PNI. Proteomic analysis may provide not only a better understanding of all the intricate signalling pathways involved in chronic PNI associated damage but also the mechanistic route of the patented spirocyclic compound.

Methods: Chronic constriction injury is a widely used rodent model for the study of sciatic nerve injury and chronic neuropathic pain. In the present experiment, we have used C57BL6/J male mice, 4-6 months old, which were subjected to 3 partial ligations in the sciatic nerve of the left hind limb. IM-1725-RS-109, a patented anti-inflammatory and neurogenic spirocyclic compound, was injected from 7^{th} day post-surgery. The dose (5mg/Kg of B.W) was given intra-peritoneally thrice a week, for 3 consecutive weeks.

Results: Our results showed a significant restoration of motor behavioural parameters (OFT, Rotarod and Pole test) in CCI-induced mice treated with the patented compound as compared to the vehicle treated group. We have isolated the gastrocnemius and bicep femoris muscle from the injured limb and have done a complete proteomic profiling of both the muscles. By validating a few differentially regulated protein markers from the analyzed data through qRT-PCR/ western blot, we would confirm the underlying molecular mechanism of action of IM-1725-RS-109.

Conclusion: The overall study might give us a better perspective on the potential of IM-1725-RS-109 in alleviating chronic peripheral nerve injury.

Ciliary Neurotrophic Factor (CNTF) Promotes Cholinergic Differentiation in Mouse Neural Stem/Progenitor Cells and Human Neuroblastoma SHSY5Y Cells

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Background: Alzheimer's disease (AD) is marked by the early loss of cholinergic neurons and impaired neurogenesis. The brain's niche microenvironment plays a critical role in the survival, maturation, and integration of newborn neurons. Pharmacological treatments for AD often target the cholinergic system and there is a critical need for approaches that can regenerate or replace lost neurons. CNTF is a pleiotropic neurocytokine that supports neuronal survival and promotes cholinergic differentiation. Exploiting CNTF's neuroregenerative and antiinflammatory properties could be a promising strategy in AD therapy. This study investigates whether CNTF can induce cholinergic differentiation in mouse neural stem/progenitor cells (NSPCs) and human neuroblastoma SH-SY5Y cells, potentially providing an in vitro model that can be used to study AD pathology.

Purpose: To evaluate the effect of CNTF on cholinergic differentiation in mouse NSPCs and human neuroblastoma SH-SY5Y cells.

Methods: Primary NSPCs were treated with CNTF for 72 hours, followed by transcriptome sequencing to identify differentially expressed genes (DEGs) compared to untreated cells. SHSY5Y cells were exposed to various CNTF-enriched media conditions. Proliferative and differentiative responses will be assessed using growth curve analysis, Ki-67 immunocytochemistry, Real – Time PCR for cholinergic gene markers, and FACS for cell cycle dynamics.

Results: RNA sequencing of CNTF-treated NSPCs revealed significant enrichment of DEGs associated with cholinergic neuron development. In SH-SY5Y cells, CNTF treatment led to reduced cell proliferation, as observed in MTT assay, and an upregulation of cholinergic neuron-related genes.

Conclusion: CNTF effectively promotes cholinergic differentiation in both mouse NSPCs and human SH-SY5Y cells, offering a potential in vitro model that can be used to study AD pathogenesis. This finding underscores CNTF's therapeutic potential in neurodegenerative diseases like AD.

Role of immunocompetent cells in degenerative changes of aging choroidal capillaries

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Background: Aging and age-related ocular diseases, including age-related macular degeneration, are linked to significant choroidal capillary loss. This loss reduces the supply of nutrients and oxygen to outer retina, leading to degeneration of photoreceptors and retinal pigment epithelium.

Purpose: The study aimed to investigate the phenotypes of immunocompetent cells involved in age-related changes in choroidal capillaries.

Methods: The choroid of four to sixteen month-old Wistar rats were examined by histochemistry, ELISA, Western blotting, immunohistochemistry, transmission electron microscopy and global proteomic profiling.

Results: The aged rats showed various pathological changes in the choroid, such as vacuolated endothelium, detached electron-dense pericytes, and disrupted basal lamina, in contrast to control rats with intact endothelial cells and pericytes. A significant upregulation of inflammatory markers, viz. CD68, TLR4, and NLRP3 were observed in the choroidal homogenates of aged rats. Further, an increase in Iba-1-positive microglia, macrophages, monocytes, and mast cells (expressing tryptase and chymase) was noted along the capillaries, with aged rats showing higher mast cell degranulation frequency. Analysis of whole-mounted choroids revealed distinct distribution patterns of mast cells and macrophages along capillary walls, with elevated CX3CR1 levels indicating inflammatory changes. Proteomic profiling identified 1129 proteins specific to the choroid, of which 334 proteins were differentially expressed using a fold change of $\geq$1.5 and a p-value $<$0.05. Pathway's analysis of these proteins suggested alterations in signalling pathways regulating degenerative changes in the choroidal vasculature.

Conclusion: The study shows that pathological changes in the choroidal vasculature along with mast cell degranulation trigger microglial/macrophage activation via upregulation of proinflammatory cytokines. Their migration towards the choriocapillaris contributes significantly to age-related capillary loss. Proteomic profiling highlights the potential to identify and target specific proteins, offering new avenues for therapeutic interventions to mitigate or reverse vascular degeneration, thereby preserving ocular health and preventing vision loss in the elderly.

Role of Novel lncRNA GM12840 in peripubertal stress induced aggressive behavior in mice

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Background: Traumatic experiences during adolescence often lead to long term neurobehavioral abnormalities and an increased susceptibility to developing neuropsychiatric disorders, though molecular correlates are still elusive. Earlier, we showed that male mice exposed to trauma during peripubertal age showed heightened aggression in adulthood, while female mice were resilient. Further, transcriptome analysis, through RNA sequencing of the brain regions of both the sexes revealed differentially expressed protein coding genes as well as non-coding RNAs. Non-coding RNAs are important epigenetic regulators of gene expression, leading to experience dependent lasting phenotype.

Purpose: We hypothesize that at the epigenetic level, ncRNAs are driving peripubertal stress induced gene expression changes.

Methods: RNA sequencing, Comparative Genome Analysis, RNA isolation followed by qPCR

Results: Transcriptome analysis, through RNA sequencing of the brain regions showed upregulated levels of novel lncRNA GM12840 in the PFC of stress induced aggressive male balb/c mice. Through qPCR it was observed that, GM12840 was upregulated in the prefrontal cortex (PFC) of early life stress induced aggressive adult balb/c males, as well as of acute stressed mice. Within the cells, GM2840 has been observed to be enriched in chromatin. Moreover, through comparative genome analysis further a possible human analog of GM12840 was observed, which might have been conserved through synteny. Tissue specific expression through qPCR of GM12840 showed its ubiquitous expression along with the brain.

Conclusion: Our data shows that levels of GM12840 are perturbed in the PFC region of both acute stressed, and stress induced aggressive male mice. Further studies would be done to decipher the role of GM12840 in stress induced aggressive behavior. This might be followed by secondary effects leading the behavioral changes.

Stable encoding of partner and grooming state during simultaneous wireless recordings of socially interacting monkeys

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Background: Traditional paradigms for studying vision and movements in non-human primates are often restrictive and far removed from natural behaviour, blinding us from studying the neural correlates of natural behaviour, and in particular of social behaviour.

Purpose: Here, our goal is to understand neural corelates of social interactions of monkeys in a more naturalistic environment. Here we report the first simultaneous wireless brain recordings from two socially interacting monkeys.

Methods: Each monkey was implanted with 256 electrodes into high-level visual areas (inferior temporal cortex - IT) and high-level motor areas (ventral premotor cortex – PMv & ventrolateral prefrontal cortex – vlPFC). Each animal was first shown a fixed set of images, which included the face images of themselves, their partner, and a third unrelated monkey. After this, they were allowed to interact freely with each other in a naturalistic setup. During both sessions, we recorded neural activity wirelessly.

Results: Our main findings are as follows: (1) Decoders trained on neural responses to self vs partner vs other face during the fixation task were able to reliably decode partner identity throughout the real-world social interaction session, regardless of whether the animals were facing or not facing each other – thus social partner identity is represented throughout the social session; (2) Grooming state (give groom/receive groom/no groom) could be reliably decoded from IT and PMv/vlPFC in both monkeys.

Conclusion: Taken together, our results show that socially important variables are encoded in both high-level visual and motor regions in monkeys.

Neuroprotective potential of Tranilast in streptozotocin-induced sporadic Alzheimer's disease model targeting ROS-TXNIP-NLRP3 pathway

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Background: Sporadic Alzheimer's disease (sAD) is a progressive neurodegenerative disorder characterised by oxidative stress, neuroinflammation, mitochondrial dysfunction and cerebral insulin resistance. Even though approximately 95% of AD cases are reported as sporadic, the exact pathogenesis remains sparse.

Purpose: Tranilast, an analogue of tryptophan metabolite, was initially endowed as an antiallergic agent and used in multiple inflammatory ailments, but the molecular mechanisms targeting sAD are yet to be investigated.

Methods: In the present study, we investigated the neuroprotective potential of tranilast by performing biochemical, molecular and histopathological assessments using both *in vivo* and *in vitro* experimental sAD models. Streptozotocin (STZ; 3 mg/kg) was bilaterally injected through the intracerebroventricular (ICV) route to Sprague Dawley rats. Neurobehavioural assessments were performed to check the alteration in cognitive deficits across the groups. Furthermore, SHSY5Y cells were exposed to STZ (1mM) and tranilast for 24 hours to validate the *in vivo* results.

Results: Three weeks of tranilast (30 and 100 mg/kg, *p.o*.) treatment attenuated the cognitive deficits in ICV-STZ-treated rats by improving neurobehavioural anomalies, ameliorating neuroinflammation, synaptic plasticity, and suppressing inflammasome formation. High-dose tranilast treatment (100 mg/kg) also improves cerebral insulin resistance and attenuates hyperphosphorylation of tau protein. In cell culture studies, 24-hour tranilast (0.03 and 0.1 mM) treatment improves mitochondrial health and inhibits intracellular reactive oxygen species (ROS) in STZ-treated SHSY5Y neuroblastoma cells. In addition, western blotting, immunofluorescence, and RT PCR analysis were performed to evaluate the protein expression and mRNA level of TXNIP, NLRP3, ASC, and Caspase-1 in STZ-treated rats hippocampus and SHSY5Y cells.

Conclusion: In summary, the results above proclaim the neuroprotective potential of tranilast in STZ induced model of sporadic Alzheimer's disease.

Identification of the molecular targets in monocrotophos-induced neuronal toxicity in SHSY-5Y cells

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Background: Persistent use of organophosphate pesticides (OP) is linked to various neurodegenerative disorders. They may further alter the small biological molecules like miRNAs, which target different genes and subsequent proteins and can serve as therapeutic targets for restoring OPmediated neurotoxicity. Monocrotophos (MCP), a non-specific organophosphate pesticide, is an expounded neurotoxicant, but its role as an epigenetic modulator is unclear.

Purpose: The study intends to investigate the dysregulated miRNAs and genes in MCP-exposed neuronal cells with the aim of targeting these miRNAs for therapeutic interventions in neurodegeneration. To restore the perturbed homeostasis in MCP-challenged cells, we used Quercetin, which is a known neuroprotectant. Further, we also aim to address whether the identified miRNAs follow similar or different molecular pathways as Quercetin toward restoring MCP-mediated damages.

Methods: The non-cytotoxic dose for MCP and Quercetin was determined by Alamar blue assay on SHSY-5Y cells. The reactive oxygen species (ROS) was assessed by 2′, 7′-dichlorodihydrofluorescein diacetate (DCFH-DA) dye via immunofluorescence. The miRNA and gene profiling were done through TaqMan-based Open Array. Further, the target identification and pathway analysis were done using *in-silico* tools.

Results: The biologically safe doses for MCP and Quercetin were 300 μM for 72h and 1 μM for 24h, respectively. The ROS generation in the exposed group was significantly high (5.946± 0.215); however, quercetin treatment reduced oxidative stress (1.053± 0.2220) w.r.t. control. The KEGG analysis of 7 dysregulated miRNAs and 15 dysregulated genes obtained through OpenArray in MCP-challenged cells revealed their involvement in cellular stress, mitophagy, and various pathways of neurodegeneration.

Conclusion: Our study revealed the altered novel miRNAs and their associated molecular targets in MCPchallenged neuronal cells that can be further exploited as predictive biomarkers in OP-induced neurotoxicity. Our preliminary studies also reflect upon the neuroprotective efficacy of Quercetin against MCP-induced neurotoxicity.

Amelioration of Synaptic and Cognitive Deficits through F-actin Stabilization in an Alzheimer's Disease Mouse Model

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Background: Synaptic dysfunction, characterized by synapse loss and structural alterations, emerges as a prominent correlate of cognitive decline in Alzheimer's disease (AD), where the actin cytoskeleton, structural backbone of synaptic architecture, is lost from synapses. Actin cytoskeleton loss compromises synaptic integrity, affecting glutamatergic receptor levels and neurotransmission. Understanding these molecular changes is crucial for developing interventions targeting synaptic dysfunction, potentially mitigating cognitive decline in AD.

Purpose: To evaluate the therapeutic potential of F-actin stabilization in restoring synaptic and cognitive impairment observed in APP/PS1 mouse.

Methods: In this study, we examined synaptic actin interactome in APP/PS1 mice using mass spectrometry, focusing on the role of PSD-95 and actin interactions in AD-related synaptic and cognitive impairments. We administered jasplakinolide to stabilize F-actin in APP/PS1 mice and evaluated behavioral deficits using the contextual fear conditioning paradigm. Synaptic AMPA/NMDA receptor levels and PSD-95-actin dynamics were analyzed in primary neuronal cultures. Additionally, we examined postmortem brain tissue from individuals with no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD to assess the PSD-95-actin association.

Results: We found significant reduction in PSD-95-actin association in synaptosomes from middle-aged APP/PS1 mice compared to wild-type mice. Treatment with jasplakinolide, an actin stabilizer, reversed deficits in memory recall, restored PSD-95-actin association, and increased synaptic Factin levels in APP/PS1 mice. Additionally, actin stabilization led to elevated synaptic levels of AMPA and NMDA receptors, enhanced dendritic spine density, suggesting improved neurotransmission in primary cortical neurons from APP/PS1 mice. Furthermore, analysis of postmortem human tissue with NCI, MCI and AD subjects revealed disrupted PSD-95-actin interactions, underscoring the clinical relevance of our preclinical studies.

Conclusion: Our study elucidates disrupted PSD-95-actin interactions in AD models, suggesting potential therapeutic targets. Stabilizing F-actin restores synaptic integrity and cognitive function in APP/PS1 mice, highlighting synaptic actin regulation as a promising strategy to combat cognitive decline in AD.

Co-localization and interaction between Olfml3 and Iba1 in LPS-Induced Neuroinflammatory Mice

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Background: Olfml3 is a microglia-specific secreted glycoprotein containing Olfactomedin domain essential for protein-protein interaction. Olfml3 interacting proteins in microglia, and its impact on the microglial activation, microglial phenotypes, neuroinflammation, and neurodegeneration are elusive.

Purpose: To analyze Olfml3 interacting partners, as well as their co-localization and coexpression in the brains of mice.

Methods: *In silico* analysis was conducted to characterize and model Olfml3 protein followed by molecular docking and MD simulation to check possible interaction with Iba1. Neuroinflammation was induced in mice upon intraperitoneal injection of lipopolysaccharide. Western blotting and qPCR were done to check expression levels, and IHC was performed to analyze the co-localization of Olfml3 and Iba1. FACS was performed to quantify Olfml3 and Iba1 dual positive cells.

Results: Results suggest that Olfml3 has putative interactors in microglia including Iba1, Tmem119, P2ry12, Fcrls, Gpr34, Siglec-h, Sall1, Tgfbr1, Csf1r, Trem2 and BMP1. Molecular docking and MD simulation showed stable physical interaction of Olfml3 with Iba1 protein involved in microglial activation and migration. Olfml3 and Iba1 expression was found to increase during neuroinflammation. Olfml3 was observed to co-localize with Iba1, and the number of Olfml3 and Iba1 dual-positive cells increased in the brain of the neuroinflammatory mice model.

Conclusion: *In Silico* analysis showed the involvement of Olfml3 in microglial cell migration, activation, and chemotaxis. Interaction between Olfml3 and Iba1 is stable, and both expressions were increased at transcript and protein levels in the brains of LPSinduced mice, indicating their putative role in neuroinflammation. The co-localization of Olfml3 with Iba1 suggests its involvement in microglial activation states. The physical interaction, co-localization, and co-expression of Olfml3 with Iba1 indicate its possible involvement in Iba1-mediated Rac-signalling and microglial membrane remodeling.

Effects of Retinal Degeneration (RD) on Cortical Inhibition and Thalamic terminals in primary visual cortex(V1)

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Background: The leading cause of blindness in inherited retinal degeneration (RD) is the death of photoreceptors such as rods and cones. Retinitis pigmentosa (RP) is the most common form of RD affecting 1 in 5000 individuals in which genetic mutation leads to progressive death of photoreceptors and loss of vision. The loss of photoreceptors leads to reduced sensory input to V1 as it makes aberrant connections in the retina, which disrupts the inhibitory and excitatory balance in V1.

Purpose: Here, we investigated whether changes in cortical functioning are associated with alterations in the population of GABAergic neurons and its two important subtypes, somatostatin (SST) and parvalbumin (PV). Additionally, the expression of Vesicular glutamate transporter 2(VGLUT2), specific to thalamocortical synapses, essential for transporting glutamate, the primary excitatory neurotransmitter.

Methods: We observed that the population of total cortical neurons (NeuN), GABA+, and PV+ neurons remain unaffected by RD, whereas SST+ neurons are significantly reduced in all layers of V1. There was also decreased immunolabeling and expression of VGLUT2 in V1 of *rd1* mice.

Results: Our findings indicate that PV+ neurons remain largely unaffected by RD, whereas SST+ neurons are significantly reduced throughout V1 layers. Additionally, there is a noticeable decrease in VGLUT2 labeling in layer IV of thalamocortical terminals and reduced VGLUT2 expression in rd1 mice.

Conclusion: The findings demonstrate the impact of impaired retinal input on GABAergic somatostatin neurons that modulate cortical processing by synapsing on to the distal dendrites of pyramidal neurons. In addition, the decreased excitatory thalamocortical expression causes hyperexcitability of the visual cortex disrupting the overall functioning. Our study provides insights into the changes that undergo in V1 and delineating their functional role will prove beneficial for a better experimental approach.

CRISPRing away inhibitory NRTFs for Mammalian Axon Regeneration

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Background: Spinal cord injury (SCI) leads to degeneration of axons below the injury site, resulting in permanent loss of communication and paralysis in humans. Axons in the spinal cord are crucial for transmitting signals between the brain and the rest of the body. In contrast to peripheral nervous system axons, axons in the central nervous system (CNS) of adult mice fail to regenerate after injury. This is due to both external inhibitory signals and intrinsic growth limitations within CNS neurons.

Purpose: We hypothesize that the removal of certain inhibitory Nuclear Receptor Transcription Factors (NRTFs) will enhance axonal regeneration and recovery in neurons following injury. These factors may act as repressors of regeneration, limiting the ability of older neurons to repair themselves after damage.

Methods: To investigate this hypothesis, we are employing CRISPR-based knockdown techniques to suppress the activity of specific NRTFs in injured neurons. Our experimental approach involves screening the effects of these repressor knockdowns in both in vitro (cell culture) and in vivo (animal model) assays of neuronal growth.

Results: Our ongoing studies have identified inhibitory factors whose knockdown via CRISPR results in enhanced axonal outgrowth. These findings suggest that targeting these specific NRTFs can promote regeneration in injured neurons.

Conclusion: This research aims to identify therapeutic targets that can be leveraged to improve axonal regeneration following neural injuries. By pinpointing key inhibitory factors, we hope to develop new treatments that facilitate recovery after spinal cord injury.

'Brain Age' Quantification as Determinant of Brain Health: Elevated White Matter Hyperintensity Load results in Increased Brain Age Gap

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Background: White matter hyperintensity (WMH), a brain lesion resulting from cerebral small vessel diseases with chronological aging, is depictive of fiber loss and fiber pruning. **WMH load beyond a threshold is likely to pose vascular insults to neuroanatomic structures thereby leading to altered cognitive and brain health compared to the subjects without WMH.** While studying the T2-FLAIR MRI and Cognitive data of the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI), it was intriguing to note that even within the set of subjects classified as Cognitively normal (CN), a significant subset of subjects had WMH load in the brain while another subset of the subjects had no/very low-WMH. It motivated us to investigate the impact of WMH on Brain Age in subjects with WMH load compared to the subjects without WMH load.

Purpose: Unravel the impact of WMH on Cognition and Brain Health by developing a quantitative model depictive of 'Brain Age' as a function of Small Vessel Disease threshold and kinetics.

Methods: WMH load, neuroanatomical volume, and cortical thickness were quantified in CN, Cognitively Impaired (CI), and Alzheimer's Disease (AD) subjects from the NACC and ADNI cohorts using T1-weighted and T2-FLAIR MRI. Chronological age (CA), along with 178 neuroanatomical structures and two small vessel disease lesions: periventricular WMH (PVWMH) and deep WMH (DWMH) volumes, were utilized to train a boosting-algorithm to predict Brain Age. Brain Age Gap (BAG) was calculated as the difference between CA and estimated Brain Age.

Results: Brain Age estimates model showed a strong correlation with chronological age ($r = 0.89 \pm 0.03$). The CN subjects with high WMH volume (5-10 ml) exhibited significantly higher BAG in the 5064 age group (2.4 ± 2.9 years) and in the 65-79 age group (2.2 ± 3.3 years) compared to those with no detectable WMH. Permutation importance analysis revealed PVWMH load as a key predictor of BA in subjects with high WMH volumes, whereas the third-ventricle was the most important predictor for the subjects with no WMH. We also established a minimum set of three optimal brain quantities: Total brain (GM+WM), CSF, and WMH volume, were sufficient to discriminate cognitive status as CN, CI, and AD.

Conclusion: The Brain Age platform establishes that elevated WMH load results in an increased Brain Age Gap depictive of WMH-induced vascular insult to brain structures as a measure of Brain Age.

Disentangling Neurotherapeutic Strategies Targeting Focal Adhesion Kinase for Redemption of Burn Injury-Induced Pain

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Background: Burn injury-induced pain (BIP) is a significant global health concern, affecting diverse population including children, military veterans, and accident victims. Current treatment, primarily opioids, presents inherent limitations such as addiction, respiratory depression, and sedation. Therefore, there is an urgent need for effective anti-pain therapeutics without these side effects.

Purpose: In the present study, we investigated the potential role of phosphorylated focal adhesion kinase (p-FAK) in BIP and sought to elucidate the associated underlying mechanisms.

Methods: Defactinib (DFT), a p-FAK inhibitor, was administered intraperitoneally at doses of 5, 10, and 20 mg/kg to burn-injured rats. The study examined the effect of DFT on pain reduction, p-FAK, p-Erk1/2, CGRP, and NR2B signaling in the dorsal root ganglia (DRG), and related neuropeptide and cytokine changes in the spinal cord.

Results: DFT effectively reduced pain without central nervous system toxicity. It downregulated p-FAK and p-Erk1/2 pathways, leading to decreased NR2B signaling in the DRG. DFT also reduced substance P and CGRP levels, inhibited microglial activation, and balanced cytokine levels, decreasing pro-inflammatory and increasing anti-inflammatory markers in the spinal cord.

Conclusion: Overall, these findings provide a thorough insight into the crucial role of p-FAK in regulating BIP and offer encouraging prospects for the development of novel therapeutics without side effects for the treatment of burn injury-induced pain.

Targeted Mitochondrial Delivery of Antioxidants using Mito PG: Evaluation of Toxicity and Neuroprotective Efficacy in an *In Vitro* Parkinson's Disease Model

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Background: Parkinson's disease (PD), the most prevalent movement disorder, is characterized by degeneration of dopaminergic neurons in the substantia nigra *pars compacta* region of brain. Mitochondrial dysfunction resulting from impaired mitochondrial dynamics, defective mitophagy and disruption of oxidative phosphorylation is shown to be a key contributor to neuronal degeneration. Although various mitochondria-targeting nano-therapeutics have been developed to target mitochondrial dysfunction, concerns regarding inherent toxicity of the nanocarriers, their clearance and long-term effects, if any, pose significant challenges.

Purpose: The main aim of the present work was to develop a neutral and non-toxic nanocarrier system, which we named, mitochondria-targeted polyglycerol (MitoPG), for selective mitochondrial localization. The second aim was to conjugate antioxidants to MitoPG and examine their neuroprotective effect in a cell line model of the disease.

Methods: Mito-PG was developed by conjugating triphenyl phosphonium (TPP) with a neutral polymeric nanoparticle, dendritic PG. The nanocarrier was optimized for efficient localization within neuronal mitochondria while avoiding mitochondrial damage or neuronal toxicity. Mito-PG was conjugated with various antioxidants, such as quercetin, curcumin, and N-acetyl cysteine. Toxicity of the conjugates and their neuroprotective effect in rotenone-induced PD in cellular model were assessed.

Results: Mito-PG was non-toxic to neurons and did not have any adverse effect on mitochondrial membrane potential and did not induce mitochondrial ROS generation. Mito-PG conjugated antioxidants exhibited significantly lower toxicity compared to free drugs. Mito-PG-Quercetin and Mito-PG-Curcumin were 2.5 times less toxic compared to their respective free drugs even at millimolar concentrations. MitoPG-Quercetin demonstrated 90% neuroprotection at a quercetin concentration of 45 μM, whereas free quercetin at this dose was toxic and did not exhibit neuroprotection. Significant reduction in the levels of mitochondrial reactive oxygen species in presence of the conjugated antioxidants was also observed.

Conclusion: Mito-PG conjugated antioxidants showed significant neuroprotection against rotenone induced Parkinsonism *in vitro*. This novel dendritic nanocarrier system opens up a new avenue for mitochondria-targeted antioxidant delivery.

Correlation of Dopamine Receptor D2 Expression and Social Behavioral Changes in Post Weaning Chronic Isolation Model of Schizophrenia

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Background: Schizophrenia (SZ) is a neurological disorder with a lifetime prevalence of 1.4% in Indian population, characterized by delusions, hallucinations and cognitive deficits. Although distinct symptoms are established, the mechanism of disease pathology remains elusive. Genetic factors contribute to the often-multifactorial neurological disorders, and synaptic gene mutations are often associated with neuropathology, ergo the term synaptopathies. Through Genome Wide Association Studies (GWAS), certain synaptic genes have been implicated in the occurrence of SZ in the Indian population groups, but the mechanism of action remains largely unknown.

Purpose: This study aims to understand the role of synaptic compartment in the development of neurological disorders through comprehensive analyses of existing synaptic gene mutations implicated in SZ in the Indian population.

Methods: We performed *in silico* analyses using open-source data analysis tools to determine deleterious Single Nucleotide Polymorphisms (SNP) implicated in Indian population with SZ, and narrowed down to one high probability deleterious SNP in the *DRD2* gene. We then established isolation-induced SZ male mice (post-weaning social isolation-PWSI) model and studied their behavior, followed by biochemical analyses of protein expression in the brain tissue of group housed control mice and isolated mice.

Results: Our analysis predicts that mutations in Dopamine Receptor D2 (DRD2) encoding gene *DRD2* (rs1801028) is very likely to be deleterious. Our *in vivo* studies indicate impaired sociosexual behavior (characterized by ano-genital sniffing) of our SZ model in male-female social interaction test. Biochemical analyses indicate reduction in expression of hippocampal DRD2 in PWSI model compared to group-housed controls. Subsequent *in silico* analyses shows that the SNP also impairs DRD2's vital interaction with Neuronal Calcium Sensor 1.

Conclusion: Altogether, our study determines that impaired DRD2 signaling and protein-protein interaction may lead to the manifestation of schizophrenia, particularly impairing sociosexual behavior as demonstrated by our *in vivo* studies.

Mesenchymal stem cell secretome as a priming strategy in restoring the chemical-induced neurotoxicity

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Background: Multi-omics coupled with the *in-silico* approaches unravel the mechanistic insights into neurotoxicity and its convalescence using the Mesenchymal Stem Cell (MSC) secretome, an amalgamation of bioactive molecules endowed with paracrine activity. The restorative and protective effects of MSC secretome and its association with epigenetic, transcriptomic, and proteomic changes on neuronal cells is still a pristine area of research.

Purpose: In the current study, we have investigated the effects of Monocrotophos (MCP) on Neural Progenitor Cells (NPCs), followed by the utilization of transcriptomic and proteomic approaches. These studies, in conjunction with in-silico analysis, identify molecular alterations in pathways and offer the foundation for future mechanistic studies connecting the restorative efficacy of MSC secretome in neurotoxicity and neurodegeneration.

Methods: OpenArray profiling and unlabelled LC-MS/MS global protein profiling were conducted to identify miRNAs, genes, and proteins deregulated by MCP exposure and subsequent treatment with MSC secretome on NPCs. *In-silico* tools were employed for target identification and pathway analysis. Furthermore, cellular bioenergetics assays were performed using a Seahorse XFp analyzer to assess mitochondrial dysfunctions and restoration.

Results: MCP-exposed NPCs depicted increased expression of miR-129, miR-138, and miR-219 and decreased expression of miR-132, miR-29c, miR-19b, and miR-15a. We observed that the treatment of MSC secretome restored the expression of de-regulated miRNAs and genes *viz.* KEAP1, PTEN, BECN1, SQSTM1, SRXN1, IGF1R, BAK1, ACHE, MAP2K3, BAX, MFF, and NRF1. These genes and proteins were involved in pathways of oxidative stress, apoptosis, autophagy, FoxO signalling, PI3KAkt signalling, etc. The MCP exposure to NPCs altered the respiration kinetics, which was restored significantly upon secretome treatment, as evidenced by levels of basal respiration, proton leak, and ATP production.

Conclusion: Our findings show that MSC secretome can indemnify the MCP-induced neuronal damage and hence restore cellular homeostasis in NPCs. These findings suggest that MSC secretome can be an effective acellular regenerative therapy against neurotoxicity and neurodegeneration.

NUO-5 as a Key Regulator of Mitochondrial Quality Control in Alzheimer's Disease: Study Employing *Caenorhabditis elegans* Model

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Background: The maintenance of mitochondrial quality is critical for neuronal function and survival, as neurons are highly energy-dependent cells. Mitochondrial quality control processes, which include proteostasis, mitochondrial dynamics, mitophagy, biogenesis, and mito-nuclear communication, are vital for sustaining neuronal health and function. Disruptions in these pathways are closely linked to neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's, highlighting the importance of mitochondria in the pathology of these conditions. *Caenorhabditis elegans*, a model organism with a significant number of homologous genes to humans, provides a powerful system for investigating these molecular mechanisms.

Purpose: This study examines the role of the nuclear-encoded mitochondrial complex I subunit gene *nuo-5*—an ortholog of the human *NDUFS1* gene—in regulating mitochondrial quality control mechanisms implicated in Alzheimer's disease.

Methods: We utilized wild-type N2, *nuo-5* knock-out, and various transgenic *C. elegans* strains. The study assessed mitochondrial and lipid content, analyzed the expression of *hsp6p*, *unc-17::GFP* (in cholinergic neurons), and *ric-19::GFP* (in M2 pharyngeal neurons), and evaluated ATP content, mitochondrial membrane potential (MMP) and amyloid-beta accumulation under *nuo-5* RNAi/knock-out conditions.

Results: RNA interference-mediated silencing of *nuo-5* resulted in reduced lifespan, locomotor dysfunction, and sensory deficits. Additionally, *nuo-5* suppression decreased amyloid-beta accumulation and related effects. Knockdown of *nuo-5* also led to reduced cholinergic signalling and increased expression of *hsp-6p*. Furthermore, several mitochondrial quality control marker genes, including *pdr-1*, *pink-1*, *skn-1*, *atp-1*, and *gas-1*, showed significant modulation in response to *nuo-5* suppression.

Conclusion: This study highlights the critical role of *nuo-5* in modulating mitochondrial quality control, particularly in the context of Alzheimer's disease. The findings suggest that targeting *nuo-5* could be a strategic approach for enhancing mitochondrial function and protecting neuronal integrity, offering new insights into potential therapeutic strategies for neurodegenerative diseases.

N-acetylcysteine elicits neuroprotection against di-2-ethylhexyl phthalate-induced neurodegeneration in zebrafish brain through regulation of endoplasmic reticulum-unfolded protein response

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Background and Purpose: At present, di-2-ethylhexyl phthalate (DEHP) is primarily commercialized towards making of plastics and its products more durable, flexible and ductile. With the report citing potential neurotoxic effect of DEHP, unravelling the fundamental mechanism of neurodegeneration and its possible amelioration through N-acetylcysteine (NAC) intervention is the paramount requisite of the present study.

Methods: The current experimental design spanned 21 days to investigate neuroprotective effect of NAC against DEHP-induced neurotoxicity in zebrafish through waterborne exposure. Neurobehavioral assessments utilized the mirror biting test. Furthermore, biochemical assays for oxidative stress indices, gene and protein expression studies associated with endoplasmic reticulum (ER) stress and unfolded protein response (UPR) were performed on adult zebrafish brain.

Result: Our basic observation strongly advocated that DEHP elicits oxidative stress induced neurotoxicity through precocious genesis of aggressive neurobehavioral response and is linked with augmented monoamine oxidase (MAO) activity and downregulation of tyrosine hydroxylase level in zebrafish brain. As sustained oxidative stress might trigger abnormal ER stress response and dysregulated calcium homeostasis in neuronal microenvironment, our findings adjunct the similar response to DEHP exposure. As heightened ER stress and unfolded protein response (UPR) can trigger death cascades, our findings showed that DEHP exposure is linked with activation of cleaved caspase 3 (CC3) mediated apoptotic death in zebrafish brain. As a prophylactic measure, NAC co-supplementation provides profound neuroprotection against DEHP-persuade neurobehavioral transformation, oxidative stress, dysregulated calcium homeostasis, endoplasmic reticulum stress and unfolded protein response in zebrafish brain.

Conclusion: In a nutshell, our findings provide experimental support towards neurodegenerative potential of DEHP through dysregulated endoplasmic reticulum-unfolded protein response in neuronal microenvironment and its possible amelioration through NAC intervention.

Encoding of light direction and object identity in the monkey inferior temporal cortex

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Background: Real world objects produce widely varying images depending on illumination direction. This makes object recognition a challenging problem, the neural basis of which has received relatively little attention.

Purpose: Our results elucidate how light direction is encoded at the neural level in order to achieve invariant object representations.

Methods: We performed wireless brain recordings from the inferotemporal (IT) cortex of the macaque (*Macaca radiata*, 2 males, aged 9 and 10 years) while the monkey fixated on images of 3- dimensional objects with varied lighting directions. In Experiment 1, we presented images of naturalistic objects lit at the same intensity but from different directions, such that while the visual appearance of the objects is sufficiently modulated by the lighting variation, the overall object structure is preserved. In Experiment 2, we extend this to *bas-relief* objects with ambiguous 3D structure (convex/concave).

Results: The main findings are as follows: (1) In Experiment 1, multi-unit neural responses were strongly modulated by object identity and only weakly by light direction, as evidenced by 29% of channels showing a main effect of only object identity, and 5% of channels showing a main effect of only light direction; 33% of channels are modulated significantly by both factors. (2) Neural selectivity for object identity arose slightly later than light direction tuning (half-maximum latency: 76ms for object identity, 48ms for light direction). (3) Decoding analyses showed that object identity and lighting direction can be reliably extracted from neural responses, with a similar delay in peak decoding accuracy; (4) In Experiment 2, we observe that the light direction tuning curve for concave and convex objects are mirrored with respect to each other.

Conclusions: IT representations of objects are largely invariant, but still retain some information about lighting direction. IT neurons initially respond to lighting variations, and later become object- tuned and invariant to illumination. When shape information is ambiguous, neurons change their light direction tuning to reflect perceived shape.

"CK2-Wnt/β-Catenin Signaling Interactions: Implications for Mesial Temporal Lobe Epilepsy"

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Background: Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of DrugResistant Epilepsy. Both the glutamate receptors in the brain Casein Kinase 2 (CK2) substrates. Wnt/β–Catenin also play role in regulation of Synaptic transmission via NMDARS.CK2 and Wnt/β–Catenin signalling gained a lot of attention due to their involvement in seizure-induced neurogenesis, aberrant neurogenesis, neuroinflammation, and hyperexcitability associated with epileptic disorder. This study focuses precisely on understanding the role of regulation of Wnt signalling by Casein Kinase 2(CK2) in MTLE.

Methods: Male SD rats, weighing 200-250 grams were used for the study. Pilocarpine induced TLE chronic model was developed and H&E staining was performed to confirm the pathophysiological changes. mRNA expressions of CK2-Wnt/β-Catenin signalling molecules (CK2α/α', CK2β, NR2B, NR2A, Dvl 2, β-Catenin, and Wnt/ β-Catenin downstream target genes (NEUROD1, FN1, LEF-1, BDNF) were evaluated by quantitative real -time PCR. Expression of proteins (CK2-Wnt/ β-Catenin) signalling was studied by western blotting and Immunohistochemistry. Colocalization was studied using Immunofluorescence. Golgi cox staining was used to study the associated morphological changes.

Results: Significant neuronal loss was observed in Chronic TLE model compared to control. Increased protein expression of CK2α', CK2β, NR2A, pNR2B, β-Catenin, Dvl 2 and LEF-1 was observed in Hippocampus and ATL region of Chronic TLE. This was further confirmed by immunohistochemistry. Significant increase of CK2 and Wnt targeted genes were observed at mRNA level in Chronic TLE. Alterations in the length of apical and basal dendrites were observed in the chronic model of TLE. Immunofluorescence showed colocalization of CK2 and β-Catenin in the hippocampus, validating the crosstalk between the two.

Conclusion: Understanding the contribution of CK2 mediated Wnt/ β-Catenin signalling in MTLE will not only provide mechanistic insights on the underlying mechanism of epileptogenesis of MTLE but also may aid in the development of novel anti-epileptogenic treatment for MTLE.

'Brain Fog after the Fight': The Cognitive Struggles of Young Adult Sarcoma Survivors

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Background: Sarcomas, primarily impact young adults (YA), and have shown improved survival rates due to advancements in diagnosis and treatment. However, YA sarcoma survivors increasingly face cognitive impairments related to cancer and chemotherapy.

Purpose: The present study examines both self-reported cognitive deficits and objective neuropsychological functions in YA sarcoma patients.

Methods: Ninety sarcoma patients aged 16-40 years and thirty matched controls were recruited from a single tertiary hospital. Participants were categorized into four groups: Pre chemotherapy, during chemotherapy, post chemotherapy, and controls. Cognitive functions were assessed subjectively using the Functional Assessment of Cancer Therapy-Cognitive Function questionnaire Version 3 (FACT-Cog v3) questionnaire, and objectively through Addenbrooke's Cognitive Examination (ACE)-III and neuropsychological tests (NPT) including Flanker's, Sternberg's, and emotional Stroop tests.

Results: FACT-Cog scores were significantly lower in the during chemotherapy and post chemotherapy groups compared to the pre chemotherapy group. Similarly, ACE-III scores were lower in the during chemotherapy and post chemotherapy groups compared to the pre chemotherapy group. Reaction times and accuracies in NPT were significantly worse in the during chemotherapy and post chemotherapy groups relative to the pre chemotherapy and control groups. In the post chemotherapy group, higher chemotherapy dosages correlated negatively with Sternberg reaction time, language scores, and attention scores on the ACE-III.

Conclusion: This study highlights persistent neurocognitive deficits in YA sarcoma survivors, even after treatment completion, with higher chemotherapy dosages exacerbating these impairments. The findings emphasize the need for a comprehensive care model, tailored for young adult sarcoma survivors to monitor and mitigate side effects, thereby enhancing their quality of life.

Combined gene therapy/stem cell transplantation to improve functional recovery after spinal injuries

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Background: Spinal cord injury (SCI) remains a significant challenge, often leading to irreversible neurological deficits. While studies have shown that transcription factors are crucial in triggering a regenerative response, they have not resulted in substantial behavioural improvements. Recent advancements using embryonic neural progenitor cells (NPCs) and induced pluripotent stem cells (iPSCs) have shown mild behavioural improvements. However, there remains a gap in research evaluating the efficacy of combinatorial approaches to overcome both intrinsic and extrinsic constraints to achieve complete functional recovery.

Purpose: This study aims to take a synergistic approach by combining gene treatment at the cell body level with supportive stem cell grafts at the injury site to address both intrinsic and extrinsic barriers to spinal cord regeneration.

Methods: We have developed protocols to generate specific subsets of neural progenitor cells (NPCs) by differentiating human induced pluripotent stem cells (hiPSCs) and implanting them at the site of injury. Functional recovery is assessed through a comprehensive battery of motor and sensory tests over defined intervals post-transplantation. Additionally, we are exploring rehabilitation and stimulation strategies to enhance functional outcomes, complementing our gene treatments and stem cell grafts.

Results: Our study focuses on accessing the degree of functional recovery observed in animal models, the success of specific NPCs in engrafting and supporting recovery, and the potential synergistic effects of combining gene therapy with stem cell transplantation.

Conclusion: The findings from this study could pave the way for future translational studies aimed at clinical application, offering a potential avenue to significantly improve outcomes for patients with spinal cord injuries through a combinatorial treatment approach.

Murine Coronavirus induced alteration of Cx47 phosphorylation: A paradigm shift in the development of Multiple Sclerosis (MS) therapeutics

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Background: Gap Junctions (GJ) made-up of Connexin (Cx) proteins are essential for the maintenance of Central Nervous System myelin, homeostasis, K+ buffering and also transfer of signaling molecules like Ca+2, ATP, cyclic AMP. Astrocytic Cx43-Oligodendrocytic Cx47 is involved in various signalling for myelin maintenance. Research shows neuronal ATP secretion triggers leukemia-inhibitory-factor (LIF) from astrocytes which enhances myelination by matureoligodendrocytes. Cx phosphorylations are crucial for its regulation. GJ intercellularcommunication (GJIC) between astrocytes-oligodendrocytes is disrupted in MS lesions and previous studies have shown that MHVA59/RSA59 infection also alters Cx43-Cx47 mediated GJIC between astrocytes-oligodendrocytes in the brain. However, the interconnection of Cx47 alteration and virus-induced demyelination are yet to be investigated.

Purpose: As both MS and Virus-induced progressive demyelination is associated with alteration of astrooligodendrocytic Cx43-Cx47 GJIC. Thus, we have explored the direct detrimental effects of virus (RSA59) infection on oligodendrocytes and its GJ protein Cx47.

Methods: Luxol-Fast Blue, Tunnel and Immunofluorescence staining were used to identify progressive demyelination, Oligodendrocyte apoptosis and altered distribution of Cx47 on primary Oligodendrocyte precursor cells (OPCs) respectively. Expression of Phosphorylation and nonphosphorylated forms of Cx47 were validated using Western blots and Cx47 mRNA expression were studied using qRT-PCR in brain samples of C57BL/6 mice.

Results: We found RSA59-infection induces chronic-progressive demyelination in the brain and spinal- cord tissues, which starts around day-5 post-infection (p.i.) and gradually aggravates towards day-30 p.i and this persistent demyelination is associated with oligodendroglial apoptosis. We have also identified RSA59 infection affects the post translational modification of Cx47, as it downregulates phosphorylated-Cx47 and simultaneously increases non-phosphorylated forms along with increased mRNA levels of Cx47. RSA59-infection also alters the surface localization of Cx47 in OPCs.

Conclusion: Our findings suggesting RSA59 causing demyelination either by directly targeting oligodendrocytes or by dysregulating it's GJ protein Cx47. Therefore, our research will aid to the development of Cx47 targeted therapeutics for MS treatment.

ELISA-based assessment of NLRP3 Inflammasome-associated markers in Serum of PD Patients

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Background: Our previous study showed Fibrinogen and CFAH as putative biomarkers to differentiate Parkinson's disease (PD) from Parkinson's disease with cognitive impairment (PDCI). Recognizing neuroinflammation as a key player in PD, we aimed to investigate a panel of inflammatory biomarkers. Inflammasomes, key components of the immune system, are known to influence the progression of neurodegenerative diseases, including PD. However, the detailed mechanisms and the specific role of inflammasomes in PD are not fully understood. This study focuses on exploring serum as a bio-fluid to understand the correlation between inflammatory cytokines and NLRP3 in PD.

Purpose: Blood-based investigations are less invasive for the patients, hence we studied the levels of NLRP3-associated inflammatory cytokines, viz., Caspase-1, IL-Iβ, IL-18, IL-33 and fibrinogen in the serum samples of PD patients.

Methods: This cross-sectional study of blood serum samples included subjects from an Indian cohort. PD patients, diagnosed by neurologists (Movement Disorder Specialists) were recruited from the Dept. of Neurology, NIMHANS. The study included: 24 PD patients (equal number of male and female) and 16 age and sex-matched controls. Blood samples were collected and serum was isolated using standard protocols. The serum samples were subjected to ELISA-based estimation, using commercially available kits.

Results: NLRP3, Caspase-1, IL-1β, IL-18, IL-33 and fibrinogen levels were elevated in the serum of PD patients compared to the controls. Amongst the proteins, IL-18 was maximally upregulated i.e. 5-folds followed by 4-fold up-regulation of Caspase-1 and IL-33. IL-1β and NLRP3 were increased by 3-fold and 2-fold respectively. The putative CSF biomarker fibrinogen was increased by 3.1-fold, in PD patients.

Conclusion: Our exploratory study confirms the role of NLRP3 inflammasome-associated markers in PD pathology. Their presence in the circulating bio-fluids suggests a need to include them in a panel for blood-based biomarkers for PD. Examination of a larger cohort will provide a better understanding.

EEG microstate stamp of working memory deficits in alcohol and opioid use disorders

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Background: Effective cognition depends on well synchronized and localized cortical activity, disruption of which is observed in neurocognitive disorders like substance use disorders(SUD). Subjects of SUD exhibit working memory deficits, a reported consequence of aberrance in switching between default mode network(DMN) and fronto-parietal-attentional network(FAN). These neuronal networks can be investigated using EEG microstates, characterized by topography of momentary scalp electric field, influencing stimulus processing in cognitive tasks.

Purpose: In our study, we investigated pre-stimulus microstates and their cortical sources in subjects of alcohol(AlAd) and opioid use disorder(OpAd) as compared to controls, while performing Sternberg task.

Methods: We acquired and analysed 128-channel EEG data from age and gendermatched participants with AlAd(n=10), OpAd(n=10), and controls(n=10) while they completed forty trials of Sternberg's task. Behavioural parameters, pre-stimulus EEG microstates and underlying sources were analysed using GraphPad Prism, Cartool and sLORETA software, and compared between SUD groups and controls.

Results: Both AlAd and OpAd had significantly lower accuracy($p < 0.01$); reaction times were significantly higher only in AlAd compared to controls($p < 0.01$) and OpAd($p < 0.01$) in Sternberg's task, reflecting working memory deficits of varying degrees in SUD subjects. Pre-stimulus EEG microstate revealed four topographic Maps 1-4: subjects of AlAd and OpAd showing significantly lower mean duration of Map 3(visual processing) and Map 2(saliency and DMN switching) respectively, compared to controls ($P < 0.05$). Increased source activation was observed in the parahippocampal gyri(DMN hub), superior and middle temporal gyri(involved in impulsivity), and insula(maintaining balance between executive reflective system and impulsive system), in both AlAd and OpAd groups.

Conclusion: Reduced mean duration of microstate maps involved in visual processing and reallocation of neural resources from DMN(resting state network) to executive network in SUD subjects and inability to suppress cortical areas involved in impulsivity can underlie their poorer performance in Sternberg's task, as compared to controls.

Evaluating the efficacy of nuclear receptor factors in promoting regeneration and plasticity in mouse models of spinal injuries

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Background: The spinal cord serves as a critical pathway for transmitting signals between the brain and the rest of the body. When injured, in mammals, there is limited regenerative capacity which leads to permanent, irreversible motor function deficits. We have recently identified nuclear receptor transcription factors (NRTFs), a class of TFs that are critical for developmental axon growth. However, their role in the regulation of regeneration and plasticity following injury is unknown.

Purpose: The purpose of the study is to virally over-express key NRTFs in the injured adult brain to test the efficacy of gene treatments in clinically relevant murine models of spinal injuries. Currently, we are specifically testing the ability of these factors to promote cross-midline sprouting via pyramidotomy models of injury.

Methods: Midline sprouting via pyramidotomy model in our study involves unilateral transection of the corticospinal tract (CST) to induce injury. We are using *in-vivo* methods to asses axonal sprouting from the intact CST across the midline into the denervated spinal cord after NRTFs treatment. The process mimics injury-induced plasticity and is used to study recovery mechanisms following spinal cord injuries.

Results: Our ongoing study has identified that combinatorial gene treatments result in better sprouting than single gene treatments alone. Simultaneously, we are also exploring optogenetics-based methods to assess the functional activity of regenerated axons.

Conclusion: Ultimately, our study is expected to reveal novel molecular targets for therapeutic intervention of spinal cord injury. It will not only help in neural regeneration, it will also promote neural reconnection with the existing nervous system.

Neuronal and microglia crosstalk in α-synuclein-induced proteotoxicity

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Background: Protein aggregation is a common hallmark feature of several neurodegenerative diseases, including Alzheimer's, Parkinson's, Huntington's, and Multiple sclerosis. Among these Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by loss of dopaminergic neurons in the substantia nigra (SN) and irreversible aggregation of α-synuclein (α-syn). Aggregation of α-syn and the mechanism associated with disease progression has been prominently studied in in vitro neuronal cell models. However, under physiological conditions, apart from neuronal cells other cells are also present in the brain nervous system such as glial cells. Glial cells play an important role in immune response and neuroprotection, thus together with neuronal cells may represent the true in vitro model system to study protein aggregation and proteotoxicity.

Purpose: Therefore, in the present study, we have evaluated the protein aggregation-induced cytotoxicity in the co-culture model consisting of neuronal (SH-SY5Y) and glial cells (HMC3).

Methods: We have optimized the cytotoxicity of preformed α-syn fibrils (PFFs) on both neuronal and microglial cells via MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). The effect of microglia condition media (CM) on α-syn treated-neuronal cells was determined. Further, the resultant affect on the cellular systems PFFs in the presence of microglia CM was determined via flow cytometry.

Results: The results showed microglia cells exhibit disease-specific activation which can contribute to neuroprotection from aggregation-induced proteotoxicity.

Conclusion: The validated co-culture system may provide information regarding neuronal-microglia interaction in the event of proteotoxicity and may be further utilized to study other pathogenic protein aggregation.

Single-cell genomics analyses reveal the molecular code that governs axon regeneration in CNS neurons

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Background: Axonal regeneration is essential for functional recovery after spinal cord injury. While central nervous system (CNS) axons can regenerate and achieve full repair during embryonic stages, this regenerative capacity significantly diminishes in adulthood, leading to long-lasting disabilities. Recent findings have highlighted the critical role of Nuclear Receptor Transcription Factors (NRTFs) in axon growth during development. However, their specific involvement in the regulation of axonal regeneration in injured adult neurons remains unclear. Understanding the molecular mechanisms driving this regeneration could reveal new therapeutic targets for spinal cord injury.

Purpose: This study aims to elucidate the roles of NRTFs in the regulation of axonal regeneration in adult CNS neurons. Specifically, it seeks to determine whether NRTFs induce developmental re-programming in injured neurons, enhancing their regenerative capacity. By profiling gene expression changes following gene treatment with specific NRTFs, we aim to uncover molecular pathways that could promote axon regeneration.

Methods: Single-cell genomics was utilized to profile genome-wide transcriptional patterns in injured neurons treated with specific NRTFs. Differentially expressed genes and pathways identified from this analysis provided insights into potential developmental re-programming. Additionally, RNA Velocity and trajectory analyses are being employed to quantify the extent of developmental re-programming and to map the trajectory of regenerating neurons.

Results: Single-cell genomics identified key differentially expressed genes linked to axon growth and developmental pathways following NRTF treatment in injured neurons. RNA Velocity and trajectory analyses confirmed that NRTF-treated neurons exhibited developmental re-programming, with enhanced regenerative potential.

Conclusion: NRTFs show promise in promoting axonal regeneration by inducing developmental re-programming in injured CNS neurons. These findings provide insights into the molecular mechanisms of regeneration and suggest potential therapeutic targets for spinal cord injury repair.

Lactobacillus fermentum prevents behavioral abnormalities through Trp/Kyn pathway in chronic unpredictable mild stressed mouse

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Background: Gut microbiota plays a significant role in many neurodegenerative and neuropsychiatric diseases by involving Tryptophan/Kynurenine (Trp/Kyn) pathway and dysregulated HPA-axis. HPA-axis dysregulation increases glucocorticoid levels that induce pro-inflammatory responses with activation of abnormal kynurenine pathway *via* metabolizing indoleamine-2,3- dioxygenase (IDO). Gut microbiota potentially correlates with Trp metabolism through indole derivative which acts as an Aryl hydrocarbon receptor signaling and plays an important role in neuroinflammation.

Purpose: Evaluate the effect of probiotics and IDO blocker on gut microbiota abundance, behavioral deficits, histopathological changes in brain and colon of chronic unpredictable mild stressed mouse (CUMS) modulation through IDO.

Methods: CUMS model was prepared. Then after, mice were placed into six experimental groups namely Control, CUMS stressed, CUMS vehicle, CUMS LF (*Lactobacillus fermentum*), CUMS 1-MT, and CUMS UT (untreated). Briefly, oral administration of LF for 4 weeks and intraperitoneal dose of 1-MT for 3 weeks were supplemented to the mice. After that different behavioural tests, enzyme assay, immunofluorescence microscopy and RT-PCR were performed to check the expression of GR, IDO and NMDAR. Additionally, 16S rRNA sequencing was performed to check the gut microbiota abundance.

Results: Herein, LF and IDO blocker supplemented mice alleviates depressive like behavior, improve motor performances and alters the level of GR, IDO and NMDAR in CUMS mice. Moreover, 16S rRNA sequencing results showed the taxonomic profile of main dominant bacteria in all the groups: *Bacteroidetes*, *Fermicutes* and *Proteobacteria*. CUMS mice have most dominantly *Bacteroidetes* whereas, LF and IDO blocker supplemented mice have increased levels of *Firmicutes.* Meanwhile, IDO blocker supplemented mice showed dominantly *Firmicutes* and decreased *Bacteroidetes* phylum across all the groups.

Conclusions: Such study shall be helpful to understand the probiotics dependent regulation through the abovementioned molecules during depression.

Identifying major regulatory sex-specific distinctive pathways in the dentate gyrus of a mouse model for stress-induced major depressive disorder

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Background: Depression remains a major global health concern, disproportionately affecting women. Persistent stress profoundly disrupts neural circuits, leading to depression, anxiety, and other behavioural issues. However, the fundamental causes and sex-specific mechanisms underlying depression continue to elude researchers despite extensive study.

Purpose: Emerging evidence suggests that stress-induced disruption of adult neurogenesis is pivotal in the progression of depression. However, comprehensive analyses of sexdependent transcriptional changes within the brain's neurogenic regions in major depressive disorder are notably lacking. Thus, our study investigates the sex-specific transcriptomic alterations in the dentate gyrus of the hippocampus in a mouse model of stress-induced depression.

Methods: Present study used chronic variable mild stress (CVMS) paradigm on C57BL/6NCrl mice of both sexes to induce depressive disorder. The entire paradigm consists of fourteen different stressors (two stressors per day) for a period of 21 days followed by various behavioural tests to analyse the mood disorder phenotypes. Afterwards, the dentate gyrus tissues were exclusively micro-dissected and processed for RNA-Sequencing. The screening of differentially expressed genes (DEGs) in both sexes were performed using DESeq2 software. Gene-ontology and Kyoto Encyclopedia of Genes and Genomes pathway analysis were performed followed by protein-protein interaction network of DEGs to identify the hub genes in both male and female using Metascape, STRING and Cytoscape platforms respectively.

Results: The study found distinct sex differences in the transcriptomic changes underlying stress-induced depression in mice. Males showed dysregulation of pathways related to mitochondrial function, synaptic plasticity, autophagy, and cell cycle, while females exhibited changes in behavioral, synaptic signalling, Wnt, and MAPK pathways. Importantly, the analysis uncovered a core set of six sex-specific hub genes, indicating profound sexdependent alterations.

Conclusion: While both sexes exhibited similar depressive phenotypes after chronic stress exposure, the underlying molecular mechanisms differed. These findings suggest the need for targeted, sex-specific approaches to understand and treat depression.

Transcriptional Control of Mammalian Axon Regeneration – Role of Nuclear Receptors (NR) family of Transcription factors

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Background: Neurons communicate through axons, which are vital for brain-body communication. While embryonic neurons regenerate robustly after injury, this ability declines sharply a week after birth. Our previous research showed that the combined action of transcription factors Klf6, Nr5a2, and Rarb partially restores regenerative ability in adult neurons, but without functional recovery, indicating a significant knowledge gap. Nuclear Receptor Transcription Factors (NRTFs) are known regulators of developmental growth, but their role in regeneration remains unknown.

Purpose: This study investigates whether specific NRTFs can promote axonal regeneration and functional recovery following injury. We aim to explore their potential to drive neurite outgrowth and reprogramming at the molecular level.

Methods: We are using in vitro and in vivo screens to assess NRTF combinations for their ability to enhance axon growth. Additionally, single-cell genomics is employed to analyze the molecular impact of these factors. Behavioral outcomes, particularly hindlimb motor function, are also being evaluated in mouse models of injury.

Results: Two NRTFs have been identified that significantly promote neurite outgrowth in vitro. Transcriptomic analysis shows that these factors drive developmental reprogramming at the molecular level. Moreover, mice treated with these NRTFs exhibit improved motor function in hindlimb tasks, indicating a positive effect on recovery.

Conclusion: This research aims to uncover molecular codes that govern axonal regeneration, identifying potential therapeutic targets. We are currently evaluating the regenerative potential of these factors in thoracic injury models, with the ultimate goal of enhancing recovery following neural injuries.

Anti-seizure medication eslicarbazepine acetate modulates excitatory and inhibitory currents and impairs synaptic plasticity at clinically relevant concentrations

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Background: Anti-seizure medications are the most common form of treatment for seizures suppression. But these drugs are commonly associated with memory and cognitive deficits which sometimes outbalance the benefits. This is due to the lack of knowledge of complete mechanism of action of ASMs.

Purpose: Eslicarbazepine acetate is a third-generation anti-seizure medication used for the treatment of epileptic seizures. Eslicarbazepine acetate is known for its action through sodium channels. This study examines the effects of eslicarbazepine acetate (ESL) on hippocampal synaptic transmission and plasticity.

Methods: Hippocampal slices were made from Wistar rat brain (P14-P28). Single cell patch clamp recordings were performed on CA1 pyramidal neurons. Field recording experiments were performed by stimulating the Schaffer collateral pathway and recording from CA1 region of the hippocampus.

Results. ESL at a clinically relevant concentration (100 μM) reduced spontaneous AMPA and GABA-A receptor currents and increased the inter-event interval of GABA-A receptor currents. ESL also enhanced the amplitude of evoked field excitatory postsynaptic field potentials (fEPSPs) due to its antagonistic effect on adenosine A1 receptors, which typically inhibit synaptic activity. Moreover, ESL impaired long-term potentiation (LTP), a key mechanism for learning and memory.

Conclusion: The study concludes that ESL, beyond targeting voltage-gated sodium channels, also affects AMPA, GABA-A, and adenosine A1 receptor-mediated transmission, possibly contributing to cognitive impairments in epilepsy patients.

Quantitative assessment of neuronal tyrosine hydroxylase and galanin expression in autopsied human locus coeruleus: relevance to age-related neurodegenerative diseases

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Background: Parkinson's disease (PD) pathology varies among ethnicities in different parts of the world, with age being a prominent risk factor. Previous studies from our lab have shown subthreshold pathology of nigral neurons in the Asian-Indian population. The present study provides a comprehensive analysis of locus coeruleus (LC) neurons.

Purpose: To evaluate the age effects on the quantitative, densitometric and morphometric attributes of human LC using autopsied tissues.

Methods: The tissues analysed extended from the level of cerebral aqueduct to the full extent of the IV ventricle. The number, volume and density of Nissl-stained LC neurons were quantified using the optical fractionator sampling design and nucleator probe using 40X magnification in a StereoInvestigator workstation equipped with a software (n=18). Every 20th section, (8-14 sections; total 200-250 sections/specimen) were quantified along the rostro-caudal extent. Secondly, tyrosine hydroxylase (TH) and galanin (Gal) immunoreactive (ir) LC neurons, roughly divided into medial (MED) and lateral (LAT) aspects based on their proximity to the ventricles, were subjected to morphometric and densitometric evaluation for neuronal diameter and expression using a 'Windows' based image analysis system (n=22).

Results: Pearson's correlation coefficient was used to assess the relationship between age and quantitative parameters. A significant correlation was observed in the LC volume on both sides: left (r=-.51; p=0.03) and right (r=-.52; p=0.02). There was a mild reduction in TH expression on both aspects with cellular hypertrophy in the lateral LC (r=-.54; p=0.01). A similar trend was noted in the medial aspect, with no statistical significance.

Conclusion: Current study shows preserved neuronal counts/Gal-ir LC in the aging Asian-Indians, which is comparable to previous findings on nigra. A significant reduction in its volume and notable increase in neuronal diameter could be indicative of sub-threshold compensatory changes. Further information on aggregation and autophagy markers would decipher its role in neurodegeneration.

Metabolomic studies of Saraswat churna against tau-mediated neurodegeneration

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Background: Neurodegeneration is the leading cause of dementia and related diseases. Among the many etiologies, tau protein aggregation and formation of Neurofibrillary tangles (NFTs) has been gaining attention. Despite having drugs to alleviate the symptoms of cognitive impairment, there are no targeted therapeutics for the tau protein pathogenesis. Traditional medicine like Ayurveda has polyherbal formulations to treat neurodegenerative diseases (NDD) and memory enhancement. For instance, Saraswat formulations have been prescribed for Alzheimer's disease, epilepsy, etc., as per Baishajya Ratnavali texts.

Purpose: It has been tested in various animal models for its acetylcholinesterase (ACHE) inhibitory activities and in some cases, reduction of tau aggregates. However, there is limited knowledge of their mechanism of action. To elucidate this, it is important to understand the metabolites and their activities against the selected targets in NDD.

Methods: In this study, we have used techniques like Liquid chromatography – Mass spectroscopy (LCMS), and *in-silico* approaches to understand the metabolites of Saraswat churna (SC) and their potential activities against protein targets in tau-mediated NDD.

Results: The LCMS profile revealed the important metabolites present in SC, which were further analyzed using various databases. *In-silico* approaches revealed their interactions with the tau protein, ACHE, and other proteins involved in tau-mediated NDD.

Conclusions: This supports the use of SC against NDD and cognitive impairment, which will be further studied using *in-vitro* models.

Determining Astrocytic Heterogeneity in Hippocampal Sub-regions and Investigating Its Alteration in Epileptic Manifestations

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Background: Astrocytes, a glial subtype, are known to modulate neuronal signaling at the cellular, synaptic, and network levels. The concept of a homogenous astrocytic population has been challenged since they are known to modulate various parts of the neural circuits differentially. However, the astrocytic heterogeneity in the hippocampus is obscure despite its neuronal heterogeneity. Furthermore, it is widely known that in cases of temporal lobe epilepsy, the hippocampal region is most affected (TLE), and evidence holds that the astrocytes are the initiators of epilepsy. Our research reinforces the heterogeneity of the astrocytes in hippocampal sub-regions and its contribution to epilepsy.

Purpose: To investigate the astrocytic population and their alterations in hippocampal sub-regions during epilepsy.

Methods: Modified Golgi-Cox staining for astrocyte morphology. Patch clamp electrophysiology for glial glutamate transporter currents and Temporal lobe epilepsy induction in rats using lithium pilocarpine.

Results: Hippocampal astrocytes display disparity in their morphology and physiology across hippocampal sub-regions. Interestingly, the astrocytes' resting membrane potentials (RMPs) remained unaltered throughout the hippocampus, although the glutamate transporter currents displayed stark differences amongst the hippocampal sub-regions. Interestingly, 24 hours post epilepsy, only the CA1 astrocytes displayed changes in their morphology and the glutamate transporter currents.

Conclusion: Hippocampal astrocytes exhibit heterogeneity in their morphology and glutamate transporter currents within the hippocampal sub-regions. However, the site-specific variation in the morphology and glutamate transporter current is altered in the acute phase of epilepsy, most prominently in the CA1 region. The study suggests that astrocyte function gets altered upon epileptogenesis, well before the appearance of neuronal loss.

Oral administration of a p300/CBP specific lysine acetyltransferase activator improves motor functions and repairs spinal cord injury

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Background: Spinal cord injury (SCI) leads to the failure of sensory-motor functions because of the limited regeneration in the mature central nervous system. Electrical stimulation and rehabilitation after SCI can increase neuronal regeneration and result in some degree of recovery, but the cure is next to impossible, which leads to long-term disability and mortality. P300/CBP lysine acetyltransferase is one of the most studied epigenetic enzymes known to be involved in the repair of spinal injuries. Previously, we have demonstrated that pharmacologically activating CBP via intraperitoneal administration of a glucose-derived carbon nanosphere (CSP) conjugated p300/CBP specific KAT activator, TTK21, induced axon regeneration, sprouting, and facilitated functional recovery in both acute and chronic rodent models of SCI.

Purpose: Here, we have explored the feasibility of orally administering the KAT activator, CSP-TTK21, which is a more common and user-friendly route for drug delivery to see its effects after SCI.

Methods: In this study, we have utilized a midthoracic dorsal hemisection model of SCI. Further, using a combination of neurobehavioral, molecular biology, and microscopy techniques, we have systematically investigated the effects of orally administered CSP-TTK21 towards functional recovery and repair after SCI.

Results: We found that oral delivery of CSP-TTK21 improves motor functions and induces histone acetylation dynamics after SCI, reflecting the effectiveness of IP administration. Mechanistically, we found that CSP-TTK21 treatment increases the expression of regeneration-associated genes (RAGs) in the prefrontal cortex and cerebellum, which are associated with restored structural and functional activity after SCI.

Conclusion: Taken together, our finding highlight the potential utility of CSP as an oral drug delivery vehicle, especially when it comes to pharmacological targeting of neurological ailments. Our finding is an important step towards the oral delivery of spinal injury therapeutics, which could be highly significant for human and animal health.

Targeted epigenetic remodelling for Nervous system regeneration

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Background: The bundle of Axons that ferry the signal back and forth between the Brain and Body is critical for normal nervous system function. When injured, this disrupts the communication vital for the nervous system's function. Recovery post-injury necessitates precise transcriptional control to initiate a regenerative response coordinated by master proteins called Transcription factors (TFs). Although transcription factors are crucial for gene activation, we and others have shown that a prerequisite for transcriptional activation is the availability of relaxed chromatin around pro-growth loci.

Purpose: Attempts at genome-wide remodelling have proven ineffective in promoting regeneration. Hence, targeted remodeling is required.

Results: Our current focus is on achieving this targeted remodeling using a novel set of proteins known as 'stripe factors, as it has been observed to alter DNA accessibility following injury in regeneration-competent neurons, bolstering our hypothesis. Currently, we tested the effects of overexpression of Stripe factors for their ability to induce targeted remodelling in injured central nervous system (CNS) neurons by observing the chromatin changes.

Methods: We use a targeted approach to assess these chromatin accessibility changes by employing the Single-Nucleus Assay for Transposase-Accessible Chromatin (sn-ATAC).

Conclusion: Ultimately, our research is expected to clarify novel fundamental molecular mechanisms that control nervous system development and regeneration. In the future, our findings could help design targeted therapeutic strategies to achieve neural repair.

Identification of ABCB1 and ABCG2 as novel drug targets in Autism Spectrum Disorder by employing Network Pharmacology and Molecular Dynamics Simulations

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Background: Autism Spectrum Disorder (ASD) is a complex disease with several interconnected pathways involved in its pathogenesis. However, therapeutic targets for ASD are still elusive. The only clinical interventions available are symptomatic drugs, such as risperidone, with numerous side effects. Therefore, targeting ASD with phytochemicals can present a novel therapeutic strategy for its treatment.

Purpose: Identify and target a network of core proteins in the pathology of ASD via phytochemicals using network pharmacology, molecular docking, and simulation studies.

Methods: Cannabidiol, Crocetin, Epigallocatechin-3-gallate, Fisetin, Quercetin, and Resveratrol were selected based on their neuroprotective properties. Simultaneously, genes/proteins implicated in ASD are screened as targets of each drug, followed by network construction using protein-protein interactions, gene ontology, and enrichment analysis. The constructed network was further narrowed down to the hub genes in the network, followed by their spatio-temporal analysis, molecular docking, and molecular dynamics simulation.

Results: Data mining suggests that Cannabidiol, Crocetin, EGCG, Fisetin, Quercetin, and Resveratrol can target 50 ASD genes. Construction of the PPI network revealed 6 proteins viz. ABCB1, ABCG2, AKR1C4, MAOB, PDE4B, and XDH are recognized as hub genes. The spatiotemporal analysis of these genes indicated their significant expression in the brain. Docking results showed that two efflux proteins present in the blood-brain barrier (BBB) i.e. ABCB1 and ABCG2 can be targeted by Resveratrol and Cannabidiol, respectively, which were further validated by MD simulation.

Conclusion: The efflux transporters ABCB1 and ABCG2 in the BBB make treating neurological illnesses cumbersome and restrict the therapeutic enrichment of drugs in the brain. Targeting these transporters can be proven beneficial as their temporary inhibition by using Resveratrol and Cannabidiol may enhance drug delivery to the brain in ASD pathology.

CD40 receptor provides protective immunity against Mouse Hepatitis Virus-induced neuroinflammatory demyelination

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Background: Intracranial inoculation of murine β-coronavirus mouse hepatitis virus (MHV) A59 or its isogenic recombinant strain RSA59 causes meningoencephalitis, demyelination, and axonal loss, mirroring the key features of the human neurological disease Multiple Sclerosis (MS). Taxonomic microarray data in RSA59-infected spinal cord samples revealed the upregulation of CD40/CD40L signaling genes. Previous studies suggest CD4+ T cells and its activation marker, CD40L, play a protective role against the infection, raising questions about the neuromodulatory role of CD40R.

Purpose: MHV infection causes a biphasic disease progression, starting with an acute-innate phase followed by a chronic-adaptive phase. The innate immune system sets the stage for adaptive immunity. CD40R and CD40L connect these two phases and ameliorate the disease course.

Methods: Intracranial inoculation of RSA59 was performed on age-matched C57BL/6 WT and CD40-/- mice at 2500 PFUs. Following this, they were sacrificed on various days (like 5,7,10, and 30) post-infection to perform Real-time PCR, Western Blot analysis, Histopathology, and Flow cytometry.

Results: The study shows that the absence of CD40 leads to severe weight loss, clinical disease symptoms, and reduced survival rate. Concurrently, impaired activation and priming of CD4+ T cells in the CLN, resulting in fewer effector CD4+ T cells (CD4+CD44+), was observed. This also caused reduced CX3CR1 expression in immune cells, hindering CD4+ T cell trafficking to the CNS. Additionally, microglia and macrophages showed reduced antigen presentation (MHCII) and lower IFN-γ production from CD4+ T cells, resulting in persistent viral particles in the CNS. This persistence shifted microglia/macrophages to a phagocytic state, leading to severe neuroinflammation in the brain and significant demyelination in the spinal cord during the chronic stage. In CD40-/- mice, neutrophils increased, possibly compensating for the reduced inflammatory response from microglia/macrophages. Furthermore, Ifit2 levels were significantly elevated during acute and chronic stages due to increased viral persistence, providing antiviral support.

Conclusion: CD40R plays a neuroprotective role in the MHV-induced demyelinating disease model of MS.

Developing and comparing the utility of two chronic stress induced zebrafish models to advance antidepressant research

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Background: In translational research, the zebrafish (***Danio rerio***) has become a model organism for applications ranging from compound library screening to pre-clinical drug development. Accelerated treatment development still demands, nevertheless, an economic effective and appropriate depression model which suits the multipurpose needs.

Purpose: Sex as a biological variable in the antidepressant response is being acknowledged now in the light of differential etiopathophysiology of depression in men and women. However, to avoid complications,'sex' as a variable can be avoided in our initial compound library screening. To address both the aspects, two stress induced zebrafish models, Chronic Unpredictable Stress (CUS) and Chronic Predator Stress (CPS) were developed and compared.

Methods: For CUS, zebrafish were exposed to a 10-day paradigm consisting of 10 different stressors, two per day in an unpredictable sequence, in forenoon and afternoon. CPS was based on the resident-intruder paradigm, wherein a single zebrafish (intruder) was subjected for 5 days of direct hostile confrontations with a resident aggressive Cichlid fish for a brief duration daily, followed by the behavioral assessment.

Results: Our results showed that both the sexes were affected with depressive phenotypes upon both CPS and CUS paradigms. Interestingly, only the CUS model has exhibited clear sex differences for apparently similar depressive phenotypes on behavioral and molecular evaluation as the immunohistochemistry of zebrafish brain displays a clear sex difference in inflammatory and neurotrophic factors expression of male and female stressed zebrafish. Unlike this, CPS model displayed more or less similar stress-response across the sexes as the resident is heterospecific.

Conclusion: CPS could be very helpful for the preliminary compound library screening to the pre-clinical studies for it is a simpler *in vivo* system. However, CUS would be more appropriate to be used further to identify new sex-specific targets for depression.

Nano-neonicotinoid pesticide induced *in vitro* toxicity and immunohistochemical changes in brain regions of mice

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Background: The use of nano formulation of pesticides has recently been increased in the agriculture sector to enhance its efficacy towards pest control. However, their non-targeted toxicity is not yet reported due to lack of studies. In view of the exposure pattern of these pesticides, there is a strong need to assess the neurotoxic effects of nano-pesticides to explore its toxicity pattern and mechanism of action.

Purpose: The present study has been carried out to explore the neonicotinoid insecticides and its nano-formulation induced *in vitro* toxicity, histological and immunohistochemical changes in brain regions of mice.

Methods: Male mice (30±2g) were divided into 4 groups and treated with nano-formulations of neonicotinoid insecticides i.e. nano-acetamiprid and nano-imidacloprid (both at the dose of 25mg/kg body weight p.o) and combination of both the formulations for 28 days. The control group of mice were administered normal saline during these days. After 28 days, mice were sacrificed, brains were dissected out and processed for analysis.

Results: The *in vitro* toxicity of neonicotinoid insecticides and its nano-formulations were assessed in L929 cell lines and it was observed that the toxicity of nano-formulations of pesticides were higher as compared to normal neonicotinoid insecticides at various concentrations (0.01 to 50 μM) and at different time points. Further, the alterations in histology and immunohistochemistry of signalling proteins were also observed in various brain regions.

Conclusion: The present study suggested that the Nano-formulations of acetamiprid and imidacloprid have higher toxicity pattern as compared to normal neonicotinoid insecticides in *in vitro* studies at various concentrations in time dependent manner. It also affects the histology and immunohistochemical expression of signalling proteins in different brain regions suggesting its neurotoxic effect.

Bulk ATAC Sequencing to Determine Differential Accessibility Patterns Around Developmental Stages

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Background: Spinal cord injuries (SCI) often lead to severe and permanent functional impairments due to the limited regenerative capacity of the adult mammalian central nervous system (CNS). The inability of axons to regenerate following SCI is a significant barrier to recovery, influenced by both intrinsic neuronal properties and the inhibitory environment of the CNS, which restricts the expression of growth-specific genes (pro-growth genes).

Purpose: It is well understood that chromatin closure is more pronounced in adult mammals compared to early postnatal stages. However, the exact stages at which chromatin closure occurs remain debated. We and others have shown that in early postnatal stages (P0), chromatin accessibility is significantly higher, facilitating active gene expression necessary for growth and development. As organisms age, chromatin progressively becomes more restricted, leading to decreased accessibility in adult stages. This reduction in chromatin accessibility likely impairs the regenerative capacity of neurons. It remains uncertain whether this reduction occurs progressively or if there is a critical period marked by a sudden decrease.

Methods: To address this, Bulk ATAC (Assay for Transposase-Accessible Chromatin) sequencing is performed in various developing stages.

Results: Currently**,** we have checked the chromatin accessibility changes along the developmental stages by collecting the required samples and proceeding with the Bulk ATAC sequencing

Conclusion: This technique enables the identification of regulatory elements and epigenetic modifications associated with axon regeneration on a genome-wide scale. Such insights can pinpoint critical periods for therapeutic intervention.

Neural correlates of sleep in the high-level visual and motor cortex of monkeys

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Background: Neural activity in monkeys is typically recorded in highly constrained and artificial environments, which limits the study of natural behaviors such as sleep. Sleep is a conserved behavioral state that is critical for brain health, but its neural correlates especially at the resolution of single neurons, remain underexplored, even in nonhuman primates, due to the lack of suitable recording setups.

Purpose: This study aimed to examine neural activity during natural sleep in monkeys, using wireless recordings from high-level visual and motor brain areas.

Methods: We recorded neural activity wirelessly from 256 electrodes implanted in high-level visual areas (inferior temporal cortex - IT) and high-level motor areas (ventral premotor cortex – PMv & ventrolateral prefrontal cortex – vlPFC) of two monkeys. They slept unrestrained in a naturalistic environment. Sleep and wake states were inferred based on the head position and body movements, from infrared video recordings, in the absence of muscle tone (EEG/EMG) measurements. Data was collected over a roughly 2-hour period in both animals, as they transitioned multiple times between sleep and wake states.

Results: (1) Neural activity in PMv was lower during sleep compared to wake, while vlPFC activity was higher during sleep; neural activity in IT showed both increases and decreases. (2) Delta-band (04 Hz) spectral power in the local field potentials (LFPs) was higher during sleep in all three regions. (3) Linear classifiers trained on both multiunit activity and LFPs could reliably distinguish sleep from wake states, with a gradual transition observed between these states.

Conclusion: Our findings reveal systematic changes in neural activity across high-level visual and motor areas during sleep in monkeys, which are broadly consistent with previous literature.

Mapping the binding dynamics of pro-growth transcription factors across development and regeneration

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Background: Spinal cord injuries cause degeneration of axons below the injury site, resulting in permanent paralysis and loss of communication. Regenerating these axons could significantly improve nerve repair and functional recovery. Transcription factors (TFs) have shown promise in promoting axon regeneration. Recently, we identified a class of proteins known as the Nuclear Receptor Family of Transcription Factors (NRTFs), which enhance neurite outgrowth in vitro. However, the specific binding locations of these factors in vivo are not well understood.

Purpose: The goal of this study is to map the binding dynamics of NRTFs across key developmental stages and following spinal cord injury. Understanding these binding sites will help infer gene regulatory networks that control axon regeneration, ultimately guiding the development of targeted therapies for nerve repair.

Methods: Traditional methods like ChIP-seq are limited by large sample requirements, high background noise, and labor-intensive processes. To address these challenges, we are using CUT&RUN technology, which provides improved signal-to-noise ratio with less input material. CUT&RUN will be employed to identify NRTF binding sites during development and post-injury, creating a detailed map of their interactions.

Results: Preliminary CUT&RUN data reveal distinct NRTF binding patterns at different developmental stages and after injury, suggesting key regulatory roles in axon regeneration. The technique's high resolution and low background have allowed us to identify specific genes potentially involved in the regenerative process.

Conclusion: Our findings advance the understanding of NRTF binding in axon regeneration. The detailed binding maps generated by CUT&RUN may uncover gene regulatory networks that are crucial for nerve repair, paving the way for new therapies to restore function after spinal cord injuries.

Single-cell genomics analyses reveal injury distance as a critical barrier to regeneration in CNS neurons

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Background: Central nervous system (CNS) injuries often result in limited regeneration, severely constraining recovery. While the regenerative responses of peripheral nervous system (PNS) neurons have been well characterized, the injury response of most CNS cell types remains largely unknown. This gap in knowledge hinders the development of effective therapies for spinal cord injuries.

Purpose: This study aims to investigate the transcriptional responses of diverse supraspinal cell types, including corticospinal tract (CST) neurons, to different types of spinal cord injuries in mice, with the goal of understanding the mechanisms underlying their limited regenerative capacity.

Methods: Single-nuclei sequencing was used to profile the transcriptional responses of various supraspinal cell types in mice subjected to thoracic spinal injury, cervical injury, and intracortical axotomy. The extent of gene expression changes was compared across these different injury types, focusing on CST neurons. Transcripts related to regeneration and apoptosis were analyzed to identify commonalities between CNS and PNS neuron responses.

Results: Thoracic spinal injury induced only modest changes in gene expression across all examined supraspinal cell populations, including CST neurons. Similarly, CST neurons exhibited a minimal response to cervical injury but showed a significantly stronger transcriptional response to intracortical axotomy. This robust response to intracortical injury included the upregulation of numerous regeneration- and apoptosis-related transcripts, which were also observed in injured dorsal root ganglion (DRG) and retinal ganglion cell (RGC) neurons.

Conclusions: The subdued transcriptional response of CST neurons to spinal cord injury appears to be related to the distant location of the injury rather than intrinsic properties of the neurons. These findings suggest that a major challenge in promoting regeneration after spinal injury is the limited detection of distant injuries, which leads to a modest baseline neuronal response. Enhancing this detection could be crucial in developing effective regenerative therapies for spinal cord injuries.

Retinal Revelations: OCT-A's insights into cognitive functioning and dementia risk in aging rural Indian population

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Background: Vascular contributions to cognitive impairment and dementia(VCID) is one of the leading causes of dementia. The shared embryological and anatomical features between retina and brain present unique opportunities to investigate cerebrovascular changes via retinal imaging.

Purpose: Optical Coherence Tomography-Angiography(OCT-A) serves as a tool for assessing retinal microvasculature, which could be explored as a potential biomarker for cognitive impairment and dementia risk.

Methods: We analysed the baseline cross-sectional data(n=609) from the Centre for Brain Research-Srinivaspura Aging, NeuroSenescence and COGnition(CBR-SANSCOG), a prospective cohort in rural southern India. Participants aged 45+ years, without dementia, underwent OCT-A(CIRRUS HD-OCT Model-6000) assessing the foveal avascular zone area(FAZ), macular vessel density(MVD) and perfusion density(MPD) for central 1mm(MVDC1,MPDC1), 3mm inner-ring(MVD3IR,MPD3IR), 6mm outerring(MVD6OR,MPD6OR) and full mean(MVDFM,MPDFM). Individuals with ocular vitreoretinal interface diseases, history of ocular surgery, high refractive errors(≥±6D), or poorquality scans were excluded. Cognition was assessed across multiple domains by using the culturally adapted neuropsychological battery-COGNITO(Computerized Assessment of Adult Information Processing). Dementia risk was assessed using the Cardiovascular Risk Factors, Ageing and Dementia(CAIDE) score(n=519). The associations of ocular parameters with cognitive performance and CAIDE were examined using the General Linear Model(GLM) adjusted for covariates and results reported as β[95%CI],p-value.

Results: Our study sample had a mean age of 54.1±7.4 years(34.97% females). Only MVDC1 was associated with the language domain(0.03[0.001,0.058],p=0.04). The CAIDE score was significantly associated with the MVDC1(-0.143,[-0.205,-0.052],p=0.001), MVD3IR(-0.255,[-0.794,- 0.404],p<0.001), MVD6OR(-0.216,[-0.690,-0.305],p<0.001), MVDFM(-0.240,[-0.786,-0.383],p<0.001), MPDC1(-0.141,[-8.816,-2.195],p=0.001), MPD3IR(-0.243,[31.805,-15.618],p<0.001), MPD6OR(-0.222,[-27.951,--12.731],p<0.001) and MPDFM(0.244,[-32.323,-15.984],p<0.001).

Conclusion: Our study demonstrates that while altered retinal vasculature and perfusion is associated with a higher dementia risk-score, reduced MVDC1 is associated with poorer performance in the language domain. These results may be leveraged to prioritize the cognitive screening of individuals with below average MVD and MPD, highlighting the utility of OCTA as an early biomarker of cognitive impairment and a potential predictor of dementia.

Altered neurovisceral integrity in individuals with comorbid alcohol use disorder and adult attention deficit hyperactivity disorder

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Background and Purpose: Attention deficit hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder which has a relation with development of substance use disorders in adulthood. Physiological link between the two disorders may involves the common network activities of the central autonomic network and frontal cortex. Hence there is a need for further research on the correlation between the cardiac, cognitive and behavioural parameters in these individuals sharing comorbid alcohol use disorder (AUD) and adult ADHD.

Materials and Methods: 90 Study subjects (males aged 18-50 years) admitted to deaddiction department of NIMHANS were divided into 3 groups with 30 subjects in each group: Alcohol use disorder (AUD) with/without co morbid Adult ADHD and compared with control subjects from general public. Study groups were subjected to heart rate variability, echocardiography, conventional autonomic function tests, pupillometry, go no go task, stop signal task and paired pulse transcranial magnetic stimulation paradigms.

Results: AUD and comorbid adult ADHD groups showed moderate to severe cardiac autonomic dysfunction, reduced parasympathetic activity, altered echo parameters, decreased reaction time implying more impulsivity. We found correlation between various neurobiological measures between individuals from all three groups with adult ADHD group showing severe impairment in all parameters. Our results implying altered neurovisceral integration in these individuals.

Conclusion: Our study demonstrates the importance of regular screening in these individuals who are vulnerable to develop severe dysfunction and in suggesting measures to improve the quality of life in these individuals.

Neuroprotective roles of daidzein in chronic unpredictable mild stress mice through ERK1/2 and mTOR-dependent pathway

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Background: Depression is a neuropsychiatric disorder that causes behavioral, biochemical, and molecular dysfunctions. Growing evidence suggests a link between depression and estrogen involving brain functions, such as cognition, memory, neuroprotection etc.

Purpose: Daidzein is a phytoestrogen that mimics the functions of mammalian estrogen and has a wide range of biological activities, such as antioxidation and neuroprotection. Daidzein regulates gene expressions through extracellular signal-regulated kinases (ERKs) and mammalian target of rapamycin (mTOR) dependent pathway. However, the significant roles of daidzein in depression involving ERK1/2, pERK1/2, and mTOR are still elusive.

Methods: Briefly, the chronic unpredictable mild stress (CUMS) mouse model was prepared, and placed in six groups, namely, control, CUMS, CUMS vehicle, CUMS DZ, CUMS PHTPP (ERβ blocker, and CUMS Untreated. Daidzein was supplemented orally to CUMS DZ mice, and PHTPP was supplemented intraperitoneally to CUMS PHTPP mice for 3 weeks. Further, behavior and enzyme assays were performed. To determine the expression of the ERK1/2, pERK1/2, and mTOR immunofluorescence and immunoblotting were done.

Results: Daidzein-supplemented CUMS mice exhibited decreased depressive and anxiety-like behavior and improved ERK1/2, pERK1/2, and mTOR expressions. Additionally, SOD, catalase and acetylcholinesterase levels were also improved. Further, CUMS PHTPP group showed deficits in behavior, low expression of ERK1/2, pERK1/2, and mTOR, and no significant changes in SOD, catalase, and acetylcholinesterase levels.

Conclusion: Collectively, this study suggests that daidzein may ameliorate depressive and anxiety-like behavior through ERK and mTOR pathways through ERK1/2, pERK1/2, and mTOR. Such a study may be useful to understand daidzein-dependent neuroprotection through ERβ in depression.

Pathology-specific lipid alterations with triacylglycerol as a potential biomarker in Focal cortical dysplasia (FCD) and Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS)

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Background: Focal cortical dysplasia (FCD) is a common pathology in drug-resistant epilepsy (DRE), accounting for one-third of surgical cases. A key challenge in treating FCD is the failure to accurately localize epileptogenic zones (EZs), leading to poor surgical outcomes. Currently, there are no molecular or cellular biomarkers to aid in defining EZs. This study aims to identify altered lipid profiles in resected tissues from FCD and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients using liquid chromatography coupled with high-resolution tandem mass spectrometry, compared to autopsy samples.

Methods: Lipids were extracted from frozen brain tissues using a modified Bligh & Dyer method. Separation was performed on an ExionLC™ system with a Waters AQUITY UPLC BEH HILIC column, followed by analysis using a SCIEX QTRAP® 6500+ LC-MS/MS system. A theoretical multiple reaction monitoring (MRM) library was generated using LIPIDMAPS for lipid identification and quantification. Data were processed using MultiQuant™ 3.0.2 software, with intensity values normalized to spiked internal standards. Missing values were imputed using MetaboAnalyst software (v5).

Results: A total of 1224 lipids were detected, with 607 in positive mode and 617 in negative mode. Thirteen lipids were significantly altered in FCD compared to autopsy samples ($p<0.05$, fold-change ≥ 2), including upregulated triacylglycerols (TAGs) and downregulated phosphatidylcholine (PC) and phosphatidylethanolamine (PE). Both FCD and MTLE-HS exhibited significant TAG upregulation. Additionally, plasma triglyceride levels were measured in FCD, MTLE-HS patients, and healthy controls.

Conclusion: Distinct lipid profiles, particularly involving TAGs, DAGs, PC, and PE, were observed in FCD tissues compared to autopsy. These lipid signatures could serve as biomarkers for defining EZs and may support the development of REIMS-based techniques for surgical guidance. Plasma TAG levels also hold potential as biomarkers, pending validation in larger cohorts.

Dysregulation of Glucocorticoid Receptor Signalling under Neuronal Insulin Resistance

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Background: Insulin signalling is INVOLVED in neuronal survival and plasticity which plays a significant role in improving learning and memory functions. The abnormalities in brain insulin signalling are associated with the aging process and altered brain plasticity. Glucocorticoid receptors (GRs) are key regulators of the brain's response to stress, playing a critical role in the modulation of gene expression involved in inflammation, metabolism, and neuroplasticity.

Purpose: This study investigates the dysregulation of glucocorticoid receptor expression on plasma membrane under neuronal insulin resistance condition.

Methodology: An insulin resistance model was generated to substantiate this hypothesis in N2a neuroblastoma cell using palmitic acid (200 μM) along with Dexamethasone (1μM) for 24 hours following insulin stimulation (100nM) at different time points (0 min, 5 min, 30 min, and 60 min). Further we have investigated GR localization and the downstream pathways in our experimental setup.

Results: Using in-vitro model, we demonstrated that GR expression on plasma membrane in PA treated cells was found to be significantly decreased ($p<0.05$) while, in whole cell lysate the expression was not significantly altered. Moreover, GR expression on plasma membrane in cells treated with PA+ Dexamethasone (1μM) was significantly decreased ($p<0.05$). Further, we observed expression of $pAKT^{S473}$, pGSK$3\beta^{S9}$ and $pCREB^{S133}$ level in whole cell lysate. A blunted response was obtained with no significance in the kinetics of $pAKT^{S473}$ and $pGSK3\beta^{S9}$ and no alterations were observed in the total AKT and GSK3β levels. Expression of $pCREB^{S133}$ level was significantly ($p <0.001$) increased in time-dependent manner and no significant change was observed in the total CREB level. Additionally, $pFOXO3^{253}$ level was decreased significantly ($p<0.001$) from 0min to 120min.

Conclusion: Insulin resistance significantly alters GR expression on the plasma membrane, which may contribute to impaired neuroplasticity under depressive conditions.

Effect of melatonin on the daily rhythms of serotonin metabolism in amyloid-β induced Alzheimer disease's (AβIAD) Male Wistar Rat model

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Background: Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by cognitive decline and memory loss. One of the primary pathological hallmarks of AD is the accumulation of amyloid-beta (Aβ) plaques in the brain, which disrupt normal cellular processes and contribute to neuronal death. Disruption of the sleep/wake cycle, highly fragmented and shifted sleep patterns, and significant behavioral abnormalities related to the circadian rhythm are key characteristics of AD. Serotonin (5-HT) metabolism is also altered in AD, leading to dysregulation of neurotransmitter levels. Melatonin is a neurohormone primarily produced in the pineal gland and may be a potential therapeutic agent for AD owing to its antioxidant, anti-inflammatory, free radical scavenging, and neuroprotective properties. Alterations in the rhythmic dynamic of interactions between various components of serotonin metabolism and the molecular clock were measured.

Purpose: The purpose of our study is to investigate the impact of melatonin on the rhythmicity of serotonin metabolism in the AβIAD Rat model.

Materials and Methods: Male Wistar rats were used to mimic the early stages of AD by using an amyloid-β induced Alzheimer's disease model (AβIAD). Samples were collected at four different time points such as zeitgeber time (ZT)-0, 6, 12, and 18 from all groups. Serotonin (5-HT) metabolism components were measured by reverse phase high-performance liquid chromatography (RP-HPLC) using an EC detector. Graph Pad Prism 8.0, and Sigma stat 11.0 software were used for statistical analysis.

Results: We have observed differential rhythmic patterns of the components of the serotonin metabolism studied in the case of Vehicle, AD, and AD+MEL groups.

Conclusion: Our work helps to understand the rhythmicity and robustness of various components of serotonin metabolism in AβIAD rat model. Hence gives insights into the role of the clock in the regulation of peripheral clocks and the progression of neurodegeneration in the case of AD.

Inducible nitric oxide synthase might play a role in myelin regeneration after demyelination caused by murine β-coronavirus.

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Background: White matter injury and axon, myelin, and oligodendrocyte loss in multiple sclerosis(MS) disrupt neurological function. Remyelination restores myelin and abets recovery. Understanding these mechanisms could ameliorate MS therapies. Our lab established an RSA59-induced demyelinating mouse-model that mimics certain pathologies of MS. A recent study from our lab showed that the absence of inducible nitric oxide synthase(NOS2), a pro-inflammatory marker of microglia/macrophage, causes early demyelination at day9/10 post-infection and severe demyelination at day30 post-infection. This result suggests NOS2 has a protective role in RSA59-induced demyelination, but its contribution to remyelination remains unclear.

Purpose: This study explores the role of NOS2 in the remyelination process following RSA59-induced demyelination. As oligodendrocyte progenitor cells(OPCs) are essential in remyelination, this study also aims to investigate how the deficiency of NOS2 affects OPC infectivity followingRSA59-infection and differentiation of OPCs into mature-oligodendrocytes.

Method: Luxol-Fast-Blue staining and immunofluorescence were performed on the spinal-cord and brain sections of C57BL/6wild-type mice, respectively, to assess myelin-restoration. The markers of active microglia, myelin, and mature-oligodendrocytes were confirmed via immunohistochemistry, immunofluorescence, and Western-blot. Gene expression was analyzed through qRT-PCR. OPCs from NOS2-/-and wild-type-mice were isolated, infected withRSA59, and characterized by immunofluorescence.

Results: Notable upregulation in mature-oligodendrocyte and myelin markers and a significant reduction in demyelinating-plaques were found in infected mice brains and spinal-cords, respectively, at day60 post-infection, indicating ongoing remyelination. In the remyelination-phase, activated microglia in the infected brain were different morphologically and functionally from those in the demyelination-phase. Moreover, the expression of NOS2 increased noticeably during remyelination.A comparative assessment of OPC infectivity and differentiation betweenNOS2-/ and wild-type-mice further suggested NOS2's involvement in myelin regeneration.

Conclusion: Differential analysis of OPC infectivity and differentiation in NOS2-/-versus wild-type-mice and increased NOS2 expression concomitant with reduced demyelination indicate the role of NOS2 in remyelination afterRSA59-induced demyelination. This study highlights NOS2 as a therapeutic target in promoting myelin-repair in demyelinating diseases.

Impact of White Matter Hyperintensity in Caudate and Frontal Horn Distance mediated by Lateral Ventricle Enlargement

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Background: With aging, the brain undergoes structural changes, including atrophy or shrinkage. Since the caudate nucleus is a part of the brain's circuitry involved in executive functions, memory, and other cognitive abilities, changes in the size or shape of the caudate nucleus, or the distance between them, may potentially lead to changes in cognitive behaviors. Simultaneous changes in frontal horn distance are indicative of neurological diseases. Changes in caudate and frontal horn distance may get accelerated in presence of White Matter Hyperintensity, leading to disrupted communication between brain regions, setting up a platform for transition of the aging subject to Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD).

Purpose: The study investigates the impact of small vessel disease and white matter hyperintensity (WMH) load on Caudate and Frontal Horn distances with aging, using brain MRI segmentation and WMH lesion segmentation.

Methods: T1-weighted and T2-FLAIR MRI images from 500 cognitively normal (CN) subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort were included in the study for neuroanatomic segmentation to determine brain regional volumes and white matter hyperintensity (WMH) load. The subjects were stratified in 3 groups based on WMH load: 0-1 ml, 3-5 ml, and 5-10 ml to explore the impact of WMH on inter-table width (IT), caudate distance (CC), and frontal-horn distance (FH), CC/IT, FH/IT, and FH/CC ratios. Further, a mediation model analysis was conducted to examine direct and indirect impacts of WMH.

Results: The CC, FH, CC/IT, and FH/IT ratios increase with age in CN subjects, whereas the FH/CC ratio declines but IT remains constant. Furthermore, the CN subject showed the enlargement of the lateral ventricle (β=1.06 ml/year, $p<0.001$) with age but caudate volume (β=-0.01 ml/year, $p=0.16$) remained constant. However, when WMH load exceeded 3ml, there was a significant increase in CC, CC/IT, and FH/IT ratios, with the lateral ventricles mediating alternations in CC(β=0.022 ml/year, $p<0.01$), FH(β=0.011 ml/year, $p<0.01$), CC/IT(β=0.151 ml/year, $p<0.01$), FH/IT(β=0.002 ml/year, $p<0.01$), and FH/CC(β=-0.022 ml/year, $p<0.01$) ratios.

Conclusion: Accumulation of White matter hyperintensity load more than 3 ml leads to significant changes in Caudate and Frontal horn distance mediated through the enlargement in lateral ventricles

Impact of LRRK2 I1371V Mutation on Membrane Dynamics and Inflammatory Responses in Astrocytes Derived from PD Patient iPSCs

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Background: LRRK2 is a key player in inherited Parkinson's disease, with different pathological variants showing ethnic biases—G2019S in Caucasians and I1371V in East Asians. Despite its prevalence, the mechanisms underlying the I1371V mutation remain underexplored, necessitating further research. Variation in symptoms and treatment responses highlight the need to comprehend the effect of different mutations on cellular function in PD. Post mortem data have revealed the presence of Lewy bodies in individuals with the I1371V mutation, suggesting distinct pathological processes compared to G2019S cases, involving extracellular α-synuclein accumulation. Astrocytes, crucially clear extracellular α-synuclein however its accumulation can perturb astrocyte function without impacting cell survival, exacerbating α-synuclein-mediated pathology. As astrocytes are vital for clearing α-synuclein, their dysfunction could contribute to dopaminergic neurodegeneration.

Purpose: To assess how the mutation affects membrane fluidity and extracellular α-synuclein interaction in astrocytes derived from PD iPSCs.

Methods: The effect of the mutation on the α-synuclein association in the astrocytes derived from HC and PD astrocytes and how the plasma membrane plays a role in it has been investigated. Additionally, the pathophysiology of extracellular α-synuclein treatment on the HC and PD astrocytes has also been looked into.

Results: Reduced extracellular α-synuclein association and uptake is observed in PD astrocytes due to alterations in membrane cholesterol and fluidity, and ganglioside expression the reason being the increased Rab8A and Rab10 phosphorylation due to the mutation. PD astrocytes shows intrinsic higher ROS and RNS levels which further elevates upon treatment with extracellular α-synuclein contributing to the increased expression of phosphorylated alpha-synuclein (p-Syn) and nitrated alpha-synuclein (n-Syn) respectively, however the cell viability is not affected.

Conclusion: The decreased association of α-synuclein in PD astrocytes, alongside reduction in cholesterol levels and membrane fluidity, highlights pathophysiology in PD, underscoring the importance of unraveling variant-specific impacts on cellular function.

Leveraging Transcription Factor EB Activation to Enhance Autophagy and Reduce Protein Aggregation: A Potential Therapeutic Approach for Parkinson's Disease

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Background: Parkinson's disease (PD) is pathologically characterized by the aggregation of α-synuclein (α-syn), which results from impaired intracellular protein degradation systems such as the ubiquitin-proteasome system and the autophagy-lysosomal pathway (ALP). Transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy, has been shown to activate ALP. However, the role of TFEB in PD pathology, particularly its potential as a therapeutic target, requires further investigation.

Purpose: This study aims to explore the role of TFEB in mitigating α-syn aggregation and neurodegeneration in *an in vitro* rotenone model of PD using differentiated human neuroblastoma SH-SY5Y cells.

Methods: Green fluorescent protein (GFP)-α-syn-overexpressing or control SH-SY5Y cells were treated with rotenone to induce α-syn aggregation and subsequent neurodegeneration. Immunostaining for phosphorylated Ser129 (pS129), a marker for PD progression, was employed to detect α-syn aggregation. TFEB sub-cellular localizations were examined by immunostaining, and lysosomal biogenesis was assessed by measuring lysosomal associated membrane protein 1 (LAMP1) expression.

Results: Rotenone treatment increased α-syn aggregation in SH-SY5Y cells, as evidenced by pS129 immunostaining. GFP-TFEB overexpression significantly reduced rotenone-induced α-syn aggregation and afforded significant neuroprotection. In control cells, TFEB predominantly localized in the cytoplasm. While acute (12 hours) rotenone treatment prompted its translocation to the nucleus, chronic treatment (72 hours) impaired it. Additionally, rotenone-treated GFP-TFEB overexpressed cells displayed elevation of LAMP1 level, indicating enhanced lysosomal biogenesis along with increased viability of rotenoneinsulted neuron-like cells.

Conclusion: Our findings demonstrate that GFP-TFEB overexpression can ameliorate α-syn aggregation, potentially through the upregulation of lysosome biogenesis. Pharmacological activation of TFEB could thus represent a promising therapeutic approach for PD. Future research will focus on identifying small molecules that activate TFEB with the goal of promoting autophagic clearance of α-syn aggregates in PD models.

The interaction of CD4+T-cells, macrophages, and Tregs is crucial in producing an effective immune response in adult C57BL/6 mice in murineβ-coronavirus induced neuroinflammation

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Background: Multiple Sclerosis (MS) is a chronic demyelinating disease of the Central Nervous System (CNS), and understanding T-cell regulation is crucial for understanding immunopathology. The Mouse-Hepatitis-Virus (MHV) induced MS model helps explain virus-induced neural-cell damage and demyelination. Previous studies have shown CD4+Tcells not only interact with microglia/macrophages, causing their activation during acute neuroinflammation, but also restore homeostasis during the chronic-phase of demyelination, unlike the Experimental-autoimmune-encephalomyelitis model, where T-cells are myelinolytic.

Purpose: This study focuses on understanding mice's age-dependent (juvenile 4-week-old and adult 6-7-week-old mice) immunological maturity post MHV-RSA59-induced acute neuroinflammation and progressive chronic-phase demyelination.

Methods: Hematoxylin&Eosin Staining, Luxol-Fast-Blue Staining, immunohistochemistry, immunofluorescence, plaque-assay, immunoblotting, q-RT-PCR, flowcytometry.

Results: Adult mice showed lesser virus replication during the acute and acute-chronic transition phases. Immunophenotyping at the acute-phase revealed higher infiltration of neutrophils, MHCII, and CX3CR1-activated macrophages, IFN-γ expressing CD4+ and CD8+T-cells in the CNS of adult mice. Immunophenotyping at transition-phase revealed higher infiltration of MHCII and CX3CR1-activated macrophages, IFN-γ expressing CD4+Tcells, and Tregs in the CNS of adult mice. However, numbers of CD8+T-cells was significantly lower in adult mice. So, the adult mice exhibited greater immune maturation, and Tregs helped restore homeostasis in CNS. Immunophenotyping of the Cervical lymph node revealed that adult mice had significantly lower numbers of effector CD4+ and CD8+Tcells and a higher number of Tregs, which probably reduced the population of effector Tcells. Furthermore, presence of a high number of central memory T-cells in adult mice typically implies an effective immune response in case of pathogen re-exposure. At the chronic-stage, adult mice suffered from significantly less demyelination. Also, persistence of amoeboid-phagocytic microglia/macrophages around demyelinating plaques was significantly less in adult mice's spinal cords.

Conclusion: CX3CR1 and MHC II-activated macrophages, IFN-γ expressing CD4+T-cells, and CD8+T-cells reduce viral load at the acute-phase. At transition-phase, adult mice had greater Tregs infiltration, which reduced effector CD8+T-cells migration, setting the stage for homeostasis.

Restorative potential of dysregulated miRNA in arsenic-induced neurotoxicity in human mesenchymal stem cells

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Background: Arsenic neurotoxicity and developmental neurotoxicity are well established in both pre-clinical experimental and clinical setups. The treatment modalities that have been explored are palliative only and need a target-specific cure against acute to chronic exposure to arsenic through environmental and occupational exposure.

Purpose: The studies have suggested the dysregulation of miRNAs following exposure to arsenic and other heavy metals. However, the status of miRNAs associated with arsenic intoxication in human Mesenchymal Stem cells (MSCs) is yet to be explored. Hence, the studies were conducted to investigate the specific miRNAs involved in arsenic intoxication and their potential applicability in the mitigation of such damages. Further, the protective potential of quercetin, a polyphenolic bioflavonoid, has also been explored in arsenic-exposed MSCs.

Methods: MSCs were exposed to $_{10\mu M\ of}$ arsenic for 48h after which detailed miRNA and mRNA profiling were performed using TaqMan-based open array systems. Furthermore, we also evaluated the restorative effects of quercetin (10μM) on MSCs exposed for 24h.

Results: MicroRNAome profiling revealed that 20 miRNAs were dysregulated in MSCs following arsenic exposure, with 11 and 9 miRNAs significantly upregulated and downregulated, respectively. These deregulated miRNAs were enriched in pathways such as cell cycle, autophagy, cell senescence, and the p53 signalling pathway. The results of mRNA profiling revealed upregulation in 5 genes along with downregulation in 53 genes. HMOX-1, a marker of oxidative stress, exhibited the most significant upregulation, indicating redox imbalance in cells. The functional enrichment of deregulated genes indicated their involvement in cell survival, genomic stability, mitochondrial homeostasis, apoptosis, and autophagy.

Conclusion: Our study revealed that miRNAs are potential mediators of arsenic-induced toxicity in MSCs. These potential pleiotropic regulators could be explored for their diagnostic and therapeutic roles in regulating toxicity mechanisms induced by heavy metal exposure.

The effect of performance and sensory errors on visuomotor adaptation

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Background: The human motor system has a remarkable ability for adaptive motor learning, driven by error caused by perturbation from the external environment or the system itself. Traditionally, in visuomotor adaptation tasks, the errors caused by the perturbations are mainly divided into Task-Based Error (TBE) – caused by failure to achieve the goal and Sensory Prediction Error (SPE) – caused by a discrepancy between expected and actual sensory outcomes, supposedly driving the explicit and implicit component of learning respectively. Further, these error signals have distinct adaptation properties such as learning rate, savings, and retention (extent of unlearning).

Purpose: Typically, these error signals co-occur in most visuomotor adaptation tasks and are inferred by an inverse approach which is supposedly considered as a linear combination. Consequently, it's not clear whether these distinct properties represent the function of these systems operating in isolation or due to their interactions.

Methods: Considering this, we conducted a Target Jump task and a Gradual Rotation task, whose perturbation leads to the adaptation of TBE and SPE, in isolation—allowing us to use a forward approach to study their contribution to motor adaptation. To study interaction of TPE and SPE, we conducted a Combined task in which subject experienced target jump and gradual rotation perturbation simultaneously and measured the properties of adaptation which had components of TBE and SPE.

Results: Expectedly, we observed that the TBE learning associates with fast learning, savings, and lack of retention. In contrast, SPE learning expressed with slow learning, no savings, and robust retention. The Combined task exhibited properties of learning and retention that reflected contributions of both TBE and SPE learning with intermediate expression of adaptation properties compared to learning of two system in isolation. A more detailed comparison with simulated data showed some degree of interaction between TBE and SPE learning, indicating the lack of total linearity which was observed by overcompensation of movements while adapting the perturbations.

Conclusion: These findings suggest that TBE and SPE-based learning are mediated in part by two distinct independent systems. Upon combination these two systems learning leads to intermediate adaptive properties with some form of interaction.

Neurodevelopmental Defects in the Hippocampus of Prenatal Valproic Acid induced mice model of autism spectrum disorder

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Background: Autism spectrum disorder (ASD) is a phenotypically diverse neurodevelopmental disorder with complex etiology, multiple risk factors, no confirmed diagnostic biomarkers and few available symptomatic medications. Multiple etiology based rodent models are used to understand the disease. Valproic Acid (VPA) is an antiepileptic drug whose prenatal exposure is used to develop idiopathic ASD rodent models. Studies suggest hippocampal development and functioning to be associated with ASD symptoms.

Purpose: We wanted to assess and understand the neurodevelopmental changes occurring in the hippocampus of ASD mice model, induced through prenatal VPA treatment.

Methods: In the study, pregnant mice were gavaged with VPA once daily from embryonic day 12.5 (E12.5) to E14.5. Behavioral tests were conducted in the mice for assessing ASD symptoms. BrdU birth-dating and immunofluorescence were used to track changes in specific neuronal populations at various embryonic and postnatal time points.

Results: After VPA treatment, behavioural analysis showed delayed development in neonatal mice, and, lower sociability, higher repetitive behaviours, higher anxiety and cognitive deficits in adults. In the hippocampal neuroepithelium, we found the proliferative cell numbers unchanged, while their distribution were reduced at E14.5. At E16.5, these populations were increased in the neuroepithelium, but decreased in the dentate migratory stream (DMS). The E14.5 birth-dated populations appeared to be increased and accumulated at the neuroepithelial region and the DMS at E16.5, while lesser number of the neurogenic populations reached the dentate gyrus (DG). By postnatal day 0 (P0), there were reduced neural stem cells and proliferative populations in the DG. We also observed reduced, ectopic and aberrant neurogenic and differentiating neuronal populations at P14 and P28.

Conclusions: Thus, we observed the core ASD symptoms and other comorbid behavioral deficits in the neonatal and adult treated mice. We also observed aberrant proliferation and migration defects at the primary, secondary and tertiary matrices at various timepoints of hippocampal development

Neural basis of real-world vision during monkey-human interactions

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Background: Vision is studied extensively by presenting images on a screen and recording neural activity in the visual cortex in restrained animals. This approach blinds us from understanding how the visual cortex responds during real-world vision, where objects are continuously present, and we interact with the environment in a far more dynamic and variable manner.

Purpose: So how does the visual cortex respond during real-world vision? To address this question, we developed a hybrid naturalistic environment in which we can record neural activity and gaze from monkeys viewing images on a touchscreen as well as record neural activity from monkeys interacting with people and objects. Our goal was to understand if there are lawful relations between neural responses to images on a screen and neural responses during real-world vision.

Methods: We performed this study on two monkeys, each implanted with 256 electrodes in high-level visual area (inferior temporal cortex - IT) and high-level motor areas (ventral premotor cortex – PMv & ventrolateral prefrontal cortex – vlPFC). Each monkey performed a series of screen-based tasks, in which they viewed images, or reached to various targets with their hands on a screen. Then they interacted with the same objects and people seen during the screen-based tasks in a naturalistic environment.

Results: Our main results are as follows: (1) Decoders trained on neural responses to images in IT cortex could reliably infer experimenter identity and food offered in the real-world task; (2) Decoders trained on neural responses to hand movements in the PMv could reliably infer hand used during the real-world task; (3) Key trial events during the real-world task elicited similar neural representations in both monkeys.

Conclusion: Our results reveal that, despite the variability intrinsic to real-world natural behaviors, neural responses to images are systematically related to neural responses to the same objects during real-world vision.

Extracellular Tau-mediated signalling of Chemokine-CX3CR1 receptor in Alzheimer's disease

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Background: Alzheimer's disease is a progressive neurodegenerative disorder. Phosphorylation of Tau makes it more prone to aggregation, leading to impaired neurotransmission. Microglia, the brain resident immune cells, are involved in the active clearance of microbes, misfolded proteins, cell debris, etc. In Alzheimer's disease, microglia play a pivotal role in clearing extracellular Amyloid-β plaques and intracellular Tau aggregates in the brain environment. Chemokines are a subset of cytokines, which are signalling proteins primarily involved in the chemotaxis of microglial cells to sites of misfolded Tau and exert their effects by binding to chemokine receptors. CX3CR1 is a G-protein-coupled receptor, interaction between misfolded Tau and CX3CR1 leads to membrane-associated actin cytoskeleton remodelling mediating microglial activation, migration and phagocytosis.

Purpose: To address the functional aspect of Chemokine receptor- CX3CR1 in Tau-induced microglial phagocytosis and endocytosis trafficking.

Methods: Different species of Tau monomer, oligomer and aggregates were prepared by various biophysical and biochemical characterization.

Results: The preparation of various species of Tau were optimized.

Conclusion(s): Tau species were prepared and ready for internalization into microglial cell lines.

Chemogenetic approaches reveal dual functions of microglia in epilepsy

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Background: Epilepsy is a brain disorder characterized by recurrent seizures which affects over 50 million people globally with 1/3rd of the patients being refractory to anti-epileptic drugs. Thus, necessitating exploration of alternative mechanisms to provide better therapeutic strategies. Microglia, the immune cells of CNS are key players in maintaining brain homeostasis and exhibit phenotypic alterations in response to epileptic stimuli. However, it is still relatively unknown if these alterations are pro- or anti-epileptic. In the present study we aim to explore the role of microglia in epilepsy by specifically manipulating microglia employing the chemogenetic approach using Designer Receptors Exclusively Activated by Designer Drugs (Dreadd).

Purpose: In the epileptic brain, microglia adopt various phenotypes depending on the disease stage and display both protective and/or deleterious functions. To unravel this dilemma, we employed precise manipulation of microglia using the artificial Gi-Dreadd receptor within a kainic acid (KA) induced murine seizure model.

Methods: Male, 8-10 weeks old, CX3CR1creER/WT: R26LSL-hM4Di/WT mice (Gi-Dreadd) and CX3CR1CRE-ER/WT mice (Control) were used for the study. Seizure induction: Intra-cerebroventricular (ICV) injection of KA 0.15 μg in 5 μL sterile PBS. Seizures were recorded as per modified Racine score. Clozapine-N-Oxide (CNO) drug (5 mg/kg body weight, i.p.) was administered to activate Dreadds.

Results: Our results indicate that acute Gi-Dreadd activation can reduce seizure severity. Additionally, we observed increased interaction between microglia and neuronal soma, which correlated with reduced neuronal hyperactivity. Interestingly, prolonged activation of microglial Gi-Dreadds by repeated doses of CNO over 3 days, arrested microglia in a less active, homeostatic-like state, which associated with increased neuronal loss after KA induced seizures. RNAseq analysis revealed that prolonged activation of Gi-Dreadd interferes with interferon β signaling and microglia proliferation.

Conclusion: Thus, our findings highlight the importance of microglial activation not only during status epilepticus but also within later seizure induced pathology.

Comparative analysis of Therapeutic Rescue by Yoga between (LOAD) Late Onset Alzheimer's Disease and (EOAD) Early Onset Alzheimer's Disease

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Background: Alzheimer's disease constitutes a multifaceted neurodegenerative condition occurring in two principal variants: Early Onset Alzheimer's disease and Late Onset Alzheimer's disease. EOAD is often linked to mutations in amyloid precursor protein (APP) gene, typically presents before age 65 and progresses rapidly. LOAD, influenced by environmental and polygenic risk factors, occurs later in life. Recent research suggests that Yoga and meditation might modulate gene expression, related to AD, potentially offering neuroprotective benefits- leading to an increase in BDNF levels, lowering cortisol levels, increase in serotonin levels which can thereby prevent harmful amyloid beta formation.

Purpose: This study aims to compare SNP's within APP gene, neuropsychiatric profiles of EOAD and LOAD patients, assessing how these differences influence disease progression and their response to non-pharmacological interventions.

Methods: 200 patients will be recruited, 100 each for EOAD and LOAD, aged 50-85, excluding those with comorbidities. Pre- and Post-intervention after 3 months would be done including cognitive evaluations- Geriatric Depression Scale, Neuropsychiatric Inventory Questionnaire, Mini Mental State Examination, Clinical dementia rating scale, clinical history and amyloid beta analysis. Genotyping of APP SNP's & rescue profile evaluation will be done based on presence of risk alleles.

Conclusion: This research will contribute to comparative analysis of effective rescue of yoga between LOAD & EOAD and will study integrative effect of mind body interventions along with pharmacological interventions. The assessments of yoga and meditation on these parameters could provide insights to treatment efficacy in managing Alzheimer's disease. The results may also demonstrate differential impacts of these interventions on cognitive and neuropsychiatric outcomes based on genetic profiles.

Carbamazepine and Eslicarbazepine: Reducing Epileptiform activity in an *in vitro* Hippocampal rat model

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Background: Antiseizure medications (ASMs) are drugs used to treat epileptic seizures in patients with epilepsy. Even though the drugs reduce seizures, it causes many side effects like depression, anxiety, learning and memory defects, and cognitive impairments in patients. To combat these ill effects, we need to understand the action of ASMs in the brain. Here we study the effect of antiseizure medications carbamazepine and eslicarbazepine in hippocampal synapses in an invitro model of epilepsy.

Purpose: The effects of antiepileptic drugs on epileptiform activity provide valuable information regarding the cellular mechanisms of epilepsy. This study aims to understand how these drugs influence neuronal activity in an *in vitro* model, potentially leading to better therapeutic strategies for epilepsy.

Methods: Hippocampal slices were prepared from Wistar rats (P14-P25) in ice-cold Artificial Cerebrospinal Fluid (ACSF) with a thickness of 400 μm using a vibrotome. The slices were incubated in normal ACSF for 30 minutes in an incubation chamber before use. The entire procedure was conducted in the presence of carbogen (95% oxygen and 5% carbon dioxide). Epileptiform activity was generated using ACSF containing high potassium (7.5 mM) and zero magnesium-(HKACSF).

Results: The hippocampal slices bathed in HK-ACSF induced epileptiform activity (within 12 min). The epileptiform activity can be characterized as ictal and interictal discharges. The effects of CBZ and ESL on the amplitude and frequency of these events were evaluated. Both CBZ and ESL significantly reduced the frequency and amplitude of epileptiform events, demonstrating their potential effectiveness in mitigating seizure-like activity in this model.

Conclusion: This experimental procedure represents a model suitable for analyzing epileptogenesis in vitro as well as for screening different drugs. Additionally, the study provides valuable insights into the cellular mechanisms underlying epilepsy. This experimental model is a useful tool for further exploration of epilepsy and the development of more effective treatments.

Neurobehavioral alterations induced by Benzo[a]pyrene through modulation of Aromatase enzyme in adult Zebrafish (*Danio rerio*): Insights from In Silico and In Vivo studies

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Background: Benzo[a]pyrene (BaP) is a well-known polycyclic aromatic hydrocarbon (PAH) and endocrine-disrupting chemical (EDC) commonly found in contaminated aquatic environments. Its neurotoxic effects raise significant concerns for aquatic organisms, particularly zebrafish (*Danio rerio*), which serve as a model organism for studying environmental toxicology. Aromatase, an enzyme crucial for the biosynthesis of estrogens, plays a vital role in neurodevelopment and behavior. However, the impact of BaP on aromatase activity and subsequent neurobehavioral changes in zebrafish remains poorly understood.

Purpose: This study aims to elucidate the neurobehavioral alterations induced by BaP exposure in adult zebrafish, specifically focusing on the modulation of aromatase enzyme activity. By employing both in silico and in vivo methodologies, the research seeks to provide insights into the molecular mechanisms underlying BaP-induced neurotoxicity.

Methods: An In-silico analysis was conducted using molecular docking to determine the binding affinity of BaP to the aromatase enzyme, predicting potential interactions. For the in vivo component, adult zebrafish were exposed to different concentrations of BaP, followed by behavioral assessments to evaluate locomotor activity and anxiety-like behavior using standardized protocols

Results: Docking results revealed that among the Benzo[a]pyrene and its metabolic intermediates showed the high binding affinity against aromatase enzyme with a binding score in between -9.5 kcal/mol to -9.7 kcal/mol with a strand score was -7.3 kcal/mol. Exposure to different concentration of BaP resulted in significant neurobehavioral changes, including increased anxiety levels and reduced locomotor activity.

Conclusion: This study demonstrates that exposure to Benzo[a]pyrene (BaP) significantly alters neurobehavioral patterns in adult zebrafish, and increase in anxiety and decreased locomotor activity, and the molecular docking showed BaP and its metabolic intermediates have a high binding affinity to the aromatase enzyme .These findings highlight the importance of monitoring BaP contamination in aquatic environments and suggest that further research is essential to elucidate the long-term effects of BaP on aquatic organisms and the broader ecological implications of its neurotoxic properties.

Lactobacillus Helveticus Improves Controlled Cortical Impact Injury-Generated Neurological Aberrations by Remodeling of Gut-Brain Axis Mediators

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Background: Several studies have indicated the potential of gut microbiota-based interventions for addressing post-traumatic brain injury complications. Earlier literature indicated the sex- specific abundance of *Lactobacillus helveticus* following controlled-cortical impact (CCI). Thus, we hypothesized the sex-specific effect of *Lactobacillus helveticus* in the CCI mouse model.

Purpose: This study aimed to illustrate the impact of L. *helveticus* on neurological complications in a mouse model of CCI and how the sex-specific disparities could influence gut-brain markers.

Methods: Adult, C57BL/6 mice (both male and female) were subjected to CCI surgery and subsequently treated with L. *helveticus* for 4 weeks. Sensorimotor dysfunctions were assessed using a neurological severity score and rotarod test. To assess the long-term effects of CCI on anxiety-like behavior and cognition, elevated-zero maze (EZM) and novel object recognition test (NORT) were performed. At the end of treatment, samples of brain perilesional area, blood, colon, and fecal samples were collected for molecular investigations.

Results: CCI-operated mice displayed profound neurological impairments at 1-, 3-, 5-, and 7 days post-injury (dpi). These animals also showed altered behavioral traits in EZM and NORT vs. sham-operated mice, which were mitigated in the L.*helveticus*-recipient group. Additionally, GFAP, Iba-1, TNF-α, and IL-1β expressions and corticotrophin-releasing hormone (CRH) levels were elevated in the perilesional cortex of CCI-operated male/female mice. L. *helveticus* treatment normalized these elevated biomarkers expression and decreased levels of BDNF seen in male/female mice. Further, treatment also modified the altered levels of short-chain fatty acids (SCFAs) in fecal samples and restored intestinal integrity. However, the declined plasma levels of progesterone and testosterone in CCI mice remained unaffected by L. *helveticus* supplementation.

Conclusion: These findings suggest that L. *helveticus* exerts neuroprotective benefits in the CCI model by mitigating inflammation and modifying gut microbiota-brain mediators.

Effect of curcumin on olfactory dysfunction in park^{13}, drosophila parkin null mutant

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Background: Parkinson's disease (PD) is the 2nd most progressive neurodegenerative disorder and is caused by the accumulation of alpha-synuclein protein. The accumulation of the alpha synuclein protein causes Lewy bodies formation and leads to cell toxicity and also causes oxidative stress which is finally leading to the neuronal death. Curcumin is used traditionally as a medicine for a very long time. Recent studies focus on the neuroprotective properties of Curcumin which reduces the Reactive oxygen species (ROS) levels which reduces the oxidative stress and it can show rescue in olfactory behaviour. *Drosophila melanogaster* is used as a model in this study as it is easy to culture, short lifecycle and its genetic similarity to human diseased genome.

Purpose: In this study the drosophila model of PD, park^{13} a parkin null mutant was used. Our lab has already characterised Olfactory dysfunction in drosophila park13 mutants. The therapeutic effects of curcumin on different stages of the drosophila PD mutant was checked. The effect of curcumin on olfactory behaviour in control and treated park^{13} mutant strains was observed.

Methods: The mutants were treated with different concentrations of curcumin and then early stages of drosophila were tested [2nd instar larvae] for the olfactory assay with 10-3 dilution factor of iso-amyl acetate and distilled water used as a control.

Results: Expected results are park^{13}, drosophila parkin null mutant when treated with curcumin will show rescue in behavioural and olfactory behaviour in the early stages of the fly.

Conclusion: Curcumin acts as a neuroprotective agent and restore the olfactory behaviour. Curcumin will have therapeutic effects on olfactory dysfunction in 2nd instar larvae of drosophila parkin null mutant park^{13}

Role of miR-149-5p in Japanese encephalitis virus-induced inflammation in microglial cells

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Background: Japanese Encephalitis (JE) is an acute neuroinflammatory disease that affects the central nervous system (CNS), caused by the Japanese encephalitis virus (JEV). Microglia, the resident macrophage of the brain, can trigger an inflammatory overdrive upon activation, leading to bystander neuronal death. miRNAs are small non-coding RNAs 18-22 nucleotides long that bind to 3' UTR of target mRNAs and negatively regulate their expression.

Purpose: Despite the availability of vaccines, approximately 70,000 symptomatic cases of JEV are reported annually, causing death in 30% of the patients while 50% of the surviving patients experience permanent neurological damage. In the current study, miR-149-5p, which was found to be increased in preliminary miRNA sequencing data of mouse microglial cells (N9), was subjected to further investigation to decipher its role in JEV-triggered neuro-inflammation. This may lead to the discovery of a potential therapeutic target to develop antivirals in JE.

Method: Bioinformatic tools like TargetScan were used to predict the target of miR-149-5p. N9 cells were infected with JEV at Multiplicity of Infection (MOI) 3. Total RNA from cells was isolated using TRI reagent. miRNA-specific cDNA was prepared using miRCURY LNA RT Kit (Qiagen) and detection of miRNA levels was done using miRCURY LNA PCR Assay (Qiagen).

Results: miR-149-5p levels are significantly upregulated in JEV-infected N9 cells at 6 hrs. TIRAP was bioinformatically predicted as a putative target of miR-149-5p. A significant downregulation of TIRAP at both mRNA and protein level was observed at 6 hours of infection.

Conclusions: We further plan to study the effect of overexpression and inhibition of miR-149 on levels of TIRAP and other downstream proteins. TIRAP acts as a key adaptor in Toll-like receptor (TLR) signaling, which leads to the activation of NF-κB signaling pathway. It would be interesting to study how miR-149-5p regulates virus-induced inflammatory response.

Effect of Anti-Seizure Medication Carbamazepine on Glutamate Receptor Subunits in the Pilocarpene Model of Epliepsy

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Background: Epilepsy is characterized by recurrent seizures and often requires long-term management. Carbamazepine is a well-established anti-seizure medication primarily known for blocking voltage-gated sodium channels to reduce neuronal excitability. However, its effects on other receptors remain unknown. Here we study the role of carbamazepine in excitatory synaptic transmission, especially the glutamate receptors. These receptors play an important role in synaptic transmission and plasticity, and understanding carbamazepine's impact on these receptors could give us insight into potential therapeutic targets.

Purpose: The aim is to investigate the effects of carbamazepine on the expression of excitatory neurotransmitter receptors, specifically α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor subtypes, in the hippocampus region of the rat brain. This study aims to elucidate the potential impact of carbamazepine on the expression of these receptors, thereby providing insight into the drug's broader mechanisms of action.

Method: Seizures were induced in Wistar rat (P30-P35) by administrating pilocarpine (340mg/kg of body weight) followed by 15 days of latency period, then we video recorded for 30 days to confirm spontaneous recurrent seizures. After confirming the seizures, two weeks of carbamazepine (40mg/kg of body weight) dosing thrice a day was given. Rats were sacrificed, and microdissections were carried out to remove the hippocampal region. The tissue was then homogenized, and western blot was performed to study the expression of the proteins.

Results: The administration of carbamazepine increased the expression of NR1, NR3B, GLUA1 and GLUA2, whereas NR2A expression was decreased in the hippocampus after the administration of carbamazepine.

Conclusion: This study gives an early insight into the effect of carbamazepine on excitatory receptors. However, further research needs to be done to elucidate the mechanism behind how these receptors are affected.

Effect of Finasteride on Cognition in Female Rats

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Background: Finasteride is used for treating benign prostatic hyperplasia and androgenetic alopecia in men, and androgenetic alopecia and hirsutism in women. Many studies have reported that finasteride use in men leads to depression, anxiety and suicidal ideation but the same has not been evaluated in women. Our lab has modelled the effects of finasteride in male and female rats and have found a sex-dependent effect, that is, depression-like and anxiety-like behavior in male rats and anxiolytic-like and antidepressant-like effects in female rats. In male rats, finasteride also induced cognitive deficits in the novel object location test (NOLT), and decreased AChE activity but its effects in female rats are not known.

Purpose: Accordingly, this study evaluated the interaction between the cholinergic system and finasteride on learning and memory.

Methods: Finasteride (Fin, dissolved in 20% 2-hydroxypropyl-β-cyclodextrin (vehicle)) was administered subcutaneously to female Wistar rats (2-2.5 months old, 200-250g) for 6 days and spatial memory was assessed using NOLT. Half of the rats from each group received an acute dose of scopolamine (Scp, 1mg/kg) 1h before the NOLT. In a separate cohort of female rats, AChE activity was assessed using modified Ellman's method in various brain regions.

Results: Finasteride administered rats preferred the novel location, while the Fin+Scp group of rats preferred the familiar location. Moreover, finasteride increased the AChE activity in the hippocampus and striatum.

Conclusion: These results point to a possible interaction between neurosteroids and the cholinergic system, in particular, acetylcholinesterase, in the regulation of cognition, which needs to be explored further. The current study has implications not only for the clinical effects of finasteride in male and female subjects but also for the possible role of neurosteroids in mood and cognition, and its interactions with the neurotransmitter systems to bring about its effects.

Early dysregulation of synaptic peroxiredoxin-V in an Alzheimer's disease mouse model

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Background: Increased oxidative stress and loss of dendritic spines have been associated with Alzheimer's disease (AD). The structure and function of dendritic spines are highly regulated by F-actin dynamics. Oxidative stress, due to increased levels of reactive oxygen species (ROS), is considered as a primary contributing factor to dendritic spine loss in AD brain. ROS has shown to be interacting with several actin regulatory proteins and affects F-actin dynamics, leading to depolymerization of actin filaments in dendritic spines, subsequently destabilizing the spine structure. In cells, most of the ROS molecules are generated from hydrogen peroxide (H_2O_2). The levels of H_2O_2 are predominantly regulated by an enzyme called peroxiredoxin-V (PrxV) in neurons. Here, we aim to determine the levels of H_2O_2 as well as the role of peroxiredoxin-V in wild type and APP/PS1 mice at different age groups.

Purpose: To study the role of peroxiredoxin-V in Aβ mediated F-actin dynamics at the synapse using AD mouse model.

Methods: Oxidative stress was measured by testing H_2O_2 levels from the lysate of the cerebral cortex and hippocampus from wild-type and APP/PS1 mice using a hydrogen-peroxide assay kit. PrxV levels were analyzed in synaptosomes isolated from one- and three-month-old wild type and APP/PS1 mice by immunoblotting.

Results: APP/PS1 mice have shown significantly increased levels of H_2O_2 in both, hippocampal and cortex tissue, compared to that of wild-type at the age of one, three, and nine months. We also observed significantly decreased levels of PrxV in synaptosomes of APP/PS1 mice at the age of one- and three-months compared to that of wild-type group.

Conclusion: We conclude that the perturbation of PrxV levels in AD may contribute to the increased H_2O_2 levels as observed in an AD mouse model. Restoring PrxV levels in AD brain may mitigate H_2O_2 accumulation and alleviate oxidative damage, thus suggesting a promising therapeutic approach against neurodegeneration.

Astrocyte secreted PTX3 is neuroprotective in a model of Alzheimer's disease

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Background: Alzheimer's disease (AD) is the most widespread neurodegenerative disease associated with neuronal death, impairment of synaptic plasticity and finally severe loss of cognitive abilities. Astrocytes respond dramatically to pathological alterations in the brain including AD through a highly heterogeneous process called astrocyte reactivity. Several types of proteins are released from reactive astrocytes that regulate neuronal health through disease stages. Recently, it has been reported that pentraxin 3 has a capacity to maintain balance between synaptic growth and synapse function in the developing brain.

Purpose: The main aim of this study was to investigate whether PTX3 is secreted from astrocyte in response to Beta-amyloid (Aβ). On the other hand whether it has an impact on survival signaling pathway as well as apoptotic pathways in cortical neuron in presence of Aβ.

Methods: In vitro, mouse primary astrocyte cells were cultured to check the secretion profile of PTX3 by ELISA and its protein levels by western blotting. Mouse primary cortical neuron cultures were co-treated with Aβ and recombinant PTX3 to check the downstream protein levels by western blotting and imaging.

Result: We found that oligomeric Aβ 1-42 treatment to primary astrocytes induced an early reactivity and detected Pentraxin 3 as a newly discovered marker of reactive astrocytes. It is one of the major candidates in the Aβ-treated astrocyte secretome that has neuroprotective roles in AD. We also found that PTX3 plays an important role on Akt signaling that is potentially central to regulating anti-apoptotic pathways.

Conclusion: - We highlight that PTX3 may have neuroprotective role against Aβ toxicity and propose it as a primary candidate in astrocyte-secreted protein in AD therapy.

Role of miRNA29 in the pathogenesis of Alzheimer's Disease

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Background: Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline, neuronal loss, and brain pathology. Extensive research have been done to understand the disease progression, however, the aetiology of the disease still remains elusive. AD is a multifactorial pathogenesis in which different paradigms are being investigated to establish new targets which may not only slow down the disease progression but also to cure it. Studies suggest that miRNAs which are widely expressed in nervous system are endogenously conserved. Small non-coding RNAs that control gene expression at the posttranscriptional level and are essential for neuronal function and survival. Dysregulation of microRNAs acts as a pivotal contributor in the AD progression.

Purpose: We evaluated the role of microRNA29 family in the pathogenesis of AD using cellular and as well as transgenic animal model in AD.

Methods: We have determined the expression of miRNA29 in PC12 cells in response to betaamyloid (Aβ) as well as in animal model of 3 months old transgenic 5xFAD model of AD using RT-PCR. We performed immunocytochemistry in miRNA29 mimic transfected PC12 cells to check the link between microRNA29 and FoxO3a in AD model and non-translocation of FoxO3a.

Results: Results show that expression of miRNA29 were dysregulated in Aβ treated PC12 cells as well as tissue isolated from 5xFAD mice model. Further, the survivability of Aβ treated PC12 cells transfected with microRNA mimic and found that there was increase in survivability in the transfected cells. Reports are there that transcription factor FoxO3a has a critical role in several neurodegenerative diseases including AD where it translocated in the nucleus in diseased condition. Also, FoxO3a has a binding domain for miRNA29 as reported previously.

Conclusion: Unravelling and characterizing the mechanistic pathways of our hypothesis will provide insights about the neuroprotective role of miRNA29 and as a potential therapeutical target of AD.

Dynamics of Inhibitory Connections during the Sensitive Period for Language Acquisition in the Human Auditory Cortex

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Background: Auditory experiences in early life shape synaptic connections in the brain and language perception throughout the lifetime. These experience-dependent changes are prominent during a restricted period called the sensitive period. Inhibitory GABAergic interneurons are closely associated with the onset of the sensitive period. Since their establishment in the human auditory cortex is still unexplored, we decided to investigate changes in somatostatin-positive interneurons (SOM) from the prenatal period until adulthood in the human auditory cortex.

Purpose: Cochlear implants are more effective when provided early during development for deaf individuals. Therefore, a detailed knowledge of auditory cortex development during the sensitive period is necessary for planning such interventions.

Methods: Post-mortem samples of the human auditory cortex were used to study the expression of inhibitory synapses and SOM, using immunohistochemistry. To quantify changes in these components of the auditory cortex, images were acquired using a confocal microscope and analysed using ImageJ. Software (Stereoinvestigator and Neurolucida, Microbrightfield, USA) was used to quantify and reconstruct SOM-positive interneurons.

Results: Our results demonstrate that the density of inhibitory synapses in the human auditory cortex increases significantly between the prenatal period and adulthood. SOM-positive interneurons first appear in white matter in intrauterine life, then migrate into higher cortical layers until childhood, after which no significant changes were observed. We also found that the neuronal complexity of SOM-positive interneurons decreases significantly with age.

Conclusions: Our results suggest that inhibitory synapses and SOM-labelled interneurons undergo pruning and remodelling between childhood and adolescence in the auditory cortex. Further studies are required to elucidate changes in other subtypes of inhibitory neurons in order to provide the normative baseline for human auditory cortex development.

Human iPSC-derived 3D organoids as a tool to understand the chemical induced neurotoxicity using a proteomic-miRNA biomic cross-talk approach

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Background: The iPSC-derived three-dimensional (3D) models are considered to be a connective link between 2D culture and *in vivo* studies. These 3D organoids may improve our understanding of the neurochemistry of mental diseases and chemical neurotoxicity.

Purpose: The amalgamation of high throughput biomics (miRNA & proteomics) profiling with a 3D organoid-based model could be a better interphase to predict the etiology of chronic mental disease and vulnerability to environmental toxicants.

Methods: We have generated a CRISPER-Cas mediated TDP-43-mutated human iPSCs (hiPSCs) derived 3D organoid model of ALS disease and normal hiPSC-derived neural progenitor cells 3D spheroid. The developed organoids were subjected to the biomics proteomic and miRNA profiling using HRMS and Open Array® Technology, respectively.

Results: We identified a total of 126 deregulated proteins, among which 39 altered proteins were already reported in human-based studies of ALS disease. These proteins were related to functions including cellular clearance system (Ubiquitin–Proteasome Pathway, endoplasmic reticulum (ER) proteostasis system and autophagy), cellular translation and transcription machinery, cell cycle, cytoskeletal and axonal integrity, cellular migration and differentiation, mitochondrial, and cellular energetics. The observed alterations in extracellular matrix proteins underscore their potential role in ALS disease, which is unattainable through conventional 2D culture systems. The developed NPCs-derived 3D spheroid model exposed to a subtoxic dose (1μM) of Sodium Arsenite (SA) was compared with a 2D monolayer culture system exposed to the same dose of SA. The biomics profiling-based findings clearly exhibited a higher number and magnitude of altered miRNAs and proteins in the 2D culture system than in 3D spheroids.

Conclusion: Our developed 3D organoid ALS model might circumvent ethical constraints in accessing neural tissue from ALS and may be used as an alternative for investigating the complex molecular mechanism in ALS. The 3D spheroid model derived from NPCs underscores the potential of 3D culture systems as valuable tools for assessing neurotoxicity in a more relevant *in vivo*-like context.

Alteration of oxidative stress in Hematopoietic Stem Cell Transplant (HSCT) recipients after yoga intervention

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Background: Hematopoietic Stem Cell Transplant (HSCT) is a therapeutic approach used to substitute bone marrow compromised due to life-threatening hematological malignancies like Aplastic Anemia, Multiple Myeloma, Lymphoma, etc. Hematopoietic stem cells (HSCs) can be harvested and transplanted from marrow, peripheral blood, and cord blood by the process of apheresis. Depending on the disease, it can be classified as autologous, allogeneic, and syngeneic. High-dose chemotherapy used in transplant increases free radicals and depletes the antioxidant system. Reactive Oxygen Species (ROS) affect cell cycle progression and growth factor signalling. Previous studies show that yoga may have positive effects on antioxidant properties that help in controlling ROS and oxidative damage.

Purpose: Enhancing the recovery of HSCT recipients by reducing oxidative stress through integration of mind-body interventions.

Methods: 100 patients will be recruited (excluding smokers and regular practitioners of mind-body practices for over 6 months), and randomized into Group A (n= 50), receiving both non-pharmacological intervention and prescribed pharmacological treatment. Group B (n= 50), receiving only pharmacological treatment each for 100 days. Clinical history and other comorbidities will be recorded. Plasma samples will be collected at baseline (Day 0, transplant day) and Day 100. Oxidative stress biomarkers Malondialdehyde (MDA), 8Hydroxy-2-deoxyguanosine (8-OHdG) along with antioxidant markers Superoxide dismutase (SOD), Glutathione peroxidase (GP_x), and total antioxidant activity (TAC) will be quantified using Spectrophotometric techniques.

Significance: Chronic stress exacerbates oxidative stress. Published evidence suggests that breathing techniques in yoga relax the parasympathetic nervous system (PNS) which reduces cortisol levels thereby, reducing ROS production. It boosts endogenous antioxidant activity of the body which neutralizes ROS and improves mitochondrial functioning and sleep quality. This study will contribute to the growing evidence supporting the integration of mind-body intervention in managing oxidative stress by boosting endogenous antioxidant activity of the body and enhancing recovery in patients facing severe hematological challenges.

Therapeutic potential of dysregulated miRNA in Amyotrophic Lateral Sclerosis

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Background: Amyotrophic Lateral Sclerosis (ALS) is a progressive neuromuscular disorder. The disease is found to be associated with a mutation in over 20 genes. The mutation in the transactive response DNA-binding protein 43 (TARDBP encoding TDP-43) gene is a prominent one among ALS patients. Autophagy and lysosomal dysfunctions triggered by accumulated mutated TDP-43 are the major contributing mechanisms for ALS. The therapeutic potential of miRNAs as ASOs (Antisense oligonucleotides) has been suggested in various clinical conditions for the management of ALS. Mitoxantrone (MTX) is a synthetic doxorubicin analogue that inhibits DNA and RNA synthesis/repair via intercalating with nitrogenous bases and inhibiting topoisomerase II. Therefore, we aimed to investigate the therapeutic potential of dysregulated miRNAs involved in the disease and compared the data with MTX using a human iPSC-derived *in vitro* model of ALS.

Methods: CRISPR Cas9 generated mutated TDP-43 hiPSCs were differentiated into NPCs. To mimic in vivo scenario, we used co-culture normal and mutated NPCs (42%). Control and co-cultured mutated NPCs were exposed to a non-cytotoxic concentration of MTX drug (1μM for 24 h). TaqMan OpenArray-based miRNA profiling, Seahorse-based bioenergetic assessment for mitochondrial dynamics, and immunocytochemistry of endoplasmic reticulum (ER) stress and autophagy-related proteins were performed to assess the therapeutic potential of MTX using a human iPSC-derived in vitro model of ALS.

Results: The findings exhibited that mutated TDP-43 protein accumulation causes stress granule formation (G3BP1), dysfunctional mitochondrial bioenergetics (OCR, proton leak, and basal and maximal respiration), SOD1 accumulation, hyperactivated autophagy (LAMP1, LC3B, and SQSTM1), and ER stress in co-cultured mutated NPCs. The study also found alterations in five miRNAs (miR-543, miR-34a, miR-200c, miR-22, miR-29b, and miR-29c) in cocultured mutated NPCs. The MTX-treated co-cultured NPCs significantly restored the abovementioned altered processes and levels of miRNAs and reduced the accumulation of mutated TDP-43 in cells.

Conclusion: The study infers that specific miRNA and Mitoxantrone hold promise as therapeutic agents for managing ALS-like pathology. *In silico* simulation studies have shown that miR-543, miR-29b, miR-22, miR-200c, and miR-34a exhibit antisense therapeutic potential, both individually and in combination with Mitoxantrone.

Behavioral aspects of Valproic Acid on Nervous System of *Hydra viridissima*

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Background: Valproic Acid a widely used drug has been cornerstone in the treatment of epilepsy, migraine prophylaxis, neuropathic pain and bipolar disorders. Apart from this it is best known for its anticonvulsant properties . It's unique mechanism of action involves the inhibition of gamma-aminobutyric acid (GABA) transaminase increasing GABA levels, and modulation of Voltage-gated Sodium channels, leading to reduction in neuronal hyperexcitability. Additionally VPA has been shown to influence histone deacetylase inhibition. However it's impact on simple Nervous System is still poorly understood. Hydra viridissima is a freshwater cnidarian with a rudimentary yet functional nervous System. Although exhibiting a primitive Nervous System it exhibits complex behaviors such as feeding response, phototactic movement and thus it is an ideal model for exploring VPA's neurobehavioral effects .

Purpose: Our project aims to investigate the effect of VPA on neuronal behavior and regeneration using Hydra viridissima as a model organism.

Method: We exposed Hydra to varying concentrations of VPA with different time intervals at 0, 24, 48, 72, 96 hrs and observed the alteration which they showed. Behavioral responses were assessed using Glutathione feeding response in which tentacle spread vs time was considered,besides this phototaxis and regeneration Assay was also performed.

Result: Typically Hydra captures prey using tentacles equipped with specialised stinging cells called nematocysts but our results conclude that VPA treated Hydra demonstrated reduced prey capture efficiency and alteration in tentacle retraction, significant delay and abnormal growth was also observed in regeneration rate of hydra treated with vpa when compared with control.

Conclusion: Based on the behavioral observations and statistical analysis our research indicates that Valproic Acid can affect the sensory motor coordination. However, the specific molecular targets involved has to be studied further.

*In Silico/*Computational Analysis of Estrogen Receptor Binding Affinity for Bioactive Compounds in *Tinospora cordifolia*

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Background & Purpose: *Tinospora cordifolia* is well-known rasayna herb having various pharmacological properties. Purpose of study is to find compounds from different fractions of *T. cordifolia* (Methanol, Ethanol, Ethyl Acetate, Butanol) having best binding affinity to Estrogen receptors which can be then experimented to use as an alternative of HRT.

Methods: *In silico* screening of *T. cordifolia* bioactive compounds involved extracting and processing estrogen receptor α and ß molecules from the Protein Data Bank (PDB) and ligands from PubChem. The receptor molecules were processed in pymol and saved in pdbqt format. The receptor and ligand were docked using a Autodock tools and results showed binding affinity in kcal/mol and output was extracted.

Results: The results of docking with different ligands were extracted into their respected folders. Magnoflorine, Palmatine and ß ecdysone showed a significant binding affinity among the ligands which have been docked till now. The above-mentioned results were obtained for ER A receptor. For reference, OHT ligand was already provided and docked; and docking with ERB receptors is currently underway.
Discussion: The molecular docking done to ER α and ß with the ligands or bioactive compounds from *T.cordifolia* showed significant binding affinity from which palamtine and ß-ecdysone showed highest affinity amongst the tested ligands. Currently, many ligands need to be docked and in compliance with that results will be updated.

Conclusion:
The results obtained from docking showed promising results and the ligands used were bioactive compounds from *Tinospora cordifolia* which indicates that the fractions of *T.cordifolia* or pure compounds from *T.cordifolia* can be used for in-vitro and in-vivo experimentation for enhancement of memory and cognition and also can be tested as alternative of ERT (Estrogen Replacement Therapy).

Characterizing the role of CLC-3 in chemosensory neurons in *Caenorhabditis elegans*

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Background: Claudins are a class of cell adhesion molecules primarily involved in formation of tight junctions in epithelial cells. Structurally, they bear a PDZ-binding motif that enables them to interact with other molecules. While claudins in *C. elegans* and vertebrates might differ at the sequence level, they are structurally conserved and perform similar functions. To explore neuronal functions of claudins, we performed an expression pattern screen for the 18 claudin-like molecules in *C. elegans* and identified neuronal expression of *clc-3*, *clc-4*, *clc-6* and *clc-7*. One of the candidate claudins, CLC-3, was found to be expressed in head neurons, tail neurons and along the ventral cord. In the head, *clc-3* appears to be present in a prominent cluster of neurons.

Purpose: The purpose of this study is to study the function of CLC-3 in chemosensory neurons in *C. elegans.*

Methods: This study uses two main experimental approaches, co-localization experiments that require viewing expression of transcriptional reporters using different fluorescent proteins and chemotaxis assays that require behavioural analysis of mutant worms to relevant volatiles.

Results: The protein CLC-3, appears to be expressed in AWB neurons, which are responsible for the worm sensing noxious volatiles. Further, CLC-3 mutants appear to be defective in avoidance of noxious volatiles. Finally, e Expression of CLC-3 in mutants restores aversion of noxious volatiles to wild-type levels.

Conclusions: CLC-3 acts in the AWB neuron to mediate aversion to noxious volatiles in *C. elegans*

Neuroprotective impact of Fisetin & Chlorogenic Acid against Amyloid Beta-induced neurotoxicity by promoting autophagy & reducing oxidative stress in an in vitro Alzheimer's disease model

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Background: Caloric restriction mimetics (CRMs) are the compounds that mimic the beneficial health-promoting effects of caloric restriction at the molecular, cellular, and physiological levels. Fisetin and chlorogenic acid (CGA), both plant flavonoids, are well established CRMs that can induce autophagy but their role in neuroprotection against the aggregation of amyloid beta (Aβ42) plaques via inducing autophagy and reducing oxidative stress is not clearly known.

Purpose: In this study, attempts have been made to examine neuroprotective effect of fisetin & CGA against amyloid beta-induced neurotoxicity using *in vitro* and transcriptional approaches.

Methods: The SHSY5Y cells were first differentiated into cholinergic phenotype using trans retinoic acid. The invitro experiments include MTT for finding out the non-cytotoxic doses of fisetin, CGA & Aβ42 at 24 h and 48 h. Mechanism of apoptosis was performed by Annexin VFITC technique, mitochondrial activity was studied by using MitoTracker dye. Oxidative stress biomarkers like ROS, LPO, Catalase & SOD etc were also measured. qRT-PCR of autophagy genes like ULK1, p62, ATG101, ATG13 and autophagy regulatory genes (AMPK & mTOR) and neuropathy marker (AChE) was also performed.

Result: Our in vitro data suggested that both CRMs can significantly decrease the pro-oxidant markers and increase the antioxidant markers. The flow cytometric analysis of apoptosis in SHSY5Y cells using AnnexinV-FITC and PI staining showed that these CRMs prevent the apoptotic cell death induced by Aβ42. The flow cytometric analysis using MitoTracker Dye showed that fisetin and CGA increased the mitochondrial membrane potential that was reduced under Aβ42 exposure. qRT-PCR data demonstrates that these CRMs significantly induce the autophagy genes expression and significantly decrease the expression level of AChE.

Conclusion: Therefore, the present study indicates that fisetin & CGA treatment can have neuroprotective effects in an in vitro model of Alzheimer's disease and can be used for the management of neurodegenerative diseases.

Inhibition of Protein X Helps in Alleviation of Neuroinflammation in A Cellular Model of Ischemic Stroke

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Background: Stroke is the fourth leading cause of death in India. Existing stroke therapies currently focus on thrombolytic drugs like tPA and mechanical thrombectomy, but these fail to address the various post-stroke complications that contribute to stroke being the fifth leading cause of disability in India. Although all cerebral strokes have the capacity to be deadly, our study is specifically focussed on cerebral ischemic stroke which accounts for the vast majority of all strokes.

Purpose: One of the major post-stroke complications is neuroinflammation caused by disturbances in mitochondrial functions. By targetting protein X which is known to be involved in various cell death pathways through the regulation of mitochondrial homeostasis, we may be able to limit the damage related to increased neuronal inflammation and reduced neuronal cell viability in post-ischemic stroke patients.

Methods: In this study, we evaluated the effect of inhibiting Protein X on various parameters associated with post-ischemic stroke neuroinflammation and resulting cell death. Using an oxygen glucose deprivation/reperfusion (OGD/R) model – a well-established model for studying ischemia/reperfusion injury in-vitro – we were able to assess various cellular factors related to post-ischemic complications.

Results: We inhibited the functioning of Protein X using specific chemical inhibitors as well as its expression by shRNA. In comparison to the OGD/R model which showed increased oxidative stress, decreased cell viability, decreased mitochondrial function, and an overexpression of neuroinflammatory markers, our knock-down models were able to reverse the observations and revealed increased anti-inflammatory properties in microglial cell lines.

Conclusion: Therefore, our current study indicates that Protein X plays a role in regulating post-ischemic-stroke cell death and neuroinflammation. Our future workplans will be focussed on understanding the exact mechanism by which Protein X brings about these effects, further emphasizing its use as a potential therapeutic target for post-ischemic-stroke-associated neuroinflammation and cell death.

Computational prediction of selected serine-threonine kinase inhibitors as potential PINK1 inhibitors significant for Parkinson's disease through molecular modelling, simulation, docking and scaffold analysis

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Background: The PTEN-induced kinase 1 (PINK1) protein plays a crucial role in mitochondrial function and quality control. Mutations in the PINK1 gene are a primary cause of mitochondrial dysfunction and lead to early-onset Parkinson's disease. This study explores the potential of selected serine threonine kinase inhibitors as PINK1 inhibitors, which could be significant for Parkinson's disease treatment.

Purpose: Prediction of potential serine-threonine kinase inhibitors as PINK1 inhibitors and design of new chemical entities (NCEs) significant for Parkinson's disease.

Methods: Molecular modeling, including 100-nanosecond simulations, was used to predict the structures of the selected PINK1 receptors, one canonical form and four natural variants characterized by point mutations: A168P (rs768091663), G309D (rs74315355), T313M (rs74315359), and L347P (rs28940285). These models were then used for docking studies of four serine-threonine kinase inhibitors reported in the literature to assess the potential of the kinase inhibitors as PINK1 inhibitors. Finally, scaffold analysis was performed on similar drug-like compounds selected through the PubChem database searching to identify potential active scaffolds for designing new PINK1 inhibitors.

Results: Homology models of the canonical PINK1 protein and its four natural variants, designed using the template structure (PDB ID: 7MP9), showed over 90% of residues in the allowed regions of the Ramachandran plots. Molecular dynamics simulations indicated the stability of these models. Docking studies of the selected kinase inhibitors yielded reasonable docking scores (-7 to -9 kcal/mol) and revealed hydrogen bond interactions with key amino acid residues in the binding site. Five potential scaffolds were identified for the chemical synthesis of new PINK1 inhibitors.

Conclusions: Despite the lack of a crystal structure for the human PINK1 protein, we successfully modeled the canonical form and four natural variants relevant to Parkinson's disease. Molecular dynamics studies confirmed the stability of these models. The docking studies showed that the selected kinase inhibitors effectively bound to the defined binding site, and the identified scaffolds offer promising leads for the design of novel PINK1 inhibitors.

circTcf20_5772 mediates neuronal survival signaling by regulating target mRNAs

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Background: Circular RNAs (circRNAs) are covalently closed single stranded circular transcripts resulting from non-canonical „back-splicing" where 3" splice-donor site attacks 5" splice-acceptor site. circTcf20_5772 is a retinal ganglion cell (RGC) specific circRNA having differential expression in optic nerve injury v/s pro-regeneration condition. CRISPR/Cas13 mediated silencing of circTcf20_5772 in Neuro2a cell line resulted in cell death whereas antisense RNA mediated rescue of knockdown reverted the phenotype. This result implied that circTcf20_5772 has essential role in neuronal cell survival.

Purpose: Characterizing the role of circTcf20 in neuronal survival has implications in understanding RGC degeneration/regeneration. circRNAs predominantly exerts their functions via micro-RNA (miRNA) sponging, where target mRNAs are competitively regulated by the levels of circRNAs and miRNAs. The study aims to identify and validate the possible survival signaling pathway(s) and downstream target genes of circTcf20_5772.

Methods: We have computationally predicted a circTcf20-miRNA-mRNA network and integrated it with optic nerve crush data to identify differentially expressed mRNA targets of circTcf20. Gene ontology and KEGG pathway enrichment were performed to identify enriched signaling pathways. Candidate genes were validated by CRISPR/Cas13 based knockdown of circTcf20_5772 *in vitro* and real-time PCR.

Results: Computational workflow identified 1131 "sponging" miRNAs of circTcf20_5772 and 9884 genes regulated via candidate miRNAs. Among these, 3632 genes were significantly differentially expressed between injury v/s pro-regeneration conditions. 213 cell survival genes, majorly (153 genes) involved in negative regulation of the apoptotic process were identified. KEGG pathway analysis found that PI3K-Akt signaling pathway is predominantly enriched among others. qPCR revealed that Akt1, Gsk3β, Cntf, Pik3ca, Bcl3, Bcl2l2 mRNA levels were downregulated upon circTcf20 knockdown compared to control in Neuro2a cells.

Conclusion: Differential circTcf20_5772 expression corresponds to differential expression of its mRNA targets in RGC injury model and *in vitro*. Thus, circTcf20 regulates gene expression in key survival signaling pathways, potentially via its target miRNAs.

A novel role of the post-synaptic density protein Preso1 in group I metabotropic glutamate receptor internalization

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Background: Group I metabotropic glutamate receptors (mGluRs) have been implicated in various neuropsychiatric disorders like Fragile X syndrome, schizophrenia, autism and also believed to be involved in multiple forms of synaptic plasticity, including learning and memory. Intracellular trafficking of these receptors not only controls the spatio-temporal localization of the receptor; it also plays an important role in the regulation of the activity of these receptors. Thus, inaccurate trafficking of the receptor might result in improper signaling with pathological consequences.

Purpose: Preso1 is a post synaptic density protein that has been implicated in pain sensation and several neurodegenerative disorders, such as schizophrenia, autism, epilepsy etc. Improper mGluR5 signaling is also known to be involved in those diseases. Preso1 interacts with the Cterminal of mGluR5 and under control conditions, Preso1 is an inhibitor of mGluR5 signaling. Therefore, we aim to unravel the role of Preso1 in regulating the agonist-mediated internalization of mGluR5.

Methods: We used primary hippocampal neurons derived from P0/P1 mouse pups as a model to study receptor endocytosis and technique like live cell dual antibody feeding assay was used to study the internalization of the receptor. We used molecular replacement strategy where we knockdown endogenous Preso1 and expressed different deletion forms of that protein.

Results: Our data suggests that Preso1 regulates the ligand-mediated internalization of mGluR1 and mGluR5. We show that Preso1 associates with Homer1 through its Homer-binding motif and anchors CDK5 through its D-domain, both of which are necessary for the ligand-mediated endocytosis of mGluR5. A point mutation at the C-terminus of Preso1 (V1312A) inhibits the binding of Preso1 to PDZ-domains of different PSD proteins also blocks mGluR5 endocytosis.
Future research- We will investigate the role of the Preso1 on the mGluR-mediated AMPA receptor trafficking, which is believed to be the cellular correlate for the mGluR-dependent synaptic plasticity.

Therapeutic Properties of Exosomes Derived from Human Dental Pulp Stem Cells: An *In Vitro* Analysis

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Background: Epilepsy affects an estimated 50 million people worldwide with no sociodemographic boundary. When there is a distortion of the normal balance between excitation and inhibition in the brain, it leads to the occurrence of a seizure. Alterations at the many levels of the brain functions, from genes and subcellular signaling cascades to widespread neuronal circuits, can result in an imbalance of excitation and inhibition. The factors that alter the balance of excitation and inhibition can be either genetic or acquired.

Purpose: In neurological disorders, exosomes derived from stem cells are emerging as a promising treatment modality for neurological diseases. Exosomes are nano-size extracellular vesicle generated by all kinds of cells that is involved in intercellular communication through transferring biomolecules to host cells.

Methodology: In the present study, using an *in vitro* model of excitotoxicity, we investigated the neuroprotective potential of exosomes derived from human dental pulp stem cells. The antineurotic, antiapoptotic, and antioxidant activities were estimated. Further, the endogenous nerve growth factor expression was analyzed.

Results: Our preliminary results revealed that exosomes could confer neuroprotection through activation of free radical scavenging enzymes and upregulation of nerve growth factors.

Conclusion: Dental pulp stem cells derived exosomes can protect hippocampal neurons in neurological conditions like epilepsy.

Celastrus paniculatus Treatment Ameliorates Rotenone-Induced Motor and Cognitive Deficits in Rats

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Background: Parkinson's disease (PD), a common neurodegenerative disorder, is marked by various motor and non-motor impairments. Rotenone exposure impairs Complex I in the mitochondrial electron transport chain of dopaminergic neurons, reducing antioxidant levels and triggering oxidative stress. *Celastrus paniculatus* (CP), a medicinal plant, is known for enhancing learning, memory, and its antioxidant properties.

Purpose: To study the effect of CP on rotenone-induced motor and cognitive impairments in rats.

Methodology: Rats received rotenone (1.5 mg/kg s.c.) every other day and CP (200 and 400 mg/kg i.p.) daily for 28 days. Behavioral tests were conducted from days 15 to 28. On day 29, after the tests, the rats were sacrificed, and hippocampal BDNF and striatal dopamine levels were measured using ELISA kits. Additionally, oxidative stress markers (SOD, GSH, CAT, and MDA) in the hippocampus and striatum were assessed.

Results and Discussion: Rotenone exposure led to significant behavioral deficits, such as reduced sucrose preference, locomotion, exploratory behaviour, muscle strength, motor coordination, balance, and recognition memory, all linked to oxidative stress with lower antioxidant levels and higher lipid peroxidation. Rotenone also lowered hippocampal BDNF and striatal dopamine levels. CP treatment improved these behaviours, increasing sucrose preference, locomotion, muscle strength, motor coordination, balance, and recognition memory. These improvements were associated with higher antioxidant levels, reduced lipid peroxidation, and increased hippocampal BDNF and striatal dopamine levels.

Conclusion: The results emphasize CP's therapeutic benefits in mitigating the behavioural and biochemical disturbances triggered by rotenone in rats, mediated by its antioxidant and neuroprotective properties.

APOE4 mediated protein synthesis response and its effect on bioenergetics is regulated by AMPK

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Background: APOE4 is a genetic risk factor for Alzheimer's disease (AD), significantly increasing its likelihood and lowering the age of onset. In heterozygous individuals, the AD frequency is 47% by age 76, while in homozygous individuals, it rises to 91% with an onset around age 68. APOE4 is linked to several AD-related pathological features, including early synaptic and mitochondrial dysfunction. It disrupts basal and activity-mediated protein synthesis by altering calcium signaling in neurons, crucial for maintaining synaptic plasticity. APOE4 elevates cytosolic calcium through NMDARs and L-VGCCs, increasing eEF2 phosphorylation and reducing protein synthesis. Protein synthesis is energy-intensive, and protein synthesis downstream of NMDAR and mGluR stimulation is linked to bioenergetics, primarily controlled by AMPK, an energy sensor activated by low ATP or elevated calcium levels. However, the impact of APOE4 on AMPK, protein synthesis, and bioenergetics remains unclear.

Purpose: This study aims to examine APOE3 and APOE4's effects on AMPK and their regulation of protein synthesis and mitochondrial dynamics.

Methods: Rat primary cortical neurons (DIV 15) were treated with recombinant APOE3 or APOE4 proteins. AMPK phosphorylation and mitochondrial fission-fusion factors (DRP1, OPA1, and MFN2) were measured using immunoblotting. The role of AMPK in regulating APOE4 mediated protein synthesis was measured using FUNCAT in the presence of compound C which inhibits AMPK activity.

Results: APOE4 treatment significantly increased AMPK phosphorylation. Inhibition of AMPK with compound C rescued APOE4-mediated protein synthesis inhibition. APOE4 also increased DRP1 phosphorylation, indicating enhanced mitochondrial fission, without affecting fusion markers.

Conclusion: APOE4 disrupts protein synthesis through AMPK activation and alters mitochondrial fission-fusion dynamics.

Putative role of sirtuin 1 (SIRT1) in post-traumatic epilepsy: evidence from the iron-induced experimental model

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Background: Epilepsy is a complex neurological disorder with multiple genetic causes. Sirtuin 1 (SIRT1) is a NAD-dependent deacetylase from the sirtuin family of intracellular regulatory proteins involved in energy balance and neuronal survival. At the same time, no published studies demonstrate the role of SIRT1 in post-traumatic epilepsy.

Purpose: The present study intended to investigate the role of SIRT1 in an iron-induced experimental model of post-traumatic epilepsy in light of electrophysiological and behavioural indices.

Methods: Male Wistar rats were given an intracortical injection of $FeCl_3$ (5 µl of 100 mM solution) in the somatosensory cortex. After 15 days, resveratrol (SIRT1 activator; orally for 15 days) and Ex-527 (SIRT1 inhibitor; i.p. 4 doses two days apart) were given 15 days later. Electrophysiological analysis, morris water maze test, and open field test were employed to evaluate the effect of SIRT1 activation and inhibition.

Results: Epileptic rats demonstrated spontaneous and recurrent seizures in the cortex and hippocampus, which coincided with multiple unit activity (MUA) counts. In contrast, epileptic rats given resveratrol displayed lesser epileptiform episodes and MUA counts. The MWM test showed increased escape latency and resveratrol treatment dramatically reduced it without affecting swimming speed. Moreover, epileptic rats covered less distance in OFT and spent less time in the center zone than controls. Resveratrol treatment for epileptic animals reduced these alterations. In contrast, epileptic rats treated with Ex-527 showed no significant change in EEG or behavioural markers. Control rats treated with resveratrol or Ex-527 showed no substantial changes in these measures.

Conclusion: Overall, the data show that activating SIRT1 has an antiepileptic impact, as seen by reduced epileptiform seizure activity, learning and memory, and locomotor activity in experimental epileptic rats.

Effect of Curcumin on Transgenerational *Caenorhabditis elegans* under high glucose diet

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Background: A high glucose diet is associated with metabolic disorders and neurodegenerative diseases, primarily through mechanisms involving inflammation and oxidative stress. Chronic elevated glucose levels can damage nerves over time, leading to neuropathy. *Caenorhabditis elegans* is a widely used model organism due to its simplicity and well-characterized biology, making it a valuable model for studying the effects of a high glucose diet and the potential transgenerational impacts. Curcumin, a bioactive compound found in turmeric, is known for its anti-inflammatory and antioxidant properties. In *C. elegans* models, curcumin has been studied for its potential to ameliorate high glucose diet and improve metabolic health

Purpose: This study aims to investigate the impact of a high glucose diet on *C. elegans*, with a specific focus on transgenerational effects. Additionally, the study evaluates the potential ameliorative effects of Curcumin, a natural polyphenol with known antioxidant and anti-inflammatory properties, on the adverse effects of a high glucose diet.

Method: *C. elegans* were exposed to a high glucose diet, and assays were attempted, including behavioral, lifespan, and antioxidant assays, to observe the impact on the F1 and F2 generations. Curcumin was administered to assess its potential to mitigate the effects of high glucose.

Result: The results indicate that a high glucose diet has a cascading effect on *C. elegans* and its subsequent F2 generation. Curcumin supplementation was found to reduce oxidative stress and improve the overall health of the worms. From our studies it is observed that Curcumin has the potential to reverse some effects of high glucose diet.

Conclusion: A high glucose diet adversely affects *C. elegans*, leading to harmful transgenerational effects. Curcumin appears to offer potential benefits by reducing oxidative stress and improving overall worm health. This suggests that curcumin could be a potential agent for reducing the effects of high glucose levels.

Early-Life Gut Dysbiosis Shapes Adult Anxiety: A Longitudinal Study of Microbiota Alterations and the Microbiota-Gut-Brain Axis in Mice

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Background: Early childhood is crucial for physical, metabolic, cognitive, emotional, and social development, with long-term impacts on adult life. Given that children constitute a significant portion of the global population, understanding factors affecting their development is paramount. The gut microbiota composition during this critical period is easily modulated by external factors such as diseases, diet, lifestyle, and drugs, leading to a widespread and increasing incidence of gut dysbiosis in this population. Such perturbations can significantly affect the microbiota-gut-brain axis, potentially altering brain development trajectories and increasing the risk for neurological issues.

Purpose: This study aims to elucidate the long-term effects of early-life gut dysbiosis on behavioural alterations and emotional regulation. We seek to address the existing gap in literature regarding the role and mechanistic insights of early-life gut dysbiosis with later-life anxiety-like behaviours.

Methods: Using antibiotics, a gut dysbiosis model was induced in C57BL/6 wild-type mice. The gut microbiota was characterized through 16S rRNA sequencing, and anxiety-like behaviours were assessed in young and adult mice using the Open Field Test and Elevated Plus Maze.

Results: Early-life gut dysbiosis in young mice led to severe microbial alterations, characterised by significant reductions in the abundance, diversity, and richness of gut microbiota. We observed a marked decrease in beneficial genera, such as *Muribaculacea_ge*, *Lachnospiraceae_NK4A136_group*, and *Rikenellaceae_RC9_gut_group*. Concurrently, there was an increase in potentially pathogenic genera, including *Escherichia-Shigella* and *Clostridia_vadinBB60_group_ge*. These dysbiotic mice exhibited anxiety-like behaviour, which positively correlated with the overgrowth of pathogen-associated genera. Notably, this anxiety-like behaviour persisted into adulthood, underscoring the enduring repercussions of early-life microbiota disruption on the microbiota-gut-brain axis.

Conclusion: Our findings provide compelling evidence for the long-term behavioural and emotional consequences of early-life gut dysbiosis, emphasising the critical need for microbiome-targeted interventions in early childhood to promote lifelong mental health.

Plasma membrane damage caused by Aβ40 and Aβ42 oligomers triggers repair by altering actin-membrane dynamics

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Background: The hallmark of neurodegenerative diseases is the progressive development of pathology. Among them, Alzheimer's disease (AD) is the most common. Oligomers of amyloid beta (oAβ) are receiving significant attention for their potential neurotoxicity. The interaction of amyloid-β (Aβ) peptides with the plasma membrane (PM) may lead to the formation of higher-order aggregates and progressive neurotoxicity in AD.

Purpose: This study could provide insight into the roles of Rab3 and PAK1 in oAβ-induced membrane damage and repair, as well as in the spread of pathology between cells in AD.

Methods: Cell culture, Western Blot, Immunocytochemistry, Confocal microscopy and Total Internal Reflection Microscopy

Results: We found that $A\beta_{1-42}$ oligomers induce the formation of intercellular membrane nanotubes. This is preceded by PM damage, which triggers a PM repair cascade involving lysosomal exocytosis, endocytosis, and actin remodeling. In our study, we demonstrated that endocytosis mediated by phosphorylated p21 Activated Kinase 1 (pPAK1) regulates Rab3a-dependent vesicle fusion/exocytosis to repair oAβ-induced PM damage in neuronal cells. The aggregation-prone peptide $A\beta_{1-42}$ oligomers significantly boost pPAK1-dependent endocytosis and Rab3a-dependent exocytosis to aid in plasma membrane repair (PMR) compared to $oA\beta_{1-40}$. We have shown, for the first time, the kinetics of Rab3a-mediated PMR in response to Aβ peptide oligomers using total internal reflection fluorescence (TIRF) microscopy. EGFP-Rab3a vesicles fuse more rapidly with the plasma membrane after treatment with $oA\beta_{1-42}$ compared to control and $oA\beta_{1-40}$ treated neuronal cells. IPA-3 is a selective inhibitor of PAK1 that works without affecting ATP. It helps prevent the internalization of oAβ and PM repair. When the expression of Rab3a is reduced, it inhibits pPAK1 and disrupts PMR, which can result in neuronal cell death.

Conclusion: Targeting molecules in PMR pathways could lead to new therapeutic approaches for AD by addressing Aβ aggregate-induced damage and spread.

Role of Inflammatory Biomarkers in Differentiating Vascular Dementia and Alzheimer's Disease from Healthy Subjects: A Comparative Study

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Background: Vascular dementia (VaD) is the second most prevalent form of dementia after Alzheimer's disease (AD), both of which are marked by progressive cognitive decline. Emerging evidence suggests that chronic inflammation plays a pivotal role in the pathogenesis of these disorders, potentially accelerating neurodegeneration and vascular dysfunction. However, the role of specific inflammatory biomarkers in differentiating these conditions remains underexplored, with previous studies yielding inconsistent results.

Objective: The present study aims to evaluate the utility of proinflammatory biomarkers—interleukin-15 (IL-15), serum amyloid-A (SAA), and procalcitonin (PCT)—in distinguishing patients with AD and VaD from healthy controls (HCs) in a North Indian population.

Methods: This cross-sectional study enrolled patients diagnosed with VaD (n=25), AD (n=23), and HCs (n=16). Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Serum concentrations of IL-15, SAA, and PCT were measured using enzyme-linked immunosorbent assays (ELISAs).

Results: SAA levels were significantly elevated in both the AD and VaD groups compared to HCs ($p < 0.05$), with AD patients exhibiting the highest concentrations. Interestingly, IL-15 and PCT levels were unexpectedly higher in HCs compared to dementia groups, presenting a paradox in the expected inflammatory profiles. In VaD patients, PCT levels negatively correlated with MMSE and MoCA scores ($p < 0.05$), suggesting a potential link between systemic inflammation and cognitive performance. Conversely, correlations in the AD group were inconsistent with initial hypotheses, requiring further exploration. Notably, multiple regression analysis identified elevated SAA as an independent risk factor for cognitive impairment in AD patients.

Conclusion: This study identifies SAA as a potential peripheral biomarker for cognitive impairment in both VaD and AD, with particular relevance to AD pathology. The unexpected elevations of IL-15 and PCT in healthy controls necessitate further investigation, potentially indicating a complex, non-linear relationship between systemic inflammation and neurodegeneration.

Differential unfolded protein response in Alzheimer's disease-related Astrocytes

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Background: Astrocyte dysfunction contributes to pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD). Since ER is a major proteostasis regulator, it is crucial for modifying the cellular environment and triggering the unfolded protein response (UPR) in neurodegenerative illnesses like these. However, the impact of inflammatory modulators is less evident when maladaptive UPR in response to increased doses of amyloid beta cause cortical astrocytes to undergo apoptosis.

Purpose: The aim of investigation is to find out whether the moderate dosage of oligomeric Amyloid beta (1-42) has impact on neuroinflammation via UPR causing metabolic alterations in astrocytes.

Methods: In this study, primary astrocyte culture maintained in serum free conditioned medium has been subjected to qRT-PCR, western blot, imaging to evaluate the effect of a moderate dose of Amyloid beta (1-42) on metabolic changes particularly on UPR response.

Results: The astrocyte culture has been characterized morphologically as well as genetically upon Amyloid beta treatment in different time points. Anti-inflammatory molecules were the major entities during early hours of Amyloid beta exposure. However, pro-inflammatory molecules were upregulated upon prolonged Amyloid beta. We found that UPR has been initiated in astrocytes. ER membrane bound stress sensor proteins like PERK and IRE1α have been activated as well as altered in its protein level in a time dependent manner in response to this moderate dose of Amyloid beta administration. We have also checked the expression profile of components of UPR response pathway in 5xFAD mice and the findings were comparable to the results of culture system.

Conclusions: Astrocytes responded differently compared to neurons upon a moderate dose of Amyloid beta treatment as per involvement of neuroinflammatory modulators and ER stress is limited to UPR.

A novel protein aggregation marker shows improved property of protein aggregate detection and quantification in models of neurodegeneration

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Background: Thioflavin T (ThT) and Thioflavin S (ThS) are fluorescent dyes widely used in the study of protein aggregation in neurodegenerative diseases such as Alzheimer's Disease (AD). These dyes are known for their high affinity for fibrils, which are aggregates of misfolded proteins that form beta-sheet-rich structures. The limitation of these fluorophore molecules is its autofluorescence and low stoke shift properties.

Purpose: A nickel (II) complex (KRS) featuring a planar bis-benzothiazole ligand was designed and tested as novel fluorophore to detect protein aggregation *in-vitro* and *in-vivo*. This novel molecule has stable photo-optic properties, broader excitation and emission spectra, noautofluorescence, cost-effective, and is biocompatible compared to other available compounds.

Methods: For *in-vitro* system, SH-SY5Y cells were challenged with amyloid-beta(Aβ) oligomers for 24 hours. Post-incubation the cells were fixed and stained with DAPI and KRS for image acquisition. *In-vivo* analysis was carried out with a pharmacological model of AD by KRS administration intravenously and 48 hours post KRS injection, brain tissues were harvested for fluorescence imaging analysis.

Results: The study explores the efficacy of KRS in binding and highlighting protein aggregates in AD. Utilizing Confocal and fluorescence microscopy, we observed that KRS selectively binds to these aggregates, enabling their visualization and quantification. Our findings indicate that KRS successfully crosses the blood-brain barrier in pharmacologically induced AD mice and predominantly diffuses into the cortical areas of the brain.

Conclusion: KRS shows an efficient binding to Aβ aggregates with better efficacy and can be used as an alternative.

Neurobehavioral health impacts of pesticide exposure in a cohort of agricultural workers

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Background: Agricultural workers are directly working with pesticides and therefore possess greater health risk of adverse effects of pesticides while the general public comes into contact with pesticides at low levels through food and water. Although a number of health conditions have been associated with pesticide exposure, clear linkages have yet to be made between exposure and neurotoxic health effects in chronic pesticide exposure.

Purpose: The present work is an attempt to study the linkage between pesticide exposure and neurobehavioral health effects including depression and suicidal ideation in pesticide exposed population.

Methods: The preliminary data were collected from around 60 agricultural workers (age 25 – 65 years) at neighbouring villages of district Bhopal (MP) through a health questionnaire along with psychological tool to assess the risk of depression and suicidal ideation. The data were assessed through SPSS software to calculate and correlate the changes in different variables.

Results: It was observed that most of the farmers are using Cypermethrin (26.5%), Profenophos (17%), Imidacloprid (11.7%), Tolfenpyrad (7.4%). The pesticide exposed farm workers reported adverse health effects in them including dizziness (28%), Itching (24%), headache (20%), vomiting (12%), irritation in skin, eyes (4% each) and others. An increase in depressive symptoms, assessed by the Beck Depression Inventory-II was observed in pesticide exposed workers. Also, the risk of suicidal ideation is also observed in few agriculture workers.

Conclusion: Farm workers are at higher risk of adverse health effects due to unawareness and injudicious use of these pesticides. It is also observed that very few workers are using protective measures while using the pesticides due to unawareness. Further studies are in progress with large sample size to represent the better association of pesticide exposure and adverse neurobehavioral effects.

Histological and Immunohistochemical Characteristics of Corpora Arenacea in Pineal Gland – A Two Group Comparative Study

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Background: The pineal gland contains several calcified concretions called brain sand or corpora arenacea. These concretions provide a useful landmark for orientation in the diagnosis of intracranial diseases. Predominantly composed of calcium and magnesium salts, corpora arenacea are numerous in old patients. Structural characterization of CA has not been explained properly for human samples in available literature.

Purpose*:* Investigation of histological and immunohistochemical characteristics of Corpora arenacea in Pineal gland.

Method*:* Two group comparative study was done including pineal glands from two young age human brains (<25 years) and two old age human brains (>50 years). Postmortem samples were collected after proper ethical clearance from institutional ethical committee. H&E, Masson's Trichrome and Immunohistochemical staining for Amyloid and Tau expression were done.

Results*:* Number and size of CAs were more in aged. Collagen deposition within the pineal gland were found around blood vessels and in core of few CAs. Amount of collagen deposition were more in aged. Expression of amyloid were not present. Tau positivity has been found around CAs in young as well as aged.

Conclusion*:* Presence of collagen deposition and Tau positivity apart from calcific deposition within CA shows its origin is multifactorial. Exploring the exact mechanism of its formation could have a great role in understanding various clinical disorders related to pineal gland.

Circular Dichroism and Computational studies of Tau-DNA complex indicates conformational changes: Implication in Alzheimer disease

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Background: The second major hallmark of Alzheimer disease (AD) pathology is the presence of intracellular tau aggregates called neurofibrillary tangles. Tau is an important microtubule associated protein that promotes assembly and stabilization of cytoskeleton microtubules. Tau has been suggested to be a multifunctional protein, known to be localized in the nuclei of both neurons and some non-neuronal cells. Previous studies have shown that tau protein binds to DNA forming beads-on-a-string complex. However, the molecular association of tau with DNA remains a fundamental problem to be clearly elucidated.

Purpose: Our present study is concerned with the interaction of tau with DNA and, as they may provide clues and correlations to AD.

Methods: We report the binding modes of Tau with the DNA sequence 5'AATCTAATCCCCCTATA3' via Circular Dichroism (CD) studies since, DNA protection is known to be mediated through Tau.

Results: Our results indicate conformation changes at 210nm suggesting possible interactions of Tau with DNA. It is also noted that the secondary structures are attained as the tau concentration increases, and further, on addition of copper the structure of DNA appears to be perturbed. *In silico* studies corroborate with the spectroscopic studies.

Conclusion: We conclude that these interaction studies could give insights into the aggregation patterns thereby understanding the physiology of AD.

The Role of Gut Microbiota in Modulating Cognitive Behaviour in Adult Zebrafish

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Background: Environmental pollutants such as Benzo[a]pyrene alter neurobehavioral responses and induce oxidative stress-mediated neurodegeneration by exhibiting neuronal pyknosis in animal experimental models. Humans are exposed to B[a]P from food ,water, air sources ,automobile exhaust by inhalation ,dermal absorption ,direct ingestion of grilled diet and cigarette smoking. Surprisingly these neurotoxic compounds are also associated with creating imbalance in the relative abundance and diversity of the gut microbiome. Hence there is a possible connection between the alteration of neurobehavioural responses and modulation of gut microbiota suggesting a link between dysbiosis in gut and Central nervous system disorders.

Purpose: The aim of the current study is to investigate the association of neurotoxic compounds and gut microbiota in the modulation of bidirectional communication between the gut and brain.

Methods: Adult Zebrafish were grouped into five groups (Naive, Control, B[a]P, Probiotic (*Lactobacillus rhamnosus* GG), B[a]P+Probiotic) and maintained in proper laboratory conditions. Each group was treated accordingly and feeded twice with the commercial food. The last two groups were supplemented with probiotic (LGG) twice along with their normal feed. After 28 days treatment, analysis of behavioural responses were studied using T-MAZE apparatus fitted with the video tracking ANYMAZE software. After dissection of Zebrafish brain and gut tissues of all five groups, histological analysis was performed using Haematoxylin and Eosin staining and microscopic imaging.

Results: Compared to the naive and control groups Zebrafish treated with neurotoxic B[a]P showed altered behavioural responses along with dysbiosis in the gut and it was restored when modulation of gut microbiota occurred after probiotic (LGG) supplementation. The probiotic treated groups showed improvement in cognition and learning memory.

Conclusion: Probiotic (LGG) supplementation maintains symbiosis in the gut which in turn also ameliorates the cognitive behaviour in groups treated with neurotoxic compound suggesting a bidirectional communication between the gut and brain.

Using a combination of social defeat and immobilization stress to model PTSD in rats

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Background: There have been several attempts to model post-traumatic stress disorder (PTSD) in rodents. However, the field is marred by a lack of consistency and reproducibility. The current study evaluates if combining two stressors would result in a better and reproducible model.

Purpose: Development of a robust and reproducible model of PTSD to contribute to the discovery of novel therapeutics.

Methods: Adult male Wistar rats (n=12 to13/group) were randomized to 5 different groups - naïve control (CTRL), Chronic Immobilization Stress (CIS), Social Defeat Stress (SDS), Single prolonged Stress (SPS) and, CIS+SDS. The stress groups underwent the respective stress for 10 days. Followed by a sucrose preference test (SPT) on days 11 and 12, an open field test (OFT) and elevated plus maze (EPM) to assess anxiety-like behaviour (day 1), and a forced swim test (FST) to assess depression-like behaviour (day 14). Further, CIS+SDS(n=5) was validated for PTSD by freezing score to contextual cues and three-chambered social interaction test (SIT) on day 11 and 12.

Results: CIS and CIS+SDS showed a significantly lower body weight gain. The stress showed no difference in EPM and OFT. SPS and CIS did not affect behaviour in SPT or FST. SDS showed a trend of reduction and CIS+SDS showed a significant reduction in sucrose preference. Similarly, SDS and CIS+SDS showed a significant reduction of latency to immobility and total immobility, while SDS showed a trend. CIS+SDS showed significant freezing behaviour to contextual cues and a decreasing trend towards social novelty in SIT.

Conclusion: Neither SPS, CIS, SDS nor CIS+SDS affected anxiety-like behaviour in the EPM or OFT. In both SPT and FST, the combination of CIS+SDS showed a stronger depressionlike behaviour. Additional characterization of CIS+SDS showed intrusion-like freezing behaviour and impaired social novelty, thus validated to be a suitable model for PTSD.

EEG microstate – a potential objective neural marker of major depressive disorder

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Background: Major depressive disorder (MDD) a prevalent psychiatric illness has intricate neurological underpinnings that involve large scale neural connections. These networks can be studied through topological constructs known as microstates, which are both transient and quasi stable and represent the temporal dynamics of neuronal activity.

Purpose: The heterogeneity in MDD patients causes notable differences in symptoms and makes it difficult to comprehend and identify an objective biomarker of the illness. Current study investigates EEG microstate as a potential neural biomarker of MDD.

Methods: Resting-state eyes closed EEG were recorded for 29 patients with MDD and 24 healthy controls (HC) using 128-channel cap. Data driven approach to identify EEG microstate maps was applied. Temporal parameters namely mean duration, number of time frames, time coverage was calculated for each topographic map. Cortical sources of microstate were also identified.

Results: A significant increase in time frame and time coverage of microstate D ($p<0.0001$) and microstate C ($p = 0.0185$ and $p = 0.0086$) whereas a decrease in mean duration, time frames and time coverage of microstate A ($p= 0.0045$, $p<0.0001$, $p=0.0106$) were observed in patients with MDD. Microstate D cortical sources showed decreased activation at Inferior Temporal Gyrus, Middle Frontal Gyrus, Middle Temporal Gyrus, Superior Temporal Gyrus in MDD. Microstate A cortical sources showed decreased activation at Middle Frontal Gyrus, Middle Temporal Gyrus, Superior Frontal Gyrus in MDD.

Conclusion: The current microstates data show that brain network temporal dynamics are altered at a sub-second level in MDD patients and the cortical areas showing deficits in activation are associated mainly with the Frontoparietal network which is involved in executive function, goaloriented, cognitively demanding tasks and the default mode network associated with mind wandering. Overall, microstates and their cortical source activity could be used as a distinguishing factor for MDD from healthy controls and potentially serve as a biomarker.

Exploring ALS Pathophysiology in Severe Transgenic Mouse Model: A Preliminary Study

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal and rapidly progressing motor neurodegenerative disorder that results in progressive muscle weakness and paralysis. The pathophysiology of ALS is not well understood. As a result, currently, there is no specific biomarker for the diagnosis of ALS. Furthermore, Riluzole, the most common FDA-approved treatment for ALS, extends the survival only for a few months.

Purpose: The major objective of the current study is to understand the pathophysiology of ALS using a transgenic mouse model.

Methods: All the experimental procedures with mice were approved by the Animal Institutional Ethics Committee of CSIR-CCMB. Human $SOD1^{G93A}$ mice were bred and maintained at CSIR-CCMB, Animal House. Mice were genotyped for the human $SOD1^{G93A}$ gene by touchdown polymerase chain reaction. Five months old male $SOD1^{G93A}$ mice (n=5) and wild-type mice (WT, n=5) were used for the study. The motor function was assessed using a paw grip meter and rota rod test. Additionally, neurological scoring was performed to assess the severity of ALS. For neurometabolic analysis, mice were anesthetized using urethane (1.5g/kg), and infused with [1,6- $^{13}C_2$] glucose through a lateral tail vein for 10 min. The ^{13}C labeling of brain metabolites will be measured in ^{1}H-[^{13}C]-NMR spectrum of the spinal cord and cerebral cortex extract.

Results: There was a significant (p=0.002) reduction in the forelimb grip strength of $SOD1^{G93A}$ mice (0.47±0.03 N, n=5) when compared with age-matched WT control mice (1.19±0.23 N, n=5). Additionally, the motor coordination assessed by rotarod indicates that the area under the curve for $SOD1^{G93A}$ mice (10.8±10.2 revolution) is significantly lower (p=0.00005) than controls (63.5±10.8 revolution). Moreover, $SOD1^{G93A}$ mice exhibited an increase in the neurological score (2.4±0.5, n=5) when compared with WT controls (0.0±0.0, n=5). The neurometabolic analysis in the spinal cord and cerebral cortex is in progress.

Conclusion: The behavioral analysis indicated the presence of severe ALS phenotype in 5-month-old $SOD1^{G93A}$ mice.

Evaluating the biochemical effect of Beta-Sitosterol on PTZ induced seizures in *Danio rerio*

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Background: Despite progression in clinical and pre clinical epilepsy research, the conventional anti epileptic drugs (AEDs) primarily offer symptomatic relief rather than interrupting the progression of the condition. Approximately 30% of patients remain resistant to pharmacological interventions. We are looking for alternatives because current drugs focus on seizure suppression rather than working on the root cause i.e. hypersynchronization and hyperexcitability of neurons. Which ultimately leads to oxidative stress, inflammation and finally neuronal death. Phytosterols are promising phytochemicals, structurally very similar to cholesterol, due to which it can pass through the BBB and into the brain. They have been shown to have anti-inflammatory, antioxidant, i.e. neuroprotective effects, and potentially be used for AEDs.

Purpose: To evaluate the biochemical effects of Beta-Sitosterol on Zebrafish larvae when exposed to PTZ to induce seizures.

Methods: The 6 dpf zebrafish larvae were treated with Beta-Sitosterol concentration ranging from 0 to 100 ug/ml. 7 dpf zebrafish larvae were exposed to 5mM PTZ and the following was observed -

The locomotion and distance travelled by the 7 dpf larvae was assessed using FIJI. GSH detection by Ellman's method was done to assess the antioxidant activity and oxidative stress, Acridine orange (AO) assay to determine the apoptosis and RT-PCR for mRNA c-fos, which is a neuronal activity marker.

Results: Beta-sitosterol treated larvae showed less locomotion (erratic movement) and distance travelled compared to PTZ treated larvae. Changes in c-fos expression, along with less apoptosis signals were seen in the AO assay. The GSH levels revealed lessened oxidative stress. 100 ug/ml concentration of Beta-Sitosterol showed notable changes in the inflammation, oxidative stress and neuronal activity.

Conclusion: Beta-sitosterol has potential to be used in anti epileptic drugs, due to its neuroprotective properties and fast expulsion from the body, restoring the neurotransmitters to their unsaturated state.

Effect of ageing on memory interference studied through spatial learning task

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Background: Our brain receives vast amounts of information from the surroundings every day. This tremendous influx of information inundates the brain and often results in interference of memories. However, when the rate of flow of incoming information is higher than the consolidation, memories lose their distinction and fail to consolidate. .In several transient amnesias, such as during epilepsy, the memory loss is attributed to such catastrophic interference. In this context, results from our lab have shown that Parvalbumin interneurons activity plays a pivotal role in memory specificity and is affected by age. However, little is known about how memory interference progresses with age.

Purpose: We developed a paradigm to systematically and quantitatively investigate interference and study it as a function of age in a spatial learning paradigm- Morris Water Maze (MWM).

Methods: We trained the mice in two similar spatial contexts (A and B) within MWM. Context A involved 2 extra-maze cues whereas Context B involved 3 extra-maze cues. Mice were trained to find the hidden platform using these cues. Group 1 was trained in both the contexts with a gap of 24 hours which is sufficient to consolidate the memory. Group 2 was alternated between the two contexts while training to cause memory interference. We also intend to see the extent of memory interference on activating or suppressing PV interneurons in PV-cre mice.

Result: We observed that in Group 1, memory of Context A and B are interfering in younger mice whereas older ones have better retention of both contexts. In Group 2, memory of Context A is being interfered by Context B in older mice whereas younger ones have memories of both contexts intact.

Conclusion: We have noted a trend between memory interference as a function of age varying with the context. Further analysis is going on to confirm these findings.

Role of Lateral hypothalamus in stress modulation of itch

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Background: Stress is a potent modulator of emotion, cognition, pain and itch perception. Clinical and preclinical studies also suggest stress to exacerbate itch by mediating the release of neuropeptides and hormones while activating the immune system. Although stress has been long known to have overlapping mechanisms with itch, yet the precise neural circuit of stress dependent itch modulation is not well understood.

Purpose: Chronic itch is one of the most common yet hard to treat symptom accompanying various dermal and systemic conditions. Understanding this complex neural mechanism might possibly help to develop a novel and effective treatment of chronic itch. Therefore, we sought to explore the stress mediated itch modulation under acute and chronic conditions in mice.

Methods: Taking advantage of TRAP2 mice along with viral genetic tools, we captured and modulated the lateral hypothalamic stress (LH^{stress}) sensitive neurons. Further, we used DREADDs to activate/inhibit the LH^{stress} neurons and fiberphotometry to record the neural activity of LH^{stress} neurons while mice were challenged to acute and chronic itch.

Results: Here, we report that activation of LH^{stress} neurons is sufficient for supressing scratching behaviour in mice. Fiberphotometry recordings from the LH^{stress} neurons suggests that these neurons are not directly involved in itch-scratch processing yet in chronic state we found the LH^{stress} neurons to be activated by scratching. Thereby suggesting the induction of some plastic changes in LH^{stress} neurons. Next, we mapped the pre- and post-synaptic sites of LH^{stress} neurons and found it to be heavily interconnected with regions that are involved in stress perception and pain and itch modulation.

Conclusion: Activation of LH^{stress} neurons can suppress itch behaviour in mice. Altogether we reveal an ensemble of LH^{stress} neurons, which can be targeted for treatment of stress-induced exacerbation of chronic itch.

Exploring The Neuroprotective Effects of PIP@CMs in Alzheimer's Disease Models

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Background: As the intricate interconnections of the several mechanisms involved in the disease make it impossible for mono-therapeutic treatments to be used in clinical contexts, multi-targeted therapy has emerged as a promising technique for the treatment of Alzheimer's disease (AD). It has received a lot of spotlight recently how mitochondrial damage contributes to the aetiology of AD. Piperine is an alkaloid isolated from black pepper, exhibits miscellaneous pharmacological properties including antidepressant, anticonvulsant and also enhancing activities of other nutraceuticals. The pharmacokinetic and bioavailability characteristics of the medications delivered are significantly regulated by the modulatory actions of piperine on drug metabolising enzymes and believes that a suitable therapeutic candidate for multifactorial degenerative disease like AD.

Purpose: Investigating the preventive efficacy and neuroprotective mechanisms of piperine against $A\beta_{(1-42)}$ induced neurotoxicity was our primary goal in the current study.

Methodology: Human recombinant protein $A\beta_{(1-42)}$ peptide was treated to human neuroblastoma SHSY.5Y cell lines and Piperine (PIP) and Piperine loaded casein micelles (PIP@CMs) was treated as dose-dependent manner. Intracellular homeostasis and cell death were evaluated using various assays like intracellular ROS generation, ATP production, Ca^{2+} measurement and mitochondrial membrane potential. Therapeutic efficacy of PIP@CMs against $A\beta_{(1-42)}$ induced neurotoxicity was explored by these aforementioned assays. An impairment in memory function was elicited in rat brain via intracerebroventricular injection of $A\beta_{(1-42)}$ oligomer. The neuroprotective efficacy of PIP@CMs were investigated including spatiotemporal memory function through MWM, NORT and HBT.

Results: Experimental data revealed that PIP@CMSs protects the SH-SY5Y cells from oxidative damage and altered mitochondrial homeostasis caused by $A\beta_{(1-42)}$ induced neurotoxicity by dose-dependent manner. In Morris water maze and Novel object recognition tests, the intraperitoneal injection of PIP@CMs lessened cognitive deficit resulting from $A\beta_{(1-42)}$. These findings suggests that at early stages of AD, PIP@CMs would be a promising therapeutic candidate.

Alterations in the hippocampal subfields on cognitive training and enrichmentenvironment supplements the impoverished cognitive reserve of aging rats

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Background: Non-pathological cognitive decline is widely prevalent among the aging population. The rate of decline is dependent on cognitive reserve, the ability of an individual to use the neural substrates effectively in executing highly demanding tasks. Ageing associated decrease in holisticsynaptic activity and structural alterations contribute to poor cognitive reserve.

Purpose: The current study was designed to assess the impact of multi modular cognitive training targeting various facets of learning and memory and exposure of environmental enrichment on thehippocampal subfield neurons.

Methods: Male Wistar rats aging 18 months were sorted into Control, Ct and Ct+ee group. Ct and Ct+ee rats were subjected to cognitive training(Ct) and cognitive training with 2hr/day of enrichedenvironment(Ct+ee) exposure respectively. Spontaneous behavioral tasks to assess working memory and recognition memory were performed on the 30th day. Hippocampal CA1(cornu ammonis), CA3 and DG(dentate gyrus) neurons were analyzed for dendrite length, arborization, and spine density. Hippocampal levels of PSD95(post synaptic density), Synaptophysin, and BDNF(brain derived neurotrophic factor) for cognition, p-tau for neurodegeneration and p53 for senescence were quantified.

Results: Ct rats performed significantly better than control rats and had altered dendrite profiles at DG and basal tree of CA1 region. Ct+ee rats outperformed Ct rats. Ct+ee rats' hippocampal neurons had increased dendrite length, arborization, and spine density at DG and apical and basal tree of CA1 and CA3. Both groups had increased PSD95, synaptophysin and BDNF expressionwhile p-tau and p53 levels were decreased.

Conclusion: The cognitive training facilitated the aged rats to utilize their working and reference memory, identify and discriminate patterns in cues to execute the tasks. The cognitive training andenriched environment supplemented the cognitive decline associated with aging and had a comprehensive effect on the neuronal health augmenting the impoverished cognitive reserve in aged rats.

Seizure-induced aberrant neurogenesis in the hippocampus is associated with alterations of neurogenic niche and cognitive impairments

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Background: Adult hippocampal neurogenesis plays a significant role in higher brain functions like synaptic plasticity, cognition and mood regulation. It is hypothesized that the impairment of some of these functions following brain insults is promoted by alteration of the neuronal activities at the neurogenic niche.

Purpose: Our present study demonstrates how the neurogenic niche of the dentate gyrus in the hippocampus is altered and is associated with aberrant neurogenesis, in response to kainic acid (KA) induced status epilepticus (SE). We also sought to evaluate the impact of these neurogenic niche-specific alterations on synaptic plasticity, mood and cognition.

Methods: KA was administered once intraperitoneally. The seizure-associated behavioural phenotypes were monitored and documented. Transcardial perfusion was performed and the brain samples were fixed and further processed by cryosection. Immunofluorescence was performed using a routine procedure. Golgi-Cox staining was employed to evaluate neuronal morphology and synaptic plasticity. Behavioural tests were performed to assess mood and cognition.

Results: We have reported an activation-dependent conversion of radial glial-like neural stem cells (NSCs) to gliogenic NSCs with a reactive morphology, in the sub-granular zone after SE. Abnormal morphological phenotypes of the DCX+ cells and granule neurons followed by their ectopic migration were observed at the neurogenic niche. Reduced dendritic spine density and low mature dendritic spine expression were found in DG, CA3 and CA1 regions. Moreover, the treated mice were observed to have behavioural deficits (anxiety; depression) and memory dysfunctions. (recognition memory and spatial memory).

Conclusion: In response to seizure, the NSCs at the neurogenic niche undergo a fate transition shifting from the neurogenic to gliogenic program to induce reactive gliosis and disruption of the neurogenic niche. Further, this phenomenon intensified aberrant neurogenesis and reduced the synaptic plasticity of the hippocampus. Additionally, it led to an anomalous rewiring of hippocampal circuitry and compromise of the hippocampal-mediated cognitive functions.

Effect of Childhood Obesity on Cognitive performance during visual Go/NoGo test: A pilot study

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Background: Childhood obesity, an emerging threat in India has been reported to hold an inverse relationship between childhood obesity and cognitive development. However, the evidence supporting this link between childhood obesity and cognitive function is still limited with debatable results.

Purpose: To investigate the relationship between childhood obesity and event-related potentials (ERP) related to higher-order cognitive functions of executive control and response inhibition.

Methods: This pilot study was conducted on 10 pediatric subjects in each group (healthy control and obese; aged 9 to 15 years). Anthropometric assessment and body composition measurement was followed by ERP recording using the visual Go-NoGo paradigm at the central electrode sites (Fz, Cz and Pz). Unpaired t test and Pearson's correlation was applied for continuous variables.

Results: NoGo N2 amplitude was decreased fronto-centrally in obese children as compared to nonobese (though not significantly) suggesting reduced response inhibition. Also significantly decreased NoGo P3 amplitude at Cz indicates reduced 'NoGo anteriorization' in obese ($p = 0.010$). Negative correlation ($r = -0.406$) of percent body fat with NoGo P3 amplitude at Cz and positive correlation ($r = 387$) with NoGo P3 latency at Pz further corroborates the fact that increased body fat leads to compromised conflict management during cognitive task.

Conclusion: The trend shows that obesity might cause an impairment in the conflict management and response inhibition in pediatric subjects which may be reflected in their mental flexibility and decision making abilities.

Synbiotics Laden with *Faecalibacterium prausnitzii*, Fructooligosaccharides, and Galactooligosaccharides Mitigate Quinpirole-induced OCD-like symptoms in Rats

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Background: Obsessive-compulsive disorder (OCD) is a debilitating mental illness of unwanted repetitive thoughts and behaviors. The significance of the microbiota-gut-brain axis has increasingly been documented in the manifestation of neuropsychiatric disorders.

Purpose: Herein, we investigated the effect of synbiotic, containing *Faecalibacterium prausnitzii* ATCC27766*(F. prausnitzii*) and prebiotics [fructooligosaccharides (FOS) and galactooligosaccharides (GOS)], on quinpirole-induced OCD-like symptoms in rats.

Methods: The repeated quinpirole injections (0.5 mg/kg) showed compulsive- and anxiety-like responses in rats assessed by marble-burying (MBT), self-grooming, hole board (HBT), and elevated plus maze (EPM) tests. Molecular and histological analyses were conducted on brain, intestine, and fecal samples using various techniques.

Results: Quinpirole-injected rats displayed less head dipping in HBT, a higher frequency of marble burying and self-grooming episodes, and avoided exploration of open areas in the EPM. Administration of *F. prausnitzii* and prebiotics (FOS+GOS) for six weeks ameliorated the quinpirole-induced repetitive, self-directed, compulsive, and anxiety-like phenotypes. The locomotor activity in the open-field test and body weight remained unaffected across the groups. In molecular studies, *F. prausnitzii* and prebiotics (FOS+GOS) treatment showed a reversal of elevated levels/mRNA expression of TNF-α and IL-6 in the frontal cortex and increased mRNA expression of tryptophan hydroxylase (TPH-1) in the colon of quinpirole-injected rats. The hippocampal brain-derived neurotrophic factor levels remained unchanged across the groups. The levels of acetate, propionate, and butyrate in fecal samples and the villi/crypt ratio and goblet cell count were restored in the synbiotics-recipient group.

Conclusions: These findings confer the potential benefits of synbiotics laden with *F. prausnitzii* and prebiotics (FOS+GOS) in quinpirole-induced OCD-like symptoms by reshaping animal gutbrain-axis mediators.

A Study on Neuropathic Pain by Partial Sciatic Nerve Ligation in Rats

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Background: Neuropathic pain results from injury to the nervous system. The exact mechanism remains poorly defined though aberrant neuronal activity may be partly responsible for it, that common conditions are diabetes, herpes zoster and nerve trauma. Previous reports indicates that the pain is poorly attenuated by opioids and NSAIDs. The present study evaluates the anti-nociceptive effect of these drugs on neuropathic pain in rats.

Purpose: To replicate neuropathic pain in rats by damage to sciatic nerve. Another objective was to confirm the effect of Morphine and Ketoprofen.

Methods: Sprague-Dawley rats (n=36;150-170g) were used for the experiment after obtaining permission from ethics committee. The animals were divided into the following groups: Group-I (n=12) and Groups-II-V (n=6 each). PSNL (Partial Sciatic Nerve Ligation) surgery was performed in Group-I rats and nociception was assessed on days 7, 14 and 21 whereas Group-II underwent sham surgery without damage to the sciatic nerve. Group III-V rats were subjected to PSNL and also received the following drugs on day 14: Morphine 10mg/kg, Ketoprofen 10mg/kg and Morphine + Ketoprofen combination respectively. Rats were euthanized by CO_2 inhalation. Sciatic nerve segments were collected for histological and ultrastructural study. Data were analysed by GraphPad prism software.

Results: Rats with PSNL showed nociception on all the days as compared to the baseline value. Nerve damage was also noted along with myelin degeneration in routine histological and ultrastructure study. Maximum nociception was observed on day 14 after nerve damage. Morphine was effective in relieving neuropathic pain though Ketoprofen was ineffective. However, Morphine + Ketoprofen showed an enhanced effect, likely due to synergistic interaction.

Conclusion: The PSNL surgery produced consistent results including neuropathic pain in rats. Contrary to some earlier reports morphine was significantly effective though Ketoprofen could not produce any antinociception. Therefore, opioid like Morphine can be administered to relief neuropathic pain under certain conditions. Morphine has severe side effects like respiratory distress which should be kept in mind.

Mapping Brain Network Disruptions in Functional Seizures: A Focus on Adolescent Females

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Background: Psychogenic non-epileptic seizures (PNES), also known as functional seizures (FS), are characterized by seizure-like episodes without the abnormal electrical activity seen in epilepsy. These episodes predominantly affect adolescent females, emphasizing the need to understand their underlying neurological mechanisms. Source-Based Morphometry (SBM) is an advanced neuroimaging technique that identifies connectivity patterns within grey matter (GM) and white matter (WM) networks, offering insights into brain network abnormalities in FS.

Purpose: This study aimed to map brain network disruptions in adolescent females with FS using SBM. To provide a comprehensive view, we also integrated structural and functional MRI data, allowing a detailed examination of connectivity patterns within GM and WM networks. FS patients were compared with healthy controls.

Methods: Seventy participants were included: 35 adolescent females (ages 11-18) diagnosed with FS and 35 healthy controls, all recruited from the Child Psychiatry Unit of the Department of Psychiatry at King George Medical University, Lucknow. Imaging was conducted using a 3T Siemens Magnetom Skyra scanner with a T1-weighted MPRAGE sequence. SBM identified independent components (ICs) representing GM and WM networks, while fusion of structural and functional MRI data enabled integrated analysis. Statistical comparisons assessed connectivity differences between FS patients and controls.

Results: FS patients showed increased connectivity between the somatosensory motor network and dorsal attention network (DAN) in GM, indicating atypical sensory-attentional integration. In WM, FS patients demonstrated heightened connectivity between the salience network and the visual/language networks, suggesting disrupted communication between emotion regulation, sensory processing, and language functions.

Conclusion: This study reveals significant brain network disruptions in adolescent females with FS, providing insights that may guide targeted therapeutic strategies.

Effect of reappraisals on the extinction of conditioned fear responses

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Background: Fear extinction is a popular approach to regulate fear responses. However, successful fear extinction could result in relapse of fear, this demands a strategy that could enhance extinction.

Purpose: The current study investigated the effect of different nature of cognitive reappraisal on fear extinction and recall.

Method: We used a 3-day screaming lady fear conditioning paradigm with 63 participants (M=43, F=20) (Mean age=20.6, SD=1.40) and fear, valence, expectancy ratings and SCR as outcome measures. The participants were randomly divided into three groups: Creative reappraisal (CR; n=23), Ordinary reappraisal (OR; n=21) and Standard extinction (SE; n=19).

Results: A one-way ANOVA revealed a significant difference on differential fear ratings during extinction [F (2,62) = .112, p = .05] with OR indicating lower fear ratings than CR group. In extinction recall phase the groups differed significantly on differential fear ratings [F (2,62) = 3.902, p = .026]. We found a trend-level significant difference between OR and CR group and a significant difference between OR and SE group. A rmANOVA of early and late trials of extinction expectancy ratings showed a significant main effect of trial type [F (1,60) = 33.011, p < .001, ηp2 = .355] with higher expectancy in early trials implying higher initial prediction error.

Conclusion: Our results imply a superior effect of OR in attenuation of fear. Believability and context of reappraisal are related to implementation cost of reappraisals. CR results in a higher implementation cost hence less effective in reducing fear. Further, targeting UCS aversiveness through reappraisal does not inhibit extinction. These results might aid with interventions for anxiety disorders using reappraisal. Cognitive reappraisal is a core part of cognitive behaviour therapy (CBT), the results could aid in improving CBT.

Comprehensive Benchmarking of CNN-Based Tumor Segmentation Methods Using Multimodal MRI Data

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Background: Magnetic resonance imaging (MRI) has become a critical and primary technique for detecting brain tumors. However, manually segmenting tumors from scans is laborious and timeconsuming, leading to a growing trend towards fully automated methods for precise tumor segmentation in MRI scans. Accurate segmentation of tumors is vital for improving diagnosis, treatment, and prognosis.

Purpose: This study benchmarks and evaluates four widely used CNN-based methods CaPTk, 2DVNet, EnsembleUNets, and ResNet50 for brain tumor segmentation using MRI scans, aiming to identify the most accurate and reliable method for clinical decision-making.

Methods: The study used 1251 multimodal MRI scans from the BraTS2021 dataset to compare the performance of four CNN-based methods against a radiologist-annotated reference dataset. Evaluation involved direct comparison of segmented images and analysis of radiomic features using the pyRadiomics library. The Dice Similarity Coefficient and Hausdorff Distance were the main accuracy metrics, with further validation on an independent dataset of 611 samples from the UPENN-GBM dataset.

Results: EnsembleUNets demonstrated superior performance among the evaluated methods, achieving a DSC of 0.93 and an HD of 18 on the BraTS2021 dataset. Comparative analysis of radiomic features further confirmed EnsembleUNets as the most precise segmentation method, with Concordance Correlation Coefficient (CCC) of 0.79, Total Deviation Index (TDI) of 1.14, and Root Mean Square Error (RMSE) of 0.53. Validation on the independent UPENN-GBM dataset supported these findings, with EnsembleUNets achieving a DSC of 0.85 and an HD of 17.5.

Conclusion: The study identifies EnsembleUNets as the most effective CNN-based method for brain tumor segmentation in MRI scans, outperforming CaPTk, 2DVNet, and ResNet50. The high accuracy of EnsembleUNets in both the primary and independent datasets highlights its potential as a reliable tool for clinical use, offering significant benefits in the diagnosis, treatment, and prognosis of brain tumor patients.

Premenstrual Dysphoric Disorder (PMDD): Characterization of a Rodent Model Using Progesterone Withdrawal

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Background: Premenstrual Dysphoric Disorder (PMDD) is a severe reproductive mood disorder characterized by cyclical presentation of symptoms in the luteal phase of the menstrual cycle. The exact pathophysiological mechanisms underlying PMDD remain poorly understood. Progesterone withdrawal model is a promising animal model for PMDD but warrants detailed characterization.

Purpose: This study aims to characterize a rodent model of PMDD in order to study the pathophysiology of the disorder and the role of neurosteroids in PMDD.

Methods: Single and multiple progesterone withdrawal protocols were carried out in which crystalline progesterone (6mg/rat), dissolved in corn oil, was administered intraperitoneally to adult female Wistar rats for 21 days. 48 hours after the last dose, assessment of anxiety-like behavior and depression-like was carried out. Progesterone and corticosterone levels were evaluated following progesterone withdrawal.

Results: The single withdrawal protocol group showed decreased number of entries to the centre in the open field test and significantly increased total immobility in the Forced swim test with no behavioral change in Elevated Plus Maze and Sucrose Preference Test. Following multiple withdrawal, the withdrawal group showed decreased number of open arm entries in EPM and increased total immobility in FST with no change in SPT. 48h of progesterone withdrawal induced depression- and anxiety-like behavior. Progesterone levels was found to be significantly reduced in both single and multiple withdrawal.

Conclusions: Complete characterization of the model will be useful for the detailed evaluation of the role of neurosteroids in the pathophysiology of PMDD. The findings in this model have ramifications in other mood disorders in women such as postpartum depresion. Further studies have implications for the development of effective therapeutics for reproductive mood disorders.

Comparative Cellular Dysfunction and Organelle Pathogenesis of LRRK2 Mutant Variants, I1371V versus G2019S

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Background: The difference between the LRRK2 mutant variants is evident through the reports showing differences with respect to disease risk, disease severity, age of onset, disease progression, brain pathology, clinical symptoms such as RBD, & drug response. LRRK2 is a kinase enzyme whose enzyme activity is fairly dependent on its interaction with membranes, therefore mutant variants may have differential effects on membrane trafficking of proteins & sterols, in turn affecting membrane fluidity & pathogenicity, cellular and organelle function. Moreover, The reports on failed clinical trials for LRRK2 inhibitors direct attention towards the differences between human and rodent membrane composition and LRRK2 protein stability.

Purpose: To understand the molecular mechanisms underlying the distinct effects of LRRK2 mutant variants on cellular processes and their diverse pathological implications, essential for target based drug discovery.

Methods: This study explores the distinct pathology manifestations of LRRK2 variants, particularly G2019S and I1371V. Focusing on SH-SY5Y cells overexpressing these variants, we observed differences in substrate phosphorylation, specifically Rab8A and Rab10, influencing membrane composition, fluidity, neurite outgrowth, Endoplasmic Reticulum (ER) and mitochondrial function.

Results: I1371V exhibited higher Rab8A and Rab10 phosphorylation compared to G2019S, resulting in increased membrane fluidity, reduced membrane cholesterol, and lower lipid-raft (Caveolin1) expression. The interaction of LRRK2 with lipid-rafts was confirmed through colocalization with Caveolin1. Lesser S1292 phosphorylation at LRRK2 corresponds to lesser neurite length. The differential effect on membrane was also reflected in differential ER function where Store-operated calcium-entry decreased in G2019S and was lowest in I1371V, a finding supported by ER stress marker validation. This differential organelle dysfunction was also seen to be extended to mitochondria ultrastructure.

Conclusion: Distinct differences in auto & substrate phosphorylation between variants was manifested through the difference in Cellular functions and pathogenesis, highlighting the heterogeneity among LRRK2 mutant variants.

Investigating the effect of glycemic fluctuations on NRG-1 gene mediated adult regenerative pathway in spinal cord and its implications during diabetes

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Background: The glycemic fluctuations between hyperglycemia and hypoglycemia severely disrupt the homeostatic microcellular environment at the molecular level, significantly influencing signaling pathways and contributing to the delineation of underlying molecular mechanisms. In response to cellular degeneration, various proliferative mechanisms are activated to replace damaged and lost neurons. Neuregulin (NRG), a key signaling protein that activates pathways such as PI3K/Akt and MAPK/ERK, plays a crucial role in cellular proliferation, survival, and differentiation. Specifically, NRG-1 contributes to synaptic activity, facilitating efficient signal transmission within the nervous system.

Purpose: The NRG-1-mediated signaling pathway plays a central role in regulating the differentiation of neural stem cells, thereby contributing to adult neurogenesis in the central nervous system (CNS). Additionally, NRG-1-mediated signaling supports spinal reflex motor responses through synaptic activity in motor neurons within the spinal cord. Recent studies suggest that hyperglycemia-induced alterations in NRG-1 gene function lead to impaired recovery and increased oxidative stress. However, the impact of hypoglycemia on NRG-1, its neurobehavioral implications, and the associated oxidative stress levels in the spinal cord during diabetes remain unexplored and require further investigation in diabetic models.

Methods: In this study, we aim to investigate the effects of glycemic stress on histopathological alterations in nerve processes and motor neurons using hematoxylin-eosin staining, as well as to evaluate oxidative stress and its impact on spinal motor reflexes through neurobehavioral assessments.

Results: Our four-week diabetic cohort study reveals elevated levels of pro-oxidants as indicators of oxidative stress, along with an evaluation of antioxidant status during recurrent hypoglycemia.

Conclusion: Furthermore, pronounced glycemic fluctuations lead to a marked enhancement in motor reflex responsiveness during diabetic hypoglycemia, which may be associated with motor behavior impairments observed during hypoglycemic shock, as reflected in neurobehavioral assessments.

Anti-Brain Cancer Potential of Amla (*Emblica Officinalis*): A Short Anti-Cancer Analysis on U87 Mg Glial Cells

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Background & Purpose: *Embilica officinalis (E. officinalis)*, is well-known for its abundance of phytochemicals and therapeutic uses since ancient times. Through various phytochemical and biological experiments, the purpose of this study is to evaluate the anti-brain cancer potential of different extracts of *E. officinalis*.

Methods: After obtaining and authenticating the *E. officinalis*, it was extracted using methanol, 50% aqueous ethanol, and water. Total Phenolic Content (TPC), DPPH radical scavenging, and Gas Chromatography Mass Spectrometry (GC-MS) were among the preliminary phytochemical tests carried out. Wiley and PubMed databases were used to examine the GC-MS results. In addition, wound scratch test and MTT assays were used to check the potential for cell migration and cytotoxicity.

Results: Different extracts of *E. officinalis* using methanol, 50% aqueous ethanol, and aqueous were made. In TPC assay of three extracts, Methanolic extract exhibited high presence of phenolics. However, 50% ethanolic extract showed highest antioxidants presence. The GC-MS analysis of the extracts revealed the presence of compounds some of which are reported to have anticancer potential. Further, MTT assays showed dose-dependent anti-proliferative potential of these extracts against U87MG, where methanolic extract exhibited the lowest IC_{50} value. Selected doses tested in wound scratch assay further showed anti-migratory potential with lowest gap closure observed in methanolic extract. When compared to the extracts, the methanolic extract of *E. officinalis* showed greater efficacy in both phytochemical and anti-cancer evaluations, exhibiting the highest antioxidant and phenolic content. This study suggests that E. officinalis could be targeted for the development of anti-brain cancer therapeutics after detailed studies.

Conclusion: Among the three evaluated, the methanolic extract of authenticated E. officinalis is the most effective due to its notable cytotoxicity, antioxidant activity, and anti-migratory activity. There is potential for development of anti-cancer drugs with medicinal applications using this extract, however, detailed studies are required which are in progress.

Interaction analysis between ApoE, tauopathy and microgliosis in a dementia cohort indicates microgliosis to be contributing to patient cognitive resilience

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Background: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by amyloid beta plaques and tau tangles, leading to dementia and functional impairment. India has 3.7 million documented dementia patients, the second highest globally, costing Rs 14,700 crore annually. The onset of this disease is not fully understood, though genetic and environmental factors are known risk factors. Dominant mutations in genes such as PSEN1/2 and APP contribute to disease progression. For late-onset sporadic Alzheimer's, the apolipoprotein E4 (ApoE4) allele is a major risk factor. A subset of at-risk demographics shows cognitive resilience despite high tau burden. The reason for this is not known and was the objective of this study.

Methods: This study examines the interaction between dementia risk factors, particularly the ApoE4 allele, tau pathology and microgliosis across different AD stages and patient cohorts. Utilizing data from the Seattle ATC and University of Washington ADRC, the research assessed biomarker levels related to tauopathy (AT8) and microgliosis (IBA1) in various brain regions and among different patient groups.

Results: AT8 levels increased significantly with tauopathy progression in the hippocampus, temporal cortex, and parietal cortex. Patients with dementia had a higher level of abnormal tau compared to those without dementia. It was observed that ApoE4 was linked to elevated tau levels. Interestingly, increased microgliosis was observed in cognitively resilient ApoE4-negative patients, suggesting at a potential neuroprotective role.

Conclusion: These findings indicates that microgliosis may have a protective role in abnormal tau environment. Hence this may be a contributing factor to cognitive resilience in a subset of demographics.

Ciliary Neurotrophic Factor (CNTF) Induces the Differentiation of Neural Stem/Progenitor Cells (NSPCs) to Glutamatergic Neurons

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Background: Ciliary Neurotrophic Factor (CNTF) is known for its Neuroprotective role in the Nervous system, and also in the Neurogenesis of the cells within the Neurogenic niches of the Brain aiding in their differentiation. The Neural Stem/Progenitor cells (NSPCs) are a heterogenous cell population found in these niches. CNTF can differentiate these NSPCs into neurons which may be Glutamatergic in function. This form of differentiation can possibly enhance synaptic plasticity by activating the glutamatergic synapse pathway. In such a case CNTF may aid in the development of learning and memory consolidation. Here we are trying to see if CNTF can differentiate the NSPCs into glutamatergic neurons.

Purpose: To study the effect of CNTF in the differentiation of NSPCs to glutamatergic neurons.

Methods: NSPCs, isolated from the neurogenic niches of the adult mouse brain, are treated with CNTF. The neuronal lineage of the CNTF – treated NSPCs are assessed through Fluorescence – Associated Cell Sorting (FACS) analysis, and by Immunocytochemistry (ICC). The CNTF – treated NSPCs are then subjected to a Proliferation analysis by MTT assay. From the sequencing data, we found genes linked to the glutamatergic synapse activated when induced with CNTF. These genes are validated by Real – Time PCR to check for their expression levels indicating whether the glutamatergic pathway is activated.

Results: The CNTF – treated NSPCs exhibited a neuronal cell population when tagged with fluorescent markers expressing neuronal lineage. The CNTF – treated NSPCs have shown a reduced cell proliferation when compared to the untreated cells from the MTT assay analysis. The CNTF – treated NSPCs have also shown an upregulated expression of genes relating to the glutamatergic pathway.

Conclusion: This work shows the induction of CNTF in the differentiation of the NSPCs into glutamatergic neurons therefore associating the influence of CNTF in the increased development of learning and memory formation.

Assessment of EEG microstates in Parkinson's Disease Patients

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Background: Topographies of scalp electric field potential corresponding to neuronal activities are stable only for 80-120 mS before abruptly switching to the next topographic state. This distinct quasi-stable EEG state is termed as "EEG Microstate" which are categorized into microstate-A, B, C, D. Of note, EEG microstate C attributed to default mode network (DMN), which involves internal mentation, social cognition, and self-referential processes. In the present study, the functionality of the DMN was assessed in PD patients using EEG microstate-C analysis.

Purpose: The objective of the current study to investigate the alteration of EEG microstate-C in Parkinson's disease (PD) patients as compared to Normal Control (NC).

Methods: Resting state EEG data of NC (n=28) and PD (n=27) patients were obtained from opensource database. Topography of local maxima GFP were entered into the K-mean clustering analysis, which clusters topographies into four subtypes of microstate depending upon the topographic similarity. These categorized topographies are then labelled as one of the microstate types and EEG is re-expressed as a sequence of these four canonical microstates in temporal domain. Microstate parameters like duration, occurrence, time coverage and transition probabilities of PD were compared with NC.

Results: Our results revealed that, occurrence, duration, time coverage and transition probabilities to microstates-C were significantly decreased in PD patients as compared to NC.

Conclusion: Our results suggest that reduced microstate-C parameters in PD patients might be due to DMN dysfunction and premature termination of microstate-C network ultimately leads to altered self-reflection and internal mentation.

Effect of ϒδ-T cells against Glioblastoma cells

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Background: Glioblastoma (GBM, WHO grade 4) is a malignant central nervous system tumor with a global incidence of 0.59 – 3.69 per 100000 cases and median survival of 15 months from diagnosis. The current gold standard for the treatment of GBM follows the Stupp protocol that includes surgery, adjuvant radiotherapy and temozolomide (TMZ) chemotherapy. Immunotherapy approaches that is beneficial in other types of cancer has had limited effectiveness in glioblastoma because of the complex tumor microenvironment (TME). GBM TME which is proven to be immunosuppressive hinders the anti-tumor potential of immune cells through immunosuppressive checkpoints and tumor endogenous factor secretion. Hence reeducating immune system components by boosting the activity of immune cells will be a more effective technique to attack the GBM TME. The use of effector T cells such as ϒδ-T cells, which is proven to have the best anti-tumor potential can be one such approach.

Methods: 5ml venous blood of GBM patients was collected. ϒδ T cells and CD3 T cell was isolated by MACS method and cultured in RPMI-1640 media supplemented with 10%FBS, 2mM L-glutamine, IL-2 (10IU/ml), IL-7 (10IU/ml),1% penicillin/streptomycin at 37°C in 5% CO2. U87 cells are cultured in DMEM media supplemented with 10%FBS and 1% penicillin/streptomycin at 37°C in 5% CO2. U87 cells and T cells are co-cultured for 24hours.

Results: ϒδ T cells which are activated by IL-2 and IL-7 showed better cytotoxic effects against U87 glioblastoma cells compared to CD3 T cells at 24hrs.

Conclusion and Future directions: These findings highlight that ϒδ -T cells have better cytotoxic ability compared to other T cell subsets against GBM cells. Understanding of the mechanism of action of these ϒδ -T cells against GBM cells is essential.

Gut Microbial Metabolites as Modulators of Proteostasis and Neurodegeneration: Insights from C. elegans Model of Parkinson's Disease

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Background: The gut microbiota has a profound influence on human physiology, particularly on the central nervous system via the gut-brain axis. Recent research highlights gut microbiota-derived metabolites as crucial mediators of this gut-brain axis. The association of gut dysbiosis with neurodegenerative disorders, such as Parkinson's disease, underscores the importance of studying these microbial metabolites and their role in cellular proteostasis.

Purpose: This study investigates the impact of key fermentation products from human gut microbiota on the disruption of proteostasis, contributing to the onset and progression of Parkinson's disease.

Methods: We selected microbial metabolites known to be disrupted in major neurodegenerative diseases and produced by Escherichia coli, a common laboratory food source for *Caenorhabditis elegans* and a significant human gut commensal. Using transgenic *C. elegans* strains expressing human alpha-synuclein, we assessed the effects of orally supplemented metabolites on various neurodegenerative markers.

Results: Succinate supplementation notably exacerbated alpha-synuclein-induced neurodegeneration by disrupting protein homeostasis. This disruption manifested through enhanced alpha-synuclein aggregation, impaired autophagic clearance, and mitochondrial dysfunction—evidenced by inhibited mitophagy, mitochondrial biogenesis, and the mitochondrial unfolded protein response (UPRmt). Furthermore, succinate-driven aggregation promoted dopaminergic neurodegeneration and downregulated *C. elegans* PMK-1/p38, crucial for neuronal integrity and lysosomal function. The lifespan of *C. elegans* was significantly reduced in the presence of alpha-synuclein, highlighting the pro-aging effects of succinate through proteostasis disruption and mitochondrial dysfunction.

Conclusion: Our findings reveal a significant role of gut microbiota-derived metabolites in the progression of neurodegenerative diseases, emphasizing the potential for enteric interventions to mitigate these effects. Understanding the pathophysiological impact of these metabolites may pave the way for novel therapeutic strategies targeting neurodegenerative conditions.

Understanding molecular pathogenesis behind emergence of non-motor symptoms in Parkinsons's disease

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Background: Parkinson's disease (PD), the second most common neurodegenerative disorder, is marked by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as rigidity, postural instability, bradykinesia, and tremors. Non-motor symptoms often precede motor symptoms before a decade, typically going undiagnosed. Various animal models are employed to study PD: neurotoxin models like MPTP and 6-OHDA induce rapid nigrostriatal dopaminergic cell loss, while transgenic models explore alpha-synuclein overexpression associated pathology. No single model fully captures PD pathology, necessitating a combination of models for comprehensive study.

Purpose: A comprehensive assessment of onset of non-motor and motor symptoms and molecular mechanisms driving the pathology in a slow-progressing Parkinson's disease model.

Methods: A sub-chronic dose of 10 mg/kg MPTP was administered subcutaneously to 4-5 months-old C57BL/6J mice over 60 days to achieve slow and progressive loss of dopaminergic neurons. Behavioral tests, including open field and elevated plus maze, were conducted on days 14-15 to assess anxiety and depression, and rotarod to assess motor symptoms on day 30. Mice were sacrificed at 15, 30, and 60 days to study progression of pathology.

Results: We observed a distinct onset of non-motor symptoms by day 15 and motor symptoms by day 30. After 60 days of MPTP treatment, there was significant loss of dopaminergic neurons in the substantia nigra and their projections to the striatum, disrupting the nigrostriatal pathway. Additionally, we detected a reduction in dopamine transporter fibers, along with notable aggregation of alpha-synuclein and its phosphorylated form post 60 days of MPTP treatment.

Conclusion: We have developed a slow-progressing MPTP neurotoxin model that replicates the early emergence of non-motor symptoms followed by the later onset of motor symptoms in a Parkinson's disease mouse model.

Fabrication of Nano-inspired Indispensable Biosensor for the Detection of Parkinson's Disease Biomarker Alpha-Synuclein

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Background: Parkinson's Disease (PD) is the second most common neurodegenerative disorder globally after Alzheimer's disease, affecting 1–4% of people over the age of 65. Recently, PD is increasingly impacting younger populations under 50, contributing to a significant social and economic burden. The population with PD is expected to reach between 8.7 and 9.3 million by 2030. Current diagnostic techniques, which rely on neuroimaging and clinical symptoms, detect PD only after substantial progression, limiting treatment efficacy. Consequently, early diagnosis is crucial for improving outcomes in PD patients.

Purpose: In light of the need for earlier detection, there is growing interest in monitoring phosphorylated α-synuclein (α-syn) aggregates, which are showing potential as biomarkers for early PD diagnosis. This study presents a simple and highly sensitive electrochemical biosensor for detecting phosphorylated α-syn aggregates to aid in the early diagnosis of PD.

Methods: The biosensor developed for early PD detection uses a nanocomposite of reduced graphene oxide (rGO), polynorepinephrine (PNE), and gold nanoparticles (AuNPs), chosen for their combined properties that enable sensitive and selective detection of phosphorylated α-syn. The structural and morphological characteristics of this nano-bioinspired composite were analyzed using UV-Vis spectroscopy, Raman spectroscopy, X-ray diffraction (XRD), and transmission electron microscopy (TEM). Field emission scanning electron microscopy (FESEM) and Fourier-transform infrared (FT-IR) spectroscopy were employed to confirm the immobilization of phosphorylated α-syn on the sensor surface. Electrochemical studies were conducted using cyclic voltammetry (CV) and linear sweep voltammetry (LSV).

Results: The biosensor exhibited high sensitivity and selective performance in detecting phosphorylated α-syn oligomers, indicating its potential for early PD diagnosis.

Conclusions: With its ultrasensitivity and reliable performance, this biosensor offers a promising and effective platform for the early detection of PD, providing new avenues for early intervention and improved disease management.

Dissecting the molecular pathways of small vessel insult leading to transient dementia: A transcriptomic analysis

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Background: Micro-infracts resulting from ischemia, microbleeds, and hemorrhage are significant factors in the development of vascular and mixed dementia among older individuals. The substantial contribution of vascular insults to the pathology of dementia necessitates the development of a model that reflects the milder forms of vascular insult associated with memory impairment. Therefore, we developed a mouse model by injecting a single dose of endothelin-1 (ET-1), a vasoconstrictor peptide, into the lateral ventricles, causing small vessel disruption followed by learning and memory deficits after 3 days. Remarkably, these deficits recovered after 30 days of single vascular insult.

Purpose: Bulk RNA sequencing of microvessels was performed to elucidate the factors involved in recovery mechanisms.

Methods: A single ET-1 injection was given to 4 groups of C57BL6/J mice, and mice were sacrificed at 3, 15, and 30 days along with their saline counterparts. Microvessels were extracted from pooled cortex and hippocampus, followed by RNA isolation. RNA samples were subjected to the cDNA library preparation, and RNA sequencing was conducted using the Illumina NovaSeq 6000®. Transcriptomic analysis was performed using R.

Results: We observed that biological processes involved in vasculature development, angiogenesis, and wound healing start upregulating after 3 days of single ET-1, whereas biological processes for mitochondrial electron transport chain and neuronal development were upregulated after 15 days of single ET-1 injection. No biological processes were affected after 30 days of a single ET-1 injection, suggesting a possible complete recovery from ET-1-mediated vascular insult by the 30th day.

Conclusion: Our analysis reveals that a singular vascular insult has significantly perturbed various biological pathways involved in angiogenesis regulation, homeostasis maintenance, and others. These results highlight the temporal dynamics of biological processes in response to a single ET-1 injection, which offers valuable insight into understanding the mechanism behind recovery after a single vascular insult.

Investigating the synaptic heterogeneity in APP processing and its role in spatio-temporal onset of Alzheimer's disease

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Background: In recent years, our laboratory has focused on understanding the components of the amyloidogenic machinery at the synaptic membrane. We have studied the organization, heterogeneity, and intricate permutations of molecules that contribute to the dynamic load of amyloid beta molecules at the level of a single synapse.

Purpose: Exploring the molecular basis for the probabilistic origin of AD within a structural context is a pertinent avenue for investigation. The precise reporting of neuronal endogenous proteins with fluorescent tags becomes significant to study the spatiotemporal expression patterns. CRISPR-Cas9 based targeted gene editing allows for sparse labelling of primary neurons via the repair of double strand breaks (DSBs) by Non-Homologous End Joining (NHEJ).

Methods: Analysing the heterogeneity in Amyloid Precursor Protein-Secretases complex distribution within synaptic and dendritic nano-domains and the differential localization of N and C terminal protein fragments across the membrane, can be achieved using combination of advanced techniques such as super-resolution microscopy, cryo-EM and CRISPR genome editing.

Results: We successfully generated CRISPR constructs to tag the C and N terminals of APP protein endogenously and tried to bypass the shortcomings of antibody-based exogeneous tagging of proteins. We have also studied the effect of a triterpenoid molecule, betulinic acid, on the nano-organization of APP.

Conclusion: Real time tracking and nano-organization studies of APP will be physiologically precise by this progress. This will also aid the studies using triterpenoid molecules to investigate the breaking of APP clusters. Further studies will be done using 3-α-akebonoic acid and roburic acid to understand how this class of molecules affect the clustering of APP and integrity of APP-secretase complexes to directly impact Aβ production.

Exploring the impact of β-Sitosterol on Anxiety and Depression like behaviour in epileptic Danio rerio

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Background: The mood and behaviour of epilepsy patients might be affected by any antiepileptic medications (AEDs). The current AEDs, Gamma-aminobutyric acid (GABA)-ergic and anti-glutamatergic antiepileptic drugs can contribute to depression and anxiety by disrupting the balance between inhibitory and excitatory neurotransmission. GABAergic AEDs enhance inhibitory effects and are depressogenic, while anti-glutamatergic AEDs reduce excitatory activity and are anxiogenic. This imbalance leads to mood disturbances. Besides AEDs, a single episode of seizure can also lead to depressive symptoms due to decreased 5-Hydroxytryptamine (5-HT) binding or increased anxiety due to the imbalance of neurotransmitters, highlighting the need for careful monitoring and individualised treatment. Pentylenetetrazole (PTZ), a convulsant that binds to GABA-A receptor inducing seizures which also leads to the manifestation of the comorbid symptoms. Phytosterols are shown to have neuroprotective properties by alleviating oxidative stress and inflammation. It is also shown to have antidepressant-like activity and can be used as a potential drug.

Purpose: To explore the effect of β-Sitosterol on depression and anxiety that arise as a comorbid condition in epilepsy using Zebrafish as a model organism and pentylenetetrazole as the epilepsy inducing agent.

Methods: PTZ concentration to be used was determined by scoring the seizure in 3mmM 10mM PTZ and 5mM PTZ was used ahead for the study. The behaviour of the Zebrafish was assessed by Novel tank, Open-field and Light-dark preference test. Geotaxis, thigmotaxis, scototaxis, exploration, and changes in their swimming patterns have been analysed for two test conditions: 5mM PTZ exposed Zebrafish and treating zebrafish with 100ug/ml β-Sitosterol before inducing epilepsy. This concentration was determined by simultaneous studies in larvae and available data from previous literature.

Results: On pre-treating the fish with β-Sitosterol, differential behaviour like freezing, geotaxis, thigmotaxis, erratic movements and exploration was observed.

Conclusion: β-Sitosterol can be a potential antiepileptic drug due to its neuroprotective properties. Additionally, it may mitigate the risk of comorbid conditions, such as depression and anxiety, often associated with epilepsy.

Generation & Characterization of 3D Midbrain Organoids from LRRK2-I1371V Parkinson's Disease Patient derived iPSCs: Electrophysiological Analysis Using Multielectrode Array

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Background: Parkinson's disease (PD) is a neurodegenerative disorder marked by the loss of dopaminergic neurons in the substantia nigra. The LRRK2 gene mutations are a common cause, with G2019S prevalent in Caucasians and I1371V in East Asians. Research on the I1371V mutation is limited, underscoring the need to understand its impact on disease mechanisms and treatment variability.

Purpose: The development of effective in vitro models that replicate the complexity of the human brain has been challenging, impacting research on neurological diseases and brain development. This study introduces a highly customized organoid system that precisely targets the midbrain, created from neuroepithelial stem cells with localized patterns.

Methods: The 84-day cultured 3D midbrain organoids were characterized by immunofluorescence and flow cytometry for early (MAP2ab, β-tubulin, Nurr1) and late-stage (TH, DAT, GFAP, O4, GIRK2) markers. Electrophysiological analysis using MEA was performed on days 83 and 84.

Results: Organoid size increased after day 15. By day 30, IF and FACS detected Floor Plate markers FOXA2 and SOX6. On day 83, mature dopaminergic markers (TH, DAT, GIRK2) and astrocyte (GFAP) and oligodendrocyte (O4) markers were expressed. KCl stimulation led to dopamine release. MEA recordings on days 83 and 84 showed increased spikes and bursts with KCl and levodopa, and improved neuronal connectivity. In contrast, MPTP exposure reduced spikes and bursts.

Conclusion: This midbrain organoid model with LRRK2 I1371V mutation offers a highly relevant platform for drug testing in Parkinson's disease. Its accurate replication of midbrain complexity and ability to assess electrophysiological properties make it an effective tool for evaluating therapeutic agents and selecting predictive populations for clinical trials.

A serotonergic brain circuit governing itch processing in mice

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Background: The rostral ventromedial medulla (RVM), a brain stem region, has been implicated in modulating pruritic behaviour in mice via a serotonergic pathway. Although the spinal and peripheral mechanisms of itch are extensively studied, the supraspinal modulation of itch is still poorly understood.

Purpose: The central mechanisms governing the itch-scratch responses is still not properly understood. The results of this study will help to distinguish ad uncover the central circuits and its associated neuromodulator driving scratching behaviour and related aversion in itch.

Methods: We use a combination of viral genetics, DREADDs, optogenetics, and fiber photometry to explore the same.

Results: Here, we show that the ascending circuitry from the RVM to the lateral hypothalamic area (LHA) orchestrates the affective aspect of chloroquine-induced itch. We demonstrate the RVM->LHA circuit to be crucial in facilitating chloroquine-mediated aversion in mice. Interestingly, we also report that inhibition of the LHA neurons that are postsynaptic to RVM leads to a significant decrease in the scratching response in mice. Since the LHA has been known to express 5-HT1a and 5-HT2c receptors, and RVM is one of the significant sources of serotonergic innervation, we suggest the RVM->LHA circuit to be a crucial regulator of itch-processing at the supraspinal level.

Conclusion: On the contrary to the previous findings that indicate that the inhibitory population of the RVM form synapses to the spinal GRPR+ and 5-HT1a receptor co-expressed neurons, we found the excitatory vglut2 neurons of the RVM to be actively involved in the central processing of the negative-valence of itch through RVM->LHA circuit. Overall, the findings uncover the promising role of the central serotonergic mechanism in governing itch modulation via novel RVM->LHA circuitry.

Neuronal integrity damage and neuroinflammatory effect of nerve agent on rat brain hippocampus

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Background: Nerve agents are highly toxic organophosphate compounds with the potential for rapid lethality if not promptly treated. Recent incidents involving nerve agent such as attacks on Syrian civilians, Japan, and assassinations in the UK and Malaysia underscore their global threat. The mechanism of toxicity involves the phosphorylation of enzyme acetylcholinesterase (AChE) by nerve agents, leading to its irreversible inhibition. This results in the accumulation of the neurotransmitter acetylcholine, causing a cholinergic crisis characterized by overstimulation of muscarinic and nicotinic receptors in both the central and peripheral nervous systems. Severe overstimulation can lead to receptor desensitization, hypoxia, vasodepression, respiratory arrest, and ultimately death.

Purpose: These findings deepen our understanding of the toxic effects of nerve agents, which is essential for developing more effective antidotes.

Methods: This study investigates the molecular basis of neurodegeneration, and oxidative damage following exposure to the Nerve agent (1XLD50). We assess AChE activity using Ellman's assay, evaluate astrocytic activation through immunohistochemistry of GFAP, and measure lipid peroxidation (LPO) using TBARS assay

Results: Significant inhibition of AChE activity following exposure to the nerve agent on 30min and 1 day compared to control animal. Additionally, lipid peroxidation levels, indicative of oxidative damage, were elevated in rats at 30 minutes and 1day post-exposure compared to control rats. Immunohistochemical analysis of astrocyte marker GFAP revealed hyperactivation of astrocytes at both 30 minutes and 1day post-exposure, with pronounced activity observed on the 7th day relative to control rats.

Conclusion: In conclusion, our results indicate that exposure to the nerve agent significantly inhibits AChE activity and highlighting the oxidative damage caused by exposure. Additionally, the hyperactivation of astrocytes post-exposure, underscores the neurodamaging response.

Anti-amnesic effect of blood plasma derived from Common Yoga Protocol (CYP) practitioners in an amnesic mice model

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Background: Neurodegeneration is a gradual and progressive loss of neuronal cells in specific regions of brain which leads to disruption of neuronal cells and cause several neurodegenerative diseaseslike Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis etc.Its prevalence is estimated to be affectedmore than 57 million people worldwide, and might increase by 13.8% in United State. In India itself, around 7.4% of people aged 60 or above are also suffering from neurodegenerative diseases. Therefore, we aim to analyse efficacy of the Common yoga protocol practitioners blood plasma in an amnesic mice model.

Purpose: Purpose of this study is to investigate the anti- amnesic effect of CYP practitioners blood plasma in an amnesic mice model to evaluate the Yoga's impact as an alternative therapy to several other treatments like drugs, exercises in the field of cognition. Further assessment will be carried out using statistical modelling.

Methods: A total 100 participants will be recruited and sampling will be carried out at 3 timeline points i.e at baseline, after 2 and 6 months of CYP intervention. We will use ELISA to analyse the expression of different proteins related to different pathways involved in neurogenesis, angiogenesis, apoptosis and inflammation in the blood plasma of the participants. An Aβ induced injury(amnesic) mice model will be created to analyse the efficacy of CYP practioners blood plasma followed by transplantation in an amnesic mice model. Further to validate the results, neurobehavioral assessment using different behavioral tests like Morris Water maze (MWM), Rota-rod and passive avoidance (PA). Further for molecular analysis q-PCR and immunohistochemistry (IHC) will be carried out followed by staining. Final evaluation will be carried out using statistical modelling.

Expected Outcome: An amnesic mice model is expected to show improvement in cognitive and memory behavior after transplantation of CYP practitioners blood plasma.

Microstate Dynamics in Schizophrenia during Sleep

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Background: Sleep has a bidirectional relationship with health and its comorbidities are a phenotypic feature of neuropsychiatric disorders. Individuals with schizophrenia (SCZ) have increased sleep stage shifts, decreased REM latency and sleep efficiency. These traits precede psychotic episodes and auditory hallucinations in the afflicted. Standardizing methods of analysis, where the changes of the brain can be visualized without using resource intensive techniques like fMRI, can assist the clinician to precisely diagnose and treat neuropsychiatric disorders. To capture microsleep dynamics with high temporal resolution, Electroencephalogram (EEG) is deployed to obtain polysomnography (PSG) recordings.

Purpose: This study aims to characterize the microstructure of sleep using microstate analysis of affected individual's PSG data and identify changes in microstates prevalent across SCZ. Complementing the conventional microstates analysis, a novel spectral microstate analysis is proposed to further explore changes in oscillations at sub-second level across the brain, one electrode at a time.

Methods: Microstate analysis of existing PSG recordings was performed in MATLAB, for each sleep stage for groups - Controls (CNT) and SCZ. Applying the method standardized for microstate analysis as the backbone, spectral microstate analysis is performed.

Results: Five conventional microstates were identified for each sleep stage per group, namely microstates A, B, C, D and E. In SCZ, Microstate B dynamics showed significant difference against CNT during Non-Rapid Eye Movement (NREM) stages, whereas microstate D differed predominantly during wake and REM stage. Fluctuations in microstate parameters of microstate C were predominant across sleep stages. The probability of self transitions (indicating stability) of a microstate during NREM was diminished in SCZ. In terms of Spectral microstate dynamics, differences in both NREM and REM stages were seen in SCZ, compared to CNT.

Conclusion: Overall, the changes observed in our study could add further evidence for aberrations in multiple brain networks in SCZ, even during sleep.

In vivo approach to understand Chemotherapy-induced Peripheral Neuropathy using mouse model

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a consequence of damage to the sensory and motor nerves of the peripheral nervous system (PNS) in cancer patients undergoing chemotherapy. This affects the patient's quality of life, often resulting in discontinuation of the treatment. CIPN is characterised by the "dying back" of neurons progressing from distal to proximal parts of the limbs. Many of these chemotherapeutic drugs target microtubules, thus affecting neuronal homeostasis. This suggests vulnerability of the microtubule network, thereby potentially affecting the long-range transport in the PNS.

Purpose: This study aims to provide a mechanistic understanding of the effect of chemotherapeutic drugs on the PNS by probing changes in post-translational modifications (PTMs) levels of tubulin, followed by looking at its effect on MT-mediated transport. This will help in identifying potential biomarkers, thereby tracking the molecular progression of CIPN pathogenesis.

Methods: This study employed behavioural tests to assess alterations in sensory and motor function using mouse models post-treatment with paclitaxel (PTX), vincristine (VCR), oxaliplatin (OXP), and bortezomib (BTZ). Western blots were done to evaluate the expression of microtubules and their PTMs in dorsal root ganglia (DRGs) and sciatic nerves (SCN).

Results: Mice under chemotherapy developed mechanical allodynia but showed normal motor coordination, suggesting predominantly sensory neuropathy. Increased fraction of polymerized microtubules was observed in the SCN of PTX-treated mice and in the DRGs of BTZ-treated mice compared to controls, consistent with the stabilizing effects of these drugs. Preliminary western blot data suggest PTM alterations in the PNS following chemotherapy.

Conclusion: Our data suggest that chemotherapy largely causes sensory neuropathy, as shown by severe mechanical allodynia. The observed increase in polymerized microtubules and variations in PTMs indicate molecular changes in the PNS caused by chemotherapy. This will aid in identifying potential biomarkers to track the molecular and behavioural progression of CIPN.

Regulation of TIMP-1 expression by p38 pathway in a model of Alzheimer's disease

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the presence of extracellular amyloid beta plaques and intracellular neurofibrillary tangles. Studies suggest that an anti-inflammatory cytokine, tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) secreted by the astrocytes protects neurons against amyloid-β (Aβ) toxicity but its secretory level rises as early as in 6 hours of Aβ treatment and then depletes at later time point.

Purpose: The underlying regulatory mechanism of TIMP-1 production in AD model is poorly understood. Therefore, the purpose of this study is to decipher the molecular mechanisms underlying regulation of TIMP-1 expression in response to Aβ in cellular models of AD.

Methods: Using known pharmacological inhibitors of different signaling pathway in the Aβ treated astrocytes, the changes in TIMP-1 expression at both protein level through Western blotting and RNA level through Real-time Polymerase Chain Reaction (RT-PCR) are checked to reveal the pathway. The binding of corresponding transcription factors to the promoter region of TIMP-1 would be deduced through Chromatin immunoprecipitation (ChIP) assay. Transcriptional activity of TIMP-1 will be examined by TIMP-1 promoter driven Luciferase assay.

Results: Our studies on the kinetics of endogenous level ofTIMP-1 in cortical astrocytes following Aβ-exposure revealed significant increase in its level as early as in 6 h. We also found that treatment with p38 inhibitor reduced the level of TIMP-1 in Aβ treated cells as compared to only Aβ treated cells.

Conclusion: Thus, we identify p38 pathway as one of the molecular mechanisms regulating the expression of TIMP-1 in Aβ mediated toxicity. However, the upstream and downstream events need to be resolved.

Differential β-Catenin Interactome in Alzheimer's Disease: Implications for synapse loss

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Background: Synapse loss is a hallmark of early-stage Alzheimer's disease (AD), and it is closely linked to the well-known decline in memory and cognitive function. Synapse loss is often attributed to disruptions in the molecular mechanisms that are crucial for maintaining synaptic structure and function. Among these mechanisms, the Wnt signaling pathway plays a key role in recruiting synaptic proteins, thereby influencing synaptic activity. Dysregulation of Wnt signaling has been implicated in synapse loss in AD, but most research to date has focused on components such as the co-receptor Lrp5/6, the kinase Gsk3β, and the antagonist Dkk1. The role of β-catenin and its interactome in synapse loss remains poorly understood. Therefore, our study aims to explore potential disruptions in β-catenin regulation by identifying differences in its interactome, which may contribute to synapse loss in AD.

Purpose: To investigate differences in the β-catenin interactome between WT and APP/PS1 mice and determine its role in synapse loss in AD.

Methods: Cytosolic fractions from the cortical tissue of 9-month-old male WT and APP/PS1 mice were isolated and subjected to immunoprecipitation with a β-catenin antibody. The immunoprecipitated samples were eluted in Laemmli buffer and analysed using LC-MS/MS spectrometry.

Results: 1,643 and 1,708 proteins were identified in the β-catenin interactome of 9-month-old WT and APP/PS1 mice, respectively. Of these, 1,601 proteins interacted with β-catenin in both groups. Additionally, 42 proteins were unique to WT and 107 to APP/PS1 mice. Notably, 49 proteins showed significant differences in β-catenin interaction, with 19 showing increased and 30 decreased interactions in APP/PS1 mice compared to WT.

Conclusion: Significant differences in the β-catenin interactome between WT and APP/PS1 mice suggest that altered β-catenin interactions may contribute to Wnt signaling dysregulation and synapse loss in AD.

Effect Of Cerebrospinal Fluid from Sporadic Amyotrophic Lateral Sclerosis Patients on Kv1.3 Channel Expression in Human Microglial Cells

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Background: Microglia mediated inflammation play a vital role in the pathophysiology of Amyotrophic Lateral Sclerosis (ALS). However, the precise mechanisms are not completely understood. Microglial activation can lead to morphological changes and altered expression of ion channels too. Enhanced expression of Kv1.3 by microglia is implicated in augmenting neuroinflammatory responses and driving them to toxic form.

Purpose: To investigate the effect of cerebrospinal fluid from sporadic ALS patients (ALS-CSF) on Kv1.3 channel in human microglial cells.

Methods: To explore the role of Kv1.3 in activated microglia in human derived model as they can better reflect patient scenario, a Human Microglial cell line, HMC3 and human microglia-like cells derived from induced pluripotent stem cells of sporadic ALS patients, iMicroglia were exposed to ALS-CSF (10% v/v) for 24 hours. The effect on human microglial cells was assessed for expression level of Kv1.3 channel by immunocytochemistry and western blotting, morphology changes through phase contrast imaging. Additionally, the morphology of neural progenitor cells (NPCs) and the viability of NSC-34 motor neuronal cells were analyzed by exposing them to conditioned medium of human microglial cells which were exposed to ALS-CSF (CM-iMGL-ALS).

Results: In view of the observed activation of HMC3 cells in response to ALS-CSF and Chitotriosidase, an enzyme present in ALS-CSF by 20 fold, our study demonstrates the up-regulation of Kv1.3 channel in human microglial cells post ALS-CSF exposure. Morphologically, transformation of ramified form to the amoeboid form also was prominently seen. Viability of NSC-34 cells was significantly reduced and NPCs had shown reduction in soma with thinning and beading of neurites in the presence of CM-iMGL-ALS.

Conclusion: Our preliminary findings demonstrate the possible role of Kv1.3 channel expression in driving microglial activation to the detrimental form in the presence of ALS-CSF. Further investigations with Kv1.3 channel blockers will provide deeper insights on driving microglial activation to protective form thereby modulating neuroinflammatory responses in ALS.

Role of Neuropeptide CART in Learning and Memory in Mice

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Background: Memory is a fundamental cognitive function that allows organisms to encode, store, and retrieve information about past experiences. It plays a critical role in shaping behaviour, decision-making, and learning. Neuropeptides, such as cocaine and amphetamine-regulated transcript (CART), are known to orchestrate these cognitive functions. CART is extensively studied for its involvement in appetite regulation and energy homeostasis, but it is also expressed in brain regions associated with cognitive functions, including the limbic system and hippocampus.

Purpose: This study aims to investigate the role of CART in learning and memory, specifically to assess recognition memory in mice. The research seeks to clarify the involvement of CART in memory processes and to explore whether the influence of CART is dependent on organism's energy state.

Methods: The study employed the Novel Object Recognition (NOR) test, a widely used behavioural assay that evaluates recognition memory in rodents. Additionally, the impact of fasting on recognition memory performance was assessed to determine if CART's role in memory formation is influenced by the energy state of the organism.

Results: Our findings reveal that CART knockout mice exhibited significant impairments in recognition memory compared to both wild-type and heterozygous controls. Importantly, fasting did not affect recognition memory performance in the NOR test, indicating that CART's involvement in memory formation is independent of the organism's energy state prior to training and testing.

Conclusion(s): This study underscores the importance of neuropeptides, particularly CART, in higher cognitive functions such as memory. The results highlight CART's significant role in memory formation and suggest avenues for future research, including the exploration of site-specific roles of CART within the NOR circuitry using chemogenetics. This research contributes to a deeper understanding of the molecular mechanisms underlying memory.

Nanoscale Molecular Cues Governing Functional Zone Separation in Synapses

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Background: Postsynaptic scaffolding proteins, such as Synapse Associated Protein-97 (SAP97)/Human Disk Large (hDLG) and Postsynaptic Density Protein 95 (PSD95), are integral to the molecular organization of synapses. These proteins, part of the disc-large (DLG) subfamily of membrane associated guanylate kinases (MAGUKs), contain three PDZ domains, an Src homology three domain (SH3), and a guanylate kinase (GK) domain, interconnected by flexible intrinsically disordered regions. The HOOK region of SAP97/hDLG, which separates the SH3 and GK domains, is responsive to elevated intracellular Ca2+ levels through interaction with the calcium-binding protein calmodulin (CaM).

Purpose: To elucidate the molecular mechanisms underlying the spatial organization of SAP97 and PSD95 within the synaptic cleft and to understand how these interactions are influenced by calcium.

Methods: We utilized advanced microscopy and spectroscopy techniques to investigate the colocalization of Calmodulin with PSD95 and SAP97 in neuronal cultures. Experimental conditions included both the presence and absence of calcium to assess the effects of calcium binding on protein interactions and phase separation.

Results: Our findings reveal distinct patterns of interaction between Calmodulin, SAP97, and PSD95. In the presence of calcium, SAP97 and PSD95 exhibited tendency towards self-organisation, which suggests a Ca2+-dependent mechanism for the spatial organization of these proteins within the synapse. The results indicate that the intrinsically disordered HOOK region of SAP97 plays a crucial role in this process by modulating interactions with Calmodulin.

Conclusion: The study provides insights into the dynamic molecular interactions that govern the spatial separation of functional zones within the synapse. Our results enhance the understanding of synaptic plasticity mechanisms and highlight the importance of calcium in regulating the organization of synaptic scaffolding proteins, with implications for synaptic function and plasticity.

Study on Exploring the Neuroprotective Potential of Curcumenol Using Biological Models of Parkinson's Disease

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Background: Curcumenol is a natural phytoderived bioactive molecule that has the potential to be developed as a promising therapeutic. Because of its lower toxicity, its development in therapeutic context will be strongly encouraged. In this scenario, where the current medical system is turning its focus to repurpose the natural bioactive molecules as a treatment option against distinct complicated diseases curcumenol becomes a possible solution.

Purpose: The present study focuses on the investigation of the ability of curcumenol as a possibility in treating Parkinson's disease (PD).

Methods: The neuroprotective ability of curcumenol was primarily analysed on 6OHDA induced SHSY5Y neuroblastoma cells. The MTT assay and flow cytometric studies were used as an initial evaluation for determining the efficiency of curcumenol in rescuing degenerated neuronal cells followed by determining the effect of curcumenol on the accumulation of alpha-synuclein. The rotenone induced *C.elegans* served as the in vivo model of PD, for studying the effect of curcumenol on dopamine-depended behaviours.

Results: MTT cytotoxic evaluation revealed that 50µG/mL was the optimum protective dosage of curcumenol with 97% viable cells. The flow cytometric evaluation displayed as similar trend, confirming the neuroprotective ability of curcumenol, principally. The molecular protective effect was ultimately justified by checking the impact of curcumenol in the expression of alpha-synuclein, key pathogenic protein in PD. The studies conducted in *C.elegans* model validated that the dopamine dependent behaviours perturbed with the induction of rotenone were restored when treated with curcumenol.

Conclusion: The current treatment for PD either replaces lost dopamine or suppresses the disease's clinical symptoms rather than stopping or reversing the neurodegeneration that is already occurring, which necessitates the identification of a novel solution. Based on initial research conducted in PD biological models via this study, curcumenol, the proposed therapeutic option, has significant efficiency in achieving notable neuroprotection and behavioral recovery.

Memantine ameliorates memory impairment caused by early-life Pb exposure

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Background: Cognitive impairment is one of the major consequences of Lead (Pb)-induced neurotoxicity. Pb exposure during the developmental stage of life is more detrimental as it can trigger some irreversible alterations in the brain impacting the memory impairment, lowered intelligence quotient, reduced fine motor skills, and auditory impairment. However, drug-induced recovery of memory in early-life Pb-exposure is not clear.

Purpose: To investigate the effects of Memantine in rescuing the memory impairments caused due to early-life Pb exposure.

Methods: Rat pups were exposed to 100 ppm lead acetate from postnatal day 0 until weaning through lactation. Memantine was administered to the 75 day-old Pb-exposed rats orally for 15 days followed by behavioural assessment (radial-arm maze) and morphometric analysis (Golgi-Cox staining).

Results: Control, Pb-exposed, and Pb-exposed + Memantine groups showed 85%, 46%, and 82% correct choice on the testing day respectively in the partially-baited radial-arm maze test. Morphometric analysis of the hippocampal CA1 neurons using Golgi-Cox stain revealed a significant reduction in the number of spines on the apical dendrites at 160 μm distance from soma (Control=22.867±5.524, Pb-exposed=0.933±0.864, $p=0.0066$) and the basal dendrites 70 μm distance from soma (Control=33.200±3.097, Pb-exposed=13.400±2.026, $p=0.0385$). The overall spine density on the apical dendrites (Control=9.156±0.788, Pb-exposed=4.395±0.319, $p<0.0001$) and basal dendrites (Control=9.136±0.788, Pb-exposed=4.401±0.314, $p<0.0001$) was significantly reduced in Pb exposed group when compared to age matched controls. Memantine-treated animals showed a significant increase in the number of spines on the apical dendrites 160 μm distance from the soma (Memantine + Pb-exposed=27.933±6.380, $p=0.0025$) and on the basal dendrites 70 μm distance from soma (Memantine + Pb-exposed=34.867±3.595, $p=0.0207$) as compared to the Pb-exposed group. Further, memantine-treated animals also showed a significant increase in their apical dendritic length (Memantine + Pb-exposed=1778.707±161.182 μm, Pb-exposed=1077.140±141.820 μm, $p=0.0050$) compared to Pb-exposed group.

Conclusion: Our data suggests that Pb exposure early in life was harmful, while memantine treatment at 2.5 months age mitigates the spatial memory deficits by alterating the dendritic length and spine density of the hippocampal CA1 neurons. The study proves the potential use of memantine as a modulatory drug to be used to alleviate the memory and learning deficits observed in Pb toxicity and other neurodegenerative disorders.

Structural insights into the modulation of SOD1 aggregation by a fungal metabolite Phialomustin-B: Therapeutic potential in ALS

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Background: Familial form of Amyotrophic lateral sclerosis (ALS) is a fatal human motor neuron disease leading to muscle atrophy and paralysis. Superoxide dismutase 1 (SOD1) mutations in ALS have a toxic-gain of function by destabilizing the functional SOD1 native homodimer, consequently inducing fibril-like aggregation with a cytotoxic non-native trimer intermediate.

Purpose: Reducing SOD1 oligomerization *via* chemical modulators is an optimal therapy in ALS. Here, we report the discovery of Phialomustin-B, an unsaturated secondary metabolite from the endophytic fungus *Phialophora mustea*, as a modulator of SOD1 aggregation.

Method: The crystal structure of the SOD1-Phialomustin complex determined using X-ray diffraction studies, shows for the first time that the ligand binds to the dimer interface and the lateral region near the electrostatic loop.

Result: The aggregation analyses of SEC and ThT fluorescence based assays of $SOD1^{WT}$ and the disease mutants $SOD1^{A4V}$ showed that Phialomustin-B reduces cytotoxic trimerization.

Conclusion: It is speculative that Phialomustin-B is a potent lead molecule with therapeutic potential in fALS.

Understanding Pathophysiology of Autism Spectrum Disorder in Valproate Mouse Model: A Preliminary Study

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Background: Autism spectrum disorder (ASD) is the fastest-growing neurodevelopmental disorder throughout the world, and is characterized by compromised social interactions, reduced verbal communication, and stereotyped repetitive behaviours. Although ASD is an early-onset disorder, it is often not diagnosed until much later due to a lack of the biomarker(s). Moreover, there is no pharmacological treatment available for ASD.

Purpose: The purpose of the study is to investigate the underlying mechanisms involved in the development of ASD through behavioural and metabolic analysis using mouse models.

Methods: Pregnant C57BL/6 mice were administered with sodium valproate (600 mg/kg) by oral gavage on 12th day of the pregnancy. Control mice were given normal saline. ASD phenotypes were assessed in the pups by Open Field Test, Elevated Plus Maze (EPM), Y-Maze, and Social Interaction test. Neuronal metabolic activity in the brain was measured using ^{1}H-[^{13}C]-NMR spectroscopy after intravenous injection of [1,6-$^{13}C_2$] glucose in mice.

Results: The pups born from Valproate treated (VAL) mice spent significantly ($p=0.04$) less time (6.9±2.6 %) in the centre of the open field arena when compared to the control mice (19.3±11.2%). Additionally, in the EPM test VAL group mice spent significantly ($p=0.02$) less time (4.7±4.7 %) in the open arms as compared to controls (12.5±6.4 %). Neurometabolic analysis suggests slightly reduced rates of glucose oxidation in glutamatergic neurons and GABAergic neurons in the VAL group of mice.

Discussion: Exposure to valproate during pregnancy produces autistic-like phenotypes in the pups such as anxiety and less exploration. Moreover, hypo-glucose metabolism suggests impaired synaptic transmission in the cerebral cortex of ASD mice.

Longitudinal Surface Based Morphometric Analysis in Traumatic Brain Injury

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Background: India has a high traumatic brain injury (TBI) burden, with 60% of head injuries from road traffic accidents (RTAs) and over 150,000 deaths annually. Surface-based morphometry estimates cortical morphology indices like volume, thickness, and surface area, revealing trauma-induced structural brain changes.

Objective: To assess cortical morphology in mild-to-moderate TBI patients during acute phase and after a 4-month follow-up, compared to healthy volunteers.

Methodology: This study included eleven healthy individuals (age 32.82±15.61, 6 males and 5 females) and 35 acute and 35 chronic TBI patients (age 33.85±13.9, 6 females and 29 males). Structural images were realigned to anterior-posterior commissure. Cortical thickness, surface area, and volume of 68 cortical parcels were analyzed with Desikan-Killiany atlas using FreeSurfer software. Group differences were assessed with Multivariate Analysis of Variance (MANOVA), adjusting for age and intracranial volume as covariate.

Result: Acute TBI patients exhibits significantly decreased surface area in left pars triangularis, left pars orbitalis, and right transverse temporal regions compared to healthy controls. Chronic TBI patients also exhibit reduced surface areas in the left lateral orbitofrontal, left parsorbitalis, left parstriangularis, and other cortical regions. The lateral orbitofrontal gyrus bilaterally shows further reduction in surface area in chronic TBI compared to the acute phase, indicating persistent morphological changes. Both acute and chronic TBI phases show significantly decreased cortical volume and thickness compared to controls, with no significant differences between the two phases in cortical volume.

Conclusion: Both acute and chronic TBI patients exhibit significant reductions in cortical surface area and volume compared to healthy individuals. Specific regions such as lateral orbitofrontal and left pars triangularis are notably affected in chronic TBI. However overall pattern of cortical atrophy remains consistent across both phases. Cortical thickness is also significantly decreased in both acute and chronic TBI, highlighting the persistent and widespread impact of TBI on cortical structure, regardless of the injury phase.

Revealing sex-specific regulatory molecular mechanism underlying hippocampal damage and recovery in the internal carotid artery occlusion mouse model

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Background: Cerebral ischemic stroke stands one of the leading causes of death and disability worldwide. Therapeutic interventions to cure cerebral ischemia induced neural damage are limited due to inadequate understanding of underlying molecular mechanisms including post-stroke cognitive impairment.

Purpose: In light of the fact that sex difference might reflect a major influence in post-stroke consequences, investigating the differential regulation of hippocampal (a primary centre for cognition) damage and subsequent recovery through neurogenesis in males and females is the focus of our study.

Methods: Adult CD1 male and female mice, aged 7 months, were utilized, and all experimental procedures were ethically approved. The animals were subjected to Internal Carotid Artery Occlusion (ICAO) and the molecular analysis utilizing western blot, qPCR and immunohistochemistry were performed in hippocampus, at different time points like 6 hours, 1, 3, 5 and 7 days after ICAO to map neurogenic dynamics. Before collecting the tissues, motor and cognitive behavioral evaluations were also performed by various assays.

Results: Our observations revealed that ICAO induces a differential hypoxic and inflammatory response in hippocampus across the sexes. Unlike males, inflammatory response and neuroplasticity activation occurred at multiple time points in females, leading to the hypothesis that males exhibit this response may be later than females. Furthermore, differential SOX-2 and BrDU expression patterns in male and female hippocampus emphasizing sex-specific variations in post-ICAO neurogenic responses. Additionally, there are a few sex-specific alterations in cognitive ability also were observed.

Conclusion: Overall, our results revealed that the faster recovery rate observed in females stems from long-term synaptic plasticity induced in females, coupled with multiple time point triggers in neurogenesis following Internal Carotid Artery Occlusion (ICAO).

Swiss-ADME predictions of pharmacokinetics and drug-likeliness properties of phytochemicals present in selected plants with putative nootropic activity

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Background: Plant bioactives are emerging as an integral part of Complementary and/or Alternative Medicine. The Indian pharmacopeia has several plants with proven bioactive properties either as single compounds or formulations. Some of the purported nootropic formulations with potential to enhance cognitive functions include Centella asiatica, Evolvulus alsinoides, Glycyrrhiza glabra, Tinospora cordifolia and Nardostachys jatamansi.

Purpose: This study was undertaken to assess the potential of phytochemicals from these plants using validated web-based platforms like Swiss-ADME and PubChem, determining physicochemical properties such as molecular weight, hydrogen bonding, lipophilicity, and solubility, while also evaluating pharmacokinetic parameters and drug-likeness.

Methods: Phytochemical properties of twenty selected compounds were retrieved from PubChem. Chemical structures were determined using canonical SMILES and a detailed analysis carried out of their physicochemical attributes, pharmacokinetic parameters and drug-likeness based on the Lipinski's rule of five.

Results: The phytochemicals screened possess a broad range of molecular weights (136.15 to 959.12 g/mol), are potential hydrogen bond donors with topological polar surface areas. Lipophilicity and solubility assessments indicated diverse solubility classes, with compounds like 2-C-methylerythritol demonstrating high solubility, while β-carotene and Lupeol exhibited poor solubility. Pharmacokinetic analysis highlighted significant variability in gastrointestinal (GI) absorption and blood-brain barrier (BBB) permeability. The majority showed low GI absorption and were non-permeable to the BBB, with bioavailability scores between 0.11 and 0.56.

Conclusion: The screened phytoconstituents included common compounds such as triterpenes, flavonoids, alkaloids, and glycosides besides plant-specific compounds. The significant variation in molecular profiles, variable GI absorption and BBB permeability indicate limitations in bioavailability. The underlying nootropic mechanism of selected individual phytochemicals needs to be further analysed using in-silico approaches.

Early Pro-Regenerative Responses After Traumatic Brain Injury (TBI) in Regeneration Competent and Non-Competent Species

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Background: Traumatic Brain Injury (TBI) due to military combats or accidents in humans is a challenging medical issue that leads to chronic disabilities and death. In the adult mammalian brain, post-TBI neuroinflammation is a dominant response, followed by neural degeneration and scar formation. These events act as significant obstacles for successful regeneration in the post-TBI mammalian brain. Conversely, teleost zebrafish possess a profound capacity to regenerate their brain tissue with little scar formation after TBI. In zebrafish, the injured brain is initially repaired with scar tissue after the onset of inflammatory events. However, the scar tissue gets resolved and replaced by new functional neurons after a period of time. This establishes zebrafish as a potent model to understand the TBI niche in a regeneration competent background.

Purpose: To understand the role of early pro-regenerative responses in the acute phase of TBI and the brain regeneration mechanism in regeneration competent versus non-competent species.

Methods: In this study, we have utilized several transcriptomic studies in TBI along with cellular, molecular and behavioural assays to study the role of early pro-regenerative responses in the acute phase of TBI and the brain regeneration mechanism in zebrafish.

Results: Our study investigated the potential role of early pro-regenerative genes in the acute phase of TBI. Several transcriptomic studies were used to prioritize the pro-regenerative genes. Characterisation of these genes deciphered their potential role in the development of a pro-regenerative niche after TBI.

Conclusion: The results mark the early expressing genes and their role after TBI. The potential differences in the expression pattern of several genes among regeneration competent and non-competent species will provide the key insights in driving successful brain tissue regeneration in humans and their significant therapeutic implication for future regenerative medicine.

Therapeutic Potential of Curcumin Encapsulated Milk Exosomes in Ventral Subicular Lesioned Rat

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Background: Subiculum, the output component of hippocampal formation is the first brain region to get affected in Alzheimer's disease. Curcumin is a plant-based phytochemical with anti-inflammatory, anti-microbial, and anti-oxidative properties. Despite significant medicinal properties, impetuses such as poor stability, solubility and bioavailability hinder the utilization of curcumin for clinical usage. To overcome these hindrances, we nanoformulated curcumin by encapsulating it into milk exosomes which improved the solubility, stability, and bioavailability.

Purpose: To assess the therapeutic effects of curcumin encapsulated milk exosomes [CEME] in Ventral Subicular Lesioned (VSL) rats following intranasal administration.

Methods: Experiments were carried out using 2-3 months old Wistar strain of albino rats. Rats were randomly divided into 6 groups (n=8/ group), normal control, VSL, VSL rats administered with curcumin or CEME. Ventral subicular lesion was induced stereotaxically using Ibotenic acid. One-week post-VSL, intranasal administration of curcumin/CEME was carried out for three days (one injection/day; 5 mg/kg). Behavioral assessment for memory, anxiety and depression was conducted. Following that, animals were euthanized for histological and biochemical analysis.

Results: Our result revealed that damage to ventral subiculum induced oxidative stress, neuroinflammation, neurodegeneration and cognitive impairment, anxiety, and depression-like symptoms in rats. Intranasal administration of curcumin/CEME mitigates oxidative stress, neuroinflammation, neurodegeneration and behavioral comorbidities.

Conclusion: Curcumin/CEME can prevent neurodegeneration, neuroinflammation and cognitive functions in subicular lesioned rats. Future studies are warranted to investigate the long-term effects of encapsulated curcumin in this animal model of ventral subicular damage.

The novel Ile1214Lys variant in SCN1A gene causes generalized epilepsy with febrile seizures plus by loss of function

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Background: Mutations in voltage-gated sodium channels (VGSCs) have emerged as key contributors to the pathophysiology of epilepsy, a common neurological disorder characterized by recurrent seizures. The impact of the mutations on VGSC function includes gain-of-function and loss-of-function effects, which lead to hyperexcitability or reduced excitability of neurons. The complexity of genotype-phenotype correlations are posing a greater challenge in treatment of the condition and there is need for more comprehensive functional analyses. We have identified a novel variant Ile1214Lys in the cytoplasmic region of SCN1A gene that encodes for NaV1.1. The functional effects of the variant are not known.

Purpose: Study the effect of missense variant on expression, localization, trafficking and gating of the ion channels, genotype-phenotype correlation, molecular mechanism of the disease.

Methods: *In-silico* tools were used for conservation analysis, prediction of protein stability and pathogenicity. MD simulations were carried out using GROMACS software. Site directed Mutagenesis (SDM) was carried out to introduce mutation. Next generation sequencing (NGS) was performed to check for spontaneous mutations. Transiently expressed native and mutant channels in HEK293T cells were analyzed via whole-cell patch clamp technique.

Result: Conservation analysis showed that isoleucine residue at 1214 position is highly conserved across species. The *in-silico* tools classified the variant to be destabilizing and pathogenic. Functional variant analysis using funNCion tool predicted the variant to be pathogenic (0.85) and loss-of-function (0.68). The RMSD analysis shows the deviations between the WT and mutant and the variable number of hydrogen bond formation throughout the simulations. The wild-type (WT) and I1214K variant channels were successfully expressed in HEK cells. Whole cell patch clamp recordings showed a 64% decrease in the peak sodium current density in the I1214K variant channel compared to WT.

Conclusion: *In-silico* study demonstrates the deleterious nature of the variant and its negative impact on tertiary structure of the protein that could impact the function. The decrease in sodium current density indicates the mild loss of function in accordance with our *in-silico* predictions and further analysis of gating mechanisms will provide a possible pathomechanism of epileptic phenotype.

Effect of *Clitoria ternatea* aqueous root extract on altered hippocampal dendritic spine density and spatial memory in perinatal maternal separation stressed rat pups

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Background: Perinatal maternal separation stress [PMSS] during early brain development results in long lasting brain morphological and cognitive changes. The present study explores the neuroprotective benefits of *Clitoria ternatea* root extract supplements during PMSS in alleviating PMSS-associated detrimental effects on brain development.

Purpose: To study and compare effects of PMSS vs PMSS rat pups supplemented with *Clitoria ternatea* aqueous root extract [CTR] on their Spatial learning & memory and hippocampal CA1 neuronal dendritic spine density.

Methods: Inbred Wistar rat pups were grouped as - Control, PMSS, and PMSS+ CTR [n= 9 rats /group]. PMSS rat pups were separated from their mothers during post-natal day (PND) 2-21 for 6 hours/day. PMSS+CTR group received CTR supplements during PND2-21. On day 28, all rats were tested for spatial learning & memory using radial arm maze following which rat pups were sacrificed, brain tissues were processed for Golgi staining to study the spine density.

Results: Latency to enter all baited arms was significantly increased [$p<0.01$] in PMSS rats compared to controls and PMSS+CTR groups. Number of correct entries were significantly increased($p<0.01$), working memory errors and reference memory errors were significantly decreased ($p<0.01$, $p<0.001$) in PMSS+ CTR group, compared to PMSS group. Also, PMSS+CTR group had significant increase in both apical and basal neuronal spine counts compared to that of PMSS group [$p<0.05$, $p<0.01$].

Conclusion: PMSS causes significant reduction in hippocampal CA1 neuronal dendritic spines and spatial learning. CTR supplementation to one-month-old PMSS rat pups significantly restores CA1 neuronal dendritic spine density and spatial learning, thus providing neuroprotection against PMSS-associated brain deficits.

Neuroprotective effects of *Desmodium giganticium* extract in *Caenorhabditis elegans* models of Parkinson's disease

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Background: Parkinson's disease (PD) is the second most prominent age-associated neurodegenerative disorder marked by α-synuclein aggregation and loss of dopaminergic (DA) neurons. Despite extensive research efforts, the therapeutic interventions presently available for PD management exhibit limited efficacy in halting or reversing disease progression, while often accompanied by a spectrum of adverse effects that further compromise patient quality of life.

Purpose: Natural extracts may offer advantages over conventional pharmacotherapies by virtue of their favourable safety profiles and reduced risk of adverse effects.

Methods: In the current study, the neuroprotective effects of *Desmodium giganticium* hexane extract (DG-HE) were evaluated using two *Caenorhabditis elegans* PD models: UA44, characterized by α-synuclein overexpression in dopaminergic neurons, and NL5901, which expresses α-synuclein in muscle cells.

Results: DG-HE, when fed to UA44 as a supplement to the E. coli HT115 feed, prevented the degeneration of dopaminergic neurons and improved several dopamine-dependent behaviours like pharyngeal pumping rate, 1-nonanol avoidance, and basal slowing response. In NL5901, DG-HE decreased the α-synuclein aggregation. From the transcriptomic data analysis, we found that genes associated with mitochondrial functions were differentially expressed after treatment with DG-HE.

Conclusion: These findings indicate the molecular pathway through which DG-HE may be exhibiting neuroprotection in PD. In conclusion, the findings of this study suggest that *Desmodium giganticium* hexane extract holds promise as a potential neuroprotective agent in Parkinson's disease.

Comprehensive Assessment of Sleep Architecture Disruptions in Alzheimer's and Sleep-Deprived Alzheimer's Disease Rat Models: A Comparative Study

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Background: Alzheimer's disease is a neurobiological disorder characterized by sleep disturbances, dementia, and cognitive impairments. The bidirectional relationship between Alzheimer's and sleep architecture is poorly understood. Furthermore, Alzheimer's pathology may disrupt spatial memory leading to cognitive decline in sleep deprived Alzheimer's rat model.

Purpose: To examine sleep architecture and spatial memory in Alzheimer's disease (AD) rats and investigate how sleep deprivation affects disruptions in sleep architecture.

Methods: Wistar rats (250-280g; n=5 per group), were utilised as experimental animals CC-control; AD; SD+AD-sleep deprived Alzheimer's model, aiming to investigate the effects of intracerebroventricular microinjection of 3mg/kg Streptozotocin (ICV-STZ) or artificial cerebrospinal fluid (ACSF) on spatial memory and sleep architecture. Sleep recordings conducted from the 11th to the 13th day post-recovery assessed the differences in Non-rapid eye movement (NREM) % and Rapid eye movement (REM) % between Alzheimer's disease rats, Control rats, and sleep-deprived plus Alzheimer's disease rats. After 30 days, Morris water maze test was used to assess the spatial memory in rats.

Results: Alzheimer's Disease induced in sleep rested animals (AD) exhibited non-significant percentage change in Quiet wake (Mean diff: -3.94), NREM sleep (Mean diff: -5.60) and REM sleep ($F(3, 24) = 75.6$; $p<0.001$; n=5). However, REM sleep was significantly reduced in SD+AD animals in comparison to Control animals (Mean diff: 6.51). In spatial memory assessment by Morris water maze, We observed that Latency significantly increased in AD and SD+AD animals during training in comparison to Control animals ($F(3, 76) = 17.5$; $p<0.001$; n=5). Two-way ANOVA results depicted that AD and SD+AD animals exhibited less time spent in platform zone during probe test.

Conclusion: In summary, REM sleep and spatial memory significantly decreased in sleep deprived Alzheimer's disease model rats highlighting the complex relationship between Alzheimer's disease, sleep, and spatial memory.

Natural Nutraceutical Restores Motor Function and Increases Tyrosine Hydroxylase in Parkinson's Disease Models

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting the basal ganglia, where neuroinflammation plays a crucial role in its pathophysiology. Due to the lack of effective treatments, novel therapies with minimal side effects are being explored. Plant-based nutraceuticals, enriched with free fatty acids and polyphenols, are typically derived from natural sources such as palm oil, coconut oil, and other plant-based fats through processes like cold pressing or solvent extraction.

Purpose: We investigated a fatty acid-based nutraceutical's potential in mitigating PD through a preclinical study using a rotenone-induced PD model.

Methods: Our study employed a multi-tiered approach combining in-silico analysis, in vitro experiments, and in vivo studies to explore the potential therapeutic effects of natural nutraceutical in Parkinson's disease (PD).

Result: Our *in-silico* analysis revealed that it could interact with key molecular targets involved in PD pathology. *In vitro* experiments demonstrated the treatment with this significantly improved the viability of neurons, reduced cell death (MTT assay), and enhanced the production of neurotransmitters (TNF-α, IL-1β, IL-6). Additionally, *in vivo* studies showed improvements in motor function and neurotransmitter levels in mice with PD.

Conclusion: These findings suggest that it may offer a novel therapeutic approach for PD by targeting specific molecular pathways. Further research is needed to fully understand its mechanisms of action and explore its potential for clinical use. We conducted ELISA and Western blot analyses to assess biomarkers associated with oxidative stress (SOD, GPx, GSH, PGC-1α, Nrf2) and neuroinflammation. The anti-inflammatory effects of this natural neutraceutical are crucial in downregulating inflammatory gene expressions such as Cox-2, iNOS, TNF-α, and IL-6. Our findings suggest that it may improve the progression of PD, with underlying mechanisms involving antioxidant and anti-inflammatory pathways. Our findings suggest that this natural nutraceutical may offer a novel therapeutic approach for PD, but further studies are needed to fully understand its mechanisms and establish optimal dosing.

The role of Annexin A1 in neuroinflammation during Hepatic Encephalopathy, study in rat model

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Background: Moderate hepatic encephalopathy (MoHE) is a metabolic brain disorder due to chronic liver disease, manifested as neurological and psychiatric alterations. Ammonia toxicity and pro-inflammatory elements leads to preliminary inflammatory reaction. Although initial inflammatory response has beneficial effects but chronic activation of microglia and astrocytes could have detrimental effects leading to neuronal damage and neurodegeneration.

Purpose: Annexin A1 (AnxA1) protein, expresses by glial cells, plays crucial role in neuroinflammation, and involved in maintaining blood brain barrier (BBB) integrity. In our study we have targeted this protein to investigate its role in HE pathophysiology.

Methods: Adult male Charles foster rats were segregated into control and MoHE groups. MoHE was induced by i.p. injection of TAA (100mg/Kg BW) and control rats received normal saline for 10 days. Learning and motor performance was evaluated by NOR and rota rod tests. Western blotting was used to detect AnxA1 expression, and immunofluorescence was used for its spatial distribution and expression in different cells. Nissl staining assessed neuron morphology and cell population, and Golgi-Cox staining characterized axonal and dendritic arborization. In vivo BBB permeability was evaluated using fluorescence tracers.

Results: The behavioural assessment revealed decreased memory, learning, and motor coordination in MoHE rats. The expression of AnxA1 was found to be increased during MoHE. Its expression in microglia, astrocytes, neurons, and endothelial cells was observed by colocalizing its markers. Nissl staining showed a reduced cell count and an increased number of cells undergoing apoptosis. Furthermore, the reduced axonal and dendritic arborization confirmed the neuronal degeneration in MoHE rats. Measurement of tracers indicated BBB extravasation in MoHE rats, suggesting compromised BBB integrity.

Conclusion: AnxA1 may be a potential therapeutic target due to its multifaceted roles in maintaining brain homeostasis.

Classification of mouse thalamic neurons using stereologic morphometric parameters

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Background: The thalamus is composed of nuclei that have unique functions. These are formed by excitatory and inhibitory neurons. There is little morphometric data available on murine thalamic neurons.

Purpose: The measurement and classification of murine thalamic neurons by unbiased stereology.

Methods: With ethical clearance, six adult albino mice were sacrificed and perfusion fixed by buffered paraformaldehyde. The brain was harvested and processed for cryosectioning (40µm-thick serial, coronal sections) and cresyl violet staining. These sections containing the thalamus were examined under a BX53 light microscope (Olympus, Japan), attached to a computer with StereoInvestigator (version 2021.1.1, Microbrightfield Inc. VT, USA) installed in it.

The nucleator probe of the program was applied on the neurons selected by the optical fractionator to estimate the neuronal volume and neuronal nuclear volume. These were used for hierarchical clustering of data. Thereafter, we used K-Means cluster analysis. The overall difference between three clusters was assessed by Kruskal-Wallis One-Way ANOVA test, followed by post-hoc pair-wise comparison using Mann-Whitney U test. For all statistical tests a two-sided probability of $p < 0.05$ was considered to be statistical significant. We carried out data analysis using SPSS statistical package for windows (IBM v23, Armonk, NY, USA).

Results: The details of the three K-mean clusters were as follows: 1- number of neurons (n) =145, neuronal volume=1855.80 (1654.35-2260.53) μm^3, neuronal nuclear volume= 679.91 (581.54-798.88) μm^3 and corresponding neuronal diameter= 15.25 µm; 2- n= 1045, neuronal volume= 556.17 (415.67-685.61) μm^3, neuronal nuclear volume= 235.19 (169.24-304.83) μm^3 and neuronal diameter= 10.20 µm; and 3- n=686, neuronal volume= 1039.29 (922.481225.09) μm^3, neuronal nuclear volume= 435.48 (366.82-516.00) μm^3 and neuronal diameter= 12.57 µm. Hence, the thalamus contains three identifiable groups of neuron populations.

Conclusion: We identified three distinct populations of small, medium and large neurons in the Swiss albino mouse thalamus.

Effect of phytochemicals on glutamatergic neurotransmission

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Background: Dysfunction in glutamatergic neurotransmission has profound health implications. Glioblastomas increase glutamate, driving tumor growth via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA-R) receptors, while neuroblastomas cause neurodegeneration through excessive *N*-methyl-D-aspartate (NMDA-R) receptor stimulation. Ionotropic pathway drugs can lead to side effects like confusion and seizures. Although dopamine was once linked to schizophrenia, glutamatergic dysfunction is now considered a contributing factor, as NMDA-R antagonists like ketamine cause schizophrenia-like symptoms. AMPA-R activation, necessary for NMDA-R function, underscores the importance of studying glutamate's role in neurodegeneration and plasticity, particularly given the age-specific impact of these cancers.

Purpose: Study the effect of phytochemicals on glutamatergic neurotransmission lies in exploring their potential as therapeutic agents for neurological and psychiatric disorders.

Methods: N2a cells (neuroblastoma cells) and C6 cells (glioma cells) were used for the study. Computational simulations were conducted using Autodock4, and Gaussian to study the predictive binding value between different phytocompounds and NMDA-R and AMPA-R receptors. The expression of neurotrophic factors was analyzed at the mRNA level using gene-specific primers.

Results: Simulation studies were conducted on NMDA-R (GluN2b) using the antagonist MK801, agonists glutamate and NMDA, and on AMPA-R (GluA2) with its agonist quisqualic acid and antagonists perampanel and SPD-502. In the rat model for both NMDA receptor (PDB:6E7R) and AMPA receptor (PDB:3SLF), beta-sitosterol exhibited significant binding affinity, scoring lower than other ligands. In the mouse model, beta-sitosterol had the lowest score for NMDA-R (AF_A0A0G2JEA7), indicating a higher affinity, though it had a higher score compared to perampanel in AMPA-R (AF_P23819), suggesting a preference for NMDA-R. Additionally, differential BDNF mRNA expression was observed post-sitosterol treatment compared to untreated cells.

Conclusion: Beta-sitosterol demonstrates a stronger binding affinity for NMDA receptors over AMPA receptors in rat and mouse models, indicating its potential as a selective modulator with neurotrophic effects, supporting its therapeutic applications.

Wnt and Hippo pathways maintain Notch-independent Hes1 (NIHes1) expressing cancer stem cells in neuroblastoma

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Background: Neuroblastoma (NB) is an childhood blastoma which is derived from embryonal or fetal stem cells. The pluripotent progenitor-based origin of NB cells endows high heterogeneity to these tumors. More than 50% of high-risk neuroblastoma relapse after current treatment modalities and this is attributed to the heterogeneity of tumor cells, primarily the cancer stem cells (CSCs). Notch signalling and its downstream Hes1 gene are involved in maintenance and metastasis of CSCs. There are two types of CSCs which differ by their activation of Hes1 promoter – Notch-dependent Hes1 expressing CSCs (NDHes1) and Notch-independent Hes1 expressing CSCs (NIHes1).

Purpose: Much of therapeutic research against NB CSCs target Notch signalling. However, this is ineffective as NDHes1 cells are only affected and the two CSCs are capable of transiting into each other. Our strategy is to target the NIHes1 CSC proliferation and/or induce its transition to NDHes1.

Methods: We have used transcriptomic analysis of NIHes1 and NDHes1 CSCs to understand key pathways involved in its maintenance. We have also identified proteins binding to Notch-independent Hes1 promoter region using JASPAR-UNIBIND databases. To verify role of these pathways in IMR32 CSCs, the cells were treated with specific inhibitors against selected pathways. We are also analyzing the role of these pathways in NIHes1 proliferation and transition.

Results: We have identified Wnt signalling to be prominently active in NIHes1 cells. We have also identified downstream effectors like Tcfl20, Tead, Smad2 and others from Wnt, Hippo and TGF-β pathways. Inhibitor assay on IMR32 cells and tumorspheres have identified significant roles of Wnt and Hippo pathways in NIHes1 CSCs in terms of tumorsphere size and transition.

Conclusion: Wnt and Hippo pathways are involved in NIHes1 cells. Targeting these pathways could effectively address NIHes1 CSCs. This can lead to a combinatorial treatment strategy against recurrence of NB.

Early diagnosis of synaptic impairment in Type-1 diabetic rat retina

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Background: Diabetic Retinopathy (DR) is the leading cause of blindness in the developing world. After approximately five years of the onset of diabetes, the pathology of the retina develops insidiously in the form of microvascular aneurysms, hemorrhages, cotton wool spots, and neovascularization. These clinical symptoms confirm the irreversible damage to the retina caused by diabetes, ultimately leading to total vision loss.

Hypothesis & Objective**:** Neurons could be the early sensors of hyperglycemia. The objective is to study the changes in the global electrophysiological response of the retina in diabetes and to find which retinal synapses are affected in early diabetes.

Methods and Results: Here, we study the effects of diabetes on retinal neurons using the in-vivo electroretinogram (ERG) and ex-vivo patch clamp techniques. ERG recorded from the diabetic rats shows a 50-60% reduction in amplitude and a 20-25% delay of 'a' and 'b' waves compared to the control. The oscillatory potentials (OP) also show a reduction in amplitude and a delay of 5-15 ms at different light intensities. This result is well complemented by the paired-pulse recordings from the RBC-AII synapse in 24-week diabetic rats, which shows a 50% reduction of the paired-pulse ratio (recovery in neurotransmission). All these results are observed in early diabetic animals and thus can be considered early signatures of diabetic retinopathy.

Conclusion: We conclude that neurotransmission at the RBC-AII synapse is affected in early diabetes. These changes can be correlated to a decrease in the amplitude of OPs in diabetic animals. The above result has a great diagnostic value in predicting diabetic retinopathy well in advance.

Effect of human umbilical cord blood plasma derived from prenatal yoga practitioners on neurocognition in aged mice

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Background & Purpose: Aging is the inevitable biological process and is one of the primary risk factor for various neurodegenerative disorders. In this study we will investigate the effect of prenatal yoga practitioner derived umbilical cord blood plasma on neurocognition in aged mice.

Methods: A total of 26 participants with uncomplicated pregnancy aging 18-35 years will be recruited at 17th -20th week. Yoga intervention will be given till delivery and umbilical cord blood collected and plasma will be separated. Doppler will be done at level 2 ultrasound at baseline and at 8th month follow-up. Systolic /diastolic (S/D), Pulsatility index (PI), Resistance index (RI) and Diastolic notch (DN) readings of right uterine, left uterine and umbilical artery will be compared at base line and at 8th month. After that we will use enzyme linked immunosorbent assay to analyse the expression of neurotrophic, inflammatory, anti-aging and stress markers in Umbilical Cord Blood plasma (UCB-plasma) and further UCB-plasma will be administered intravenously in aged mice. Neurobehavioral assessment will be done using behavioural tests like MWM (Morris Water Maze), NOR (Novel Object Recognition) and OFT (Open Field Test) and molecular assessment will be done using qPCR and IHC (Immunohistochemistry) for neurotrophic, neurogenesis, apoptotic and memory associated markers. Data will be analysed using SPSS statistical software. T-test, chi-square and ANOVA test will be done to compare different groups. <0.05 will be considered as a statistical significance.

Expected Outcome: A total of 8 patients recruited with baseline doppler reading of right uterine artery (S/D 2.87 ± 0.71, PI 1.22 ±0.28, RI 0.85 ±0.58), left uterine (S/D 2.7 ±0.71, PI 1.22 ±0.26, RI 0.54 ±0.13 and umbilical artery (S/D 2.98 ±0.54, PI 1.07 ±0.31, RI 0.64 ± 0.067) further yoga intervention is ongoing and expected to see changes due to prenatal yoga and further analysing the effect of UCB-plasma in aged mice.

Investigating the Role of Masoprocol, a Protein Translation Inhibitor, in Neurodegenerative Disorders

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Background: Masoprocol, a phenolic lignan derived from *Larrea tridentata*, has demonstrated therapeutic potential in various diseases. Despite its promising preclinical evidence, the role of Masoprocol in Parkinson's disease (PD) remains underexplored.

Purpose: This study aims to elucidate Masoprocol's mechanism of action in PD, with a particular focus on its impact on protein translation and mitochondrial homeostasis.

Methods: Employing network pharmacology, we identified potential molecular targets of Masoprocol implicated in PD pathogenesis. Western blot analysis was employed to delve deeper into the modulation of the mitophagy pathway.

Results: Subsequent *in vitro* studies assessed Masoprocol's anti-apoptotic effect and identified an optimal therapeutic dose. Comparative proteomics was utilized to identify differentially expressed proteins, providing insights into Masoprocol's mechanism of action. This, in conjunction with the modulation of mitochondrial dynamics, as evidenced by alterations in key protein markers (DRP1, OPA-1, AFG3L2, PGC1α, SPG-7, Parkin, PINK-1, LC3), contributes to its therapeutic efficacy. Furthermore, Masoprocol demonstrated anti-inflammatory properties, as indicated by reduced levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ).

Conclusion: Our findings suggest that Masoprocol exerts its neuroprotective effects by inhibiting protein translation through the eIF4/4EBP1 pathway. These results highlight Masoprocol as a promising therapeutic candidate for PD, with potential implications for other neurodegenerative diseases. Further investigations are warranted to elucidate the precise molecular mechanisms underlying its effects and to evaluate its clinical efficacy.

Neuroprotective Effect of Trehalose in Alzheimer's Disease Phenotypes in *Drosophila melanogaster*

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Background: Trehalose (TRS), is a non-reducing sugar found in plants, insects, microorganisms and invertebrates, owns antioxidant and anti-inflammatory activities. Aluminum chloride (Al) is a neurotoxic chemical that used to induce oxidative stress mediated Alzheimer's disease (AD) in both animal and *D. melanogaster,* hence the model.

Purpose: In the current study we evaluated whether TRS can reverse oxidative stress and other markers of AD induced by Al in *D. melanogaster.*

Methods: The flies were fed with diet containing varying concentrations of TRS to determine survival rates. Subsequently, the neuroprotective effect of TRS was determined in *D. melanogaster that were* subjected to Al neurotoxicity after seven days.

Results: The result shows that flies exposed to Al and treated with 150 mM and 300 mM of TRS exhibit 1.47- and 1.52-fold increase in climbing assay and also longevity. The other biochemical markers such as Catalase, Glutathione-*S*-transferase, total Glutathione and Superoxide dismutase increases 2.82, 2.72, 2.82, 1.92 and 2.68, 2.98, 2.68, 2.05 folds with the treatment of 150 mM and 300 mM of TRS respectively. However, Acetylcholinesterase decreases by 2.17-fold and 2.90-fold respectively that has been corroborated with the binding affinity energy (ΔG = -11.593 kcal/mol) studies using molecular docking.

Conclusion: Hence the study concludes that the survival, behavioral and biochemical markers of AD induced in *D. melanogaster* was mitigated by TRS.

Role of Oligodendroglia in Sporadic Amyotrophic Lateral Sclerosis: Insights from *in-vitro* Experimental Models

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Background: Amyotrophic Lateral Sclerosis (ALS) is a debilitating disorder with no known curative treatment. It is multifactorial, with complex genetic and molecular mechanisms affecting not only motor neurons but also glia. Both, astrocytes and microglia get activated and contribute significantly to neurodegeneration.

Purpose: To study the role of oligodendroglia in sporadic form of ALS (SALS), which contributes to 90% of the total ALS cases.

Methods: Human oligodendroglial cell line, MO3.13 was used for the study and the cells were exposed to cerebrospinal fluid from SALS patients (ALS-CSF; 10% v/v for 48hrs). Viability of these cells in response to ALS-CSF was measured by MTT assay, while marker proteins and trophic factor expressions were studied using ICC and western blotting techniques. The levels of L-Lactate, a glycolytic metabolite and its transporter was also estimated. Further, to investigate the effect of oligodendroglia on motor neurons, NSC-34 motor neuronal cells were co-cultured with MO3.13 cells. To extend the findings in a patient specific model, iPSCs derived from healthy control and sporadic ALS patient are being differentiated to iOligodendroglia and iMotor neurons.

Results: ALS-CSF significantly reduced the viability of MO3.13 cells and down-regulated the expression of oligodendroglia-specific proteins, CNPase and Olig2, confirming its toxic effects on these cells. Live cell imaging experiments revealed failure of ALS-CSF to induce degenerative changes in NSC-34 cells, instead, resulted in better neuronal differentiation. This neuroprotective effect was presented by the oligodendroglial cells via trophic and metabolic support as evidenced by sustained BDNF, GDNF levels and increased L-lactate and its transporter MCT-1 expression upon ALS-CSF treatment.

Conclusion: Findings from our study indicate that oligodendroglia are protective to the degenerating motor neurons when the other glial cells turn detrimental. Deeper investigations using patient specific neural cells will provide better insights into oligodendroglial contribution to SALS.

Impaired immunomodulation and pathophysiology of Mesenchymal Stromal Cells (MSC) correlates with Schwann Cell (SC) degeneration & increased peripheral & neuroinflammation in PD

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Background: Studies on neurodegenerative diseases like PD has indicated that immune cell activation and chronic inflammation is not merely a consequence of neurodegeneration but also a significant factor in the initiation and progression of the disease. Activation of peripheral immune cells can occur due to multiple reason however under physiological condition, it is known to get modulated by endogenous BMMSCs (Bone-marrow-MSC) by its array of immunomodulatory cytokines. Transplanting ex-vivo expanded autologous BMMSCs into PD patients to combat inflammation has failed in advanced clinical trials, which indicates impaired function of endogenous BMMSCs.

Purpose: To assess the timepoint of alteration in endogenous BMMSCs in *in-vivo* chronic PD model and validating these cellular modifications in human iPSC derived MSCs of sporadic PD patients.

Methods: Protein and myelin expression in cells and tissues was evaluated through immunocytochemistry and immunohistochemistry. Basal reactive oxygen species levels were measured via H_2DCFDA fluorescence with spectrophotometer. Apoptosis and proliferation were analysed by flow cytometry using Annexin-PI and Ki67 staining. Immunomodulatory and paracrine factor secretion was assessed using MLR assay and ELISA.

Result: In PD rat BMMSCs, there was a significant increase in basal ROS levels and apoptotic cells, along with decreased migration, proliferation, self-renewal, and paracrine properties compared to controls. Concurrently, midbrain gliosis, SC degeneration and elevated TNF-α levels, were observed. MSCs and SCs derived from sporadic PD patient iPSCs exhibited similar pathophysiological impairments as seen in the rat model.

Conclusion: Impairment of the physiological and functional parameters of endogenous MSCs begins at an early stage and worsens as the disease progresses. This impairment of BMMSCs occurs concurrently with midbrain gliosis and SC degeneration indicating the involvement of bone marrow niche cells in the neurodegeneration observed in PD. Consequently, autologous MSC transplantation may not be beneficial for PD patients, highlighting the necessity of using allogenic MSCs from healthy individuals.

Hypo-Kaptin to Hyperbranching: A tale of cytoskeleton and neural circuits

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Background: Neurological disorders arise due to defects in neuronal circuit development and functioning. The proper functioning of the brain circuits relies on appropriate interneuronal signalling and efficient communication at the synapses achieved through the coordination of the neuronal cytoskeleton by its regulators. We aim to study one poorly characterised actin binding protein named Kaptin.

Purpose: Malfunctioning of such cytoskeletal proteins causes neurodevelopmental disorders due to improper neuronal connectivity, which affects a vast world population. Mutations in the Kaptin gene in humans cause neurodevelopmental delays, macrocephaly, and seizures. Understanding Kaptin's role in neural circuit development will give us crucial insights into the pathophysiology of Kaptin-mediated disorders.

Methods: We developed Kaptin homozygous mutant in zebrafish via CRISPR Cas9 to investigate neural circuit formation in zebrafish larvae. Whole body In Situ Hybridization (WISH) technique was used to study the localisation of Kaptin mRNA. Transgenic lines were used to study Kaptin's role in axonal branching and excitability in zebrafish larval brain during seizure. Immunofluorescence studies were utilised to characterise neuromuscular junctions in zebrafish motor neurons. Behavioural studies were carried out to understand motor circuit functionality. PTZ convulsant administration was performed to study seizure susceptibility.

Results: WISH showed Kaptin mRNA expression to be present throughout developmental stages and enriched in the brain regions. Behavioural and morphological studies on Kaptin mutants suggest impaired motor circuitry with increased axonal branching in motor neurons. Rescue experiments with full-length kaptin and actin binding deficient (K55D) variant revealed that the actin binding property of kaptin is crucial for regulating axonal branching. Seizure behavioural assay using a convulsant reagent PTZ revealed that Kaptin mutants are more susceptible to seizure. Preliminary Calcium imaging on Kaptin mutants shows early increased calcium activity in the hindbrain during seizure.

Conclusion: Kaptin's actin binding ability regulates axonal branching in motor neurons. Loss of Kaptin leads to an increase in seizure susceptibility. Understanding the mechanisms behind these processes will be important in finding the treatment for neurodevelopmental disorders.

Impact of High Glucose on Astrocytic Calcium Signaling and Gap Junction Coupling: Insights into their Potential Role in Cognition

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Background: Astrocytes are crucial for maintaining neuronal function, particularly in the hippocampus, where their extensive network supports synaptic activity and information processing. This network is sustained by extensive intercellular coupling among astrocytes facilitated by gap junctions. However, the effects of disrupted coupling on essential hippocampal functions, such as cognition, remain unclear.

Purpose: Investigating the impact of high glucose condition (HGC) on calcium signalling and gap-junction coupling in hippocampal astrocytes and whether these impairments affect cognition.

Methods: Primary hippocampal astrocyte cultures were prepared from P0 Wistar rats. HGC was induced with 25 mM Glucose. Intracellular calcium activity was measured using Fluo-4 AM. Radial arm maze (RAM) was performed in Streptozotocin model of Type-1 diabetic rats. The whole-cell patch-clamp technique was used to measure astrocytic passive membrane properties and electrical coupling.

Results: In HGC, the calcium wave propagation in astrocytes was reduced by over 50% within 60 seconds after mechanical stimulation, along with the absence of the prolonged calcium wave component in proximal cells. Similar to HGC, rapid calcium buffering was observed with U73122 (IP3 synthesis blocker) and Meclofenamic acid (MFA, gap-junction blocker) treatments. Interestingly, danegaptide (gap-junction activator) restored the buffering time. The connexin43 expression significantly increased in HGC. A reduction in astrocyte connectivity, indicated by reduced dye coupling and decreased input resistance, was noted in diabetic rats, along with significantly increased reference memory errors (3.03 vs. 0.44) and working memory errors (1.71 vs. 0.66) compared to controls.

Conclusion: Our findings reveal distinct spatiotemporal patterns of calcium signalling in astrocytes under HGC. IP3-induced signalling and gap-junction coupling may have been altered in the HGC. The recovery of calcium kinetics in the presence of Danegaptide was also observed. The results strongly indicate that gap junction coupling is significantly impaired along with short-term and long-term memory deficits in Type-1 diabetes.

Investigation of D-Galactose-induced brain ageing through various route and their behavioral effects in Swiss Mice

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Background: According to the United Nations' "World Population Prospects 2022" report, the number of aged people will double from 2022 to 2050, and the world will face various age-associated pathological conditions. Age-associated neurodegenerative diseases like Alzheimer's and Parkinson's are most common in aged people, that retard a person's 'healthy and happy' life. For the development of new drugs and therapies, various ageing models are being used, and 'D-galactose induced ageing model' is one of them, that was first introduced by Chinese researchers in 1985. After that, it is widely used for ageing and associated disease research, in which a sub-acute dose of D-galactose is injected intraperitoneally or sub-cutaneous, which may cause additional stress to animals apart from the effect of galactose.

Purpose: We administered D-galactose to Swiss mice orally and compared it with intraperitoneally injected D-galactose. This nonconventional administration route of D-galactose can reduce additional pain and stress to the experimental mice and can showcase the mechanistic effect of the compound itself.

Methods: We have done various neuro-behavioral studies of anxiety, locomotion, analgesia and cognition, which are usually altered in aged mice. We also checked oxidative stress parameters with Malondialdehyde, Nitric oxide, and Glutathione. We have also performed western blotting for biomarkers of ageing p21, p16 & p53.

Result: We found oral administration also shows ageing Biomarkers (p21, p16 & p53) as present in conventional intraperitoneally injected mice. Galactose-administered mice show learning and cognitive impairment. However oral galactose-administered mice show low anxiety-like behavior.

Conclusion: This study concludes that we can use oral administration of D-Galactose for the ageing model in research experiments but with some limitations.

Age-Related Effects of Napping on Cognitive Performance

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Introduction: Sleep is a critical biological process that is essential for cognitive function, memory consolidation, and overall health. Napping is a short period of sleep during the day that can provide a number of benefits, including improved alertness, mood, and performance. However, the effects of napping on brain activity may vary with age. In this study, we investigated the effects of napping cognitive performance in young and old adults.

Methods: Healthy young [YNG] (n = 17, aged 19 to 34 years, mean age 24.6 ± 4.17) and old [OLD](n = 13, aged 50 to 78 years, mean age 64.2 ± 8.85) subjects participated in this study. Participants performed two cognitive tasks, the Psychomotor Vigilance (PMV) Task and Visuo-Spatial Memory (VSM) task, before and after an afternoon nap. Both tasks measured response time and accuracy. Statistical analysis included descriptive statistics, t-tests, Pearson correlation, and RMANOVA, conducted using Jamovi (version 2.3.21), with a significance level set at p=0.05.

Results: In the PMV Task, response time in OLD is longer, and accuracy is lower compared to YNG, irrespective of nap status. In the VSM Task, response time in OLD is longer compared to YNG, and it increases further post-nap. Accuracy in OLD is lower compared to YNG and decreases further post-nap. For older participants, napping appears to exacerbate declines in cognitive performance, particularly in terms of increased response times and decreased accuracy in the VSM Task. The difference in accuracy PMV Task is negatively correlated with N2 duration in OLD. This might mean longer N2 duration is associated with lower accuracy in the PMV task for older participants.

Conclusion: Older participants show consistently poorer performance than younger participants across both tasks, with napping leading to further declines in performance for older individuals. The findings suggest age-related differences in the effects of napping on cognitive performance. The decreased cognitive performance in older individuals may be attributed to sleep inertia, which could indicate impaired homeostatic regulation of sleep.

Role of Hypoxia inducible factor on regeneration of *Hydra viridissima*

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Background: *Hydra viridissima* is a model organism known for its extraordinary capacity for regeneration. The importance of hypoxia-inducible factors (HIFs) in a number of biological processes, including regeneration, has been brought to light by recent studies. As hypoxia inducible factors control genes related to angiogenesis, metabolism, and cell survival, HIFs are essential for adaptation to hypoxic conditions. By altering cellular pathways that control oxygen levels and encourage tissue regeneration, HIFs appear to influence the regenerative response in *Hydra viridissima*. To elucidate the impact of HIF on *Hydra viridissima* regeneration, we exposed regenerating hydras to cobalt chloride, assessing changes in regeneration efficiency, tissue morphology, and gene expression associated with HIF activity.

Purpose: To assess the role of Hypoxia inducible factor on regeneration of *Hydra viridissima* by inducing cobalt chloride as HIF inhibitor.

Method: Specimens of *Hydra viridissima* were cultivated and put through controlled regeneration experiments. Cobalt chloride was utilized to block HIF activity in order to evaluate the function of Hypoxia Inducible Factor (HIF). The effects of different cobalt chloride concentrations on regenerating hydras were observed over a predetermined duration of time.

Result: As cobalt chloride was present, *Hydra viridissima's* ability to regenerate was significantly changed, as well as changes in tissue morphology were also ben observed as compared to untreated controls.

Conclusion: The presence of cobalt chloride, as an inhibitor of Hypoxia Inducible Factor (HIF), significantly impairs the regeneration of *Hydra viridissima*. These findings underscore the critical role of HIF in the regenerative processes of Hydra viridissima and highlight the potential for HIF inhibitors to modulate regenerative capabilities.

Role of *basl-1*, the *C. elegans* Orthologue of Human Dopa Decarboxylase (DDC), in Neuroprotection and Axonal Regeneration

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Background: Glial cells are essential for the structural and functional integrity of the nervous system, influencing synapse formation, neurite outgrowth, and axon guidance. *Caenorhabditis elegans* glial cells share many functional and molecular similarities with vertebrate glia. Our previous research identified *basl-1*, the *C. elegans* orthologue of human dopa decarboxylase (DDC), as a critical gene in the glial cell-mediated maintenance of dopaminergic neuronal circuits and neuroprotection. Transcriptomic analysis of the *ptr-10* knockout strain (RB1693) revealed significant downregulation of *basl-1*, with KEGG pathway analysis suggesting its involvement in axonal regeneration.

Purpose: This study investigates the role of *basl-1*, the *C. elegans* orthologue of human DDC, in neurodegeneration, neuroprotection, and axonal regeneration, particularly within the context of glial cell function.

Method: We employed wild-type N2 and transgenic *C. elegans* strains to conduct behavioral assays, lifespan studies, and 6-OHDA-based injury model experiments. These methods, combined with molecular techniques, were used to examine the role of *basl-1* in neurodegeneration, focusing on its impact on alpha-synuclein expression, neuronal function, and ageing.

Results: Knockdown of *basl-1* led to aggravated alpha-synuclein expression, reduced lifespan, and impaired behavior in *C. elegans*, highlighting its crucial role in dopaminergic neuron function and ageing. The gene's involvement in serotonin and catecholamine biosynthesis further underscores its importance in maintaining neuronal integrity under neurodegenerative conditions.

Conclusion: Our findings suggest that *basl-1*, the *C. elegans* orthologue of human DDC, plays a pivotal role in neuroprotection and axonal regeneration. This study enhances our understanding of glial cell-mediated neuroprotection and suggests that targeting *basl-1* could offer new avenues for therapeutic strategies in neurodegenerative diseases. Further research into the functional interactions of *basl-1* will be crucial for elucidating the molecular mechanisms underlying these processes.

Role of Blood Platelets in Parkinson's Disease: An Intricate Journey from Platelet Dysfunction to Platelet Therapeutics

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Background: Parkinson's disease (PD), the second most prevalent neurodegenerative disorder, is characterized by progressive neuromotor impairment. It is often associated with the risk of cardiovascular complications, such as ischemic stroke, myocardial infarction, congestive heart failure, and coronary heart disease. Platelets, essential components of circulating blood, are considered potential contributors to regulating these complications.

Purpose: Since blood platelets store and secrete several neuron-specific biomolecules, their role in PD is particularly interesting. Recent studies have shown reduced platelet aggregation in PD, but other key platelet functions, including the underlying molecular mechanisms, are yet to be fully understood. Additionally, given that platelets are a therapeutic source of different factors, their potential role in neuroprotection is also of considerable interest.

Methods: To investigate the role of platelets in PD, we examined the impact of rotenone (ROT), a compound that induces PD by damaging dopaminergic neurons, on platelets. We measured platelet adhesion, activation, secretion, and aggregation using a microplate reader, flow cytometer, confocal, and phase-contrast microscope. Additionally, we assessed ROS and Ca^{2+} levels and evaluated the neuroprotective effects of the platelet enrichment by microplate reader and confocal microscope.

Results: Our study revealed that ROT reduces thrombin-induced platelet functions, including adhesion, activation, secretion, and aggregation, in platelets. ROT, known for generating ROS, was found to stimulate ROS production in platelets by increasing Ca^{2+} mobilization from the IP_3R. Additionally, ROT triggered ROS production *via* PKC-associated NOX in platelets. Moreover, platelet enrichment was found to be neuroprotective in neuronal cell lines, where it promoted neurogenesis and reduced toxin-induced neuronal death.

Conclusion: Our findings indicate that platelet dysfunction exists in PD, as ROT inhibited agonistinduced platelet functions. The reduced platelet activity appears to be mediated by ROS through the IP_3R-Ca^{2+}-NOX signaling pathway in platelets. Additionally, platelets may play a role in promoting neuroprotection in PD.

Identification of potential drug like molecules obtained from *Elettaria cardamomum* and *Curcuma angustifolia* against Glioblastoma through Computer Aided Drug Discovery

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Background: *Elettaria cardamomum* and *Curcuma angustifolia* are two very common plants of the Zingiberaceae family, known to produce a host of compounds which have healing properties. All the identified compounds from these species were computationally examined for their efficacy as drugs against glioblastoma cells.

Purpose: Glioblastoma is marked by genetic instability, an angiogenic phenotype, apoptosis resistant, resemblance with stem cells, immunosuppressive microenvironment, a disordered bloodbrain barrier, epigenetic dysregulation, cellular heterogeneity and adaptive metabolic reprogramming. Its complex biology and adaptability present significant challenges for treatment, demanding scrupulous research for developing novel therapeutic approaches.

Methods: The structures of the compounds were analysed for the presence of the pharmacophore and only the compounds which have it and qualified the Lipinski's rule of five were considered for the study. Following that, the ADMET (absorption–distribution–metabolism–excretion– toxicity) properties and molecular descriptors (physicochemical properties, topological indices, molecular fields, fingerprints and maximum common substructures) of the compounds were thoroughly scrutinized and drug like molecules were identified. Conformational flexibility, scaffold hopping and similarity coefficient were also taken into consideration. A comprehensive literature review and data acquisition led to the identification of proteins and receptors which can be prospective targets of the drug-like ligands, followed by the evaluation of binding sites of a particular target. The chemical and spatial structure of the targets helped in understanding the possibility of an interaction. The binding pockets in a target were identified by developing Voronoi diagrams and the active site of the target was identified using volume, depth, area and amino acid composition matrices.

Results & Conclusion: Following the identification of druggable sites, flexible molecular docking will be performed between the ligands and the proteins, followed by elucidation and comprehension of downstream cell signalling. This might lead us to designing of possible drugs against glioblastoma.

Chitotriosidase-1 Polarizes HMC3, Human Microglial Cells to Pro-Inflammatory Form

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Background: Contribution of non-neuronal cells, specifically the microglia, have been implicated in several neurodegenerative disorders including, Amyotrophic lateral sclerosis (ALS), an adult-onset progressive neurodegenerative disorder. In ALS, microglia get activated and contribute to motor neuronal loss via neuroinflammatory responses. Studies from our laboratory which focus primarily on sporadic ALS representing 90% of the total cases have shown detrimental effects of CSF from ALS patients (ALS-CSF) on not only motor neurons but also induced marked gliosis. Proteomic analysis of ALS-CSF revealed up-regulation of Chitotriosidase (CHIT-1) by more than 20 folds. CHIT-1 expressed exclusively by microglia in the CNS caused marked microgliosis and astrogliosis when injected into rat neonates. However, its precise effect on microglia still remains obscure.

Purpose: To investigate the effect of recombinant CHIT-1 exclusively on microglia using HMC3, a human microglial cell line

Methods: Human microglial cell line, HMC3, was used for the study and the cells were exposed to four increasing concentrations of CHIT-1(7.5, 17.5, 25, 50 pg/µl) at different time points (6h, 12h, 24h and 48h). Changes induced by CHIT-1 on the morphology and viability of HMC3 cells were investigated by MTT and LDH assays. Additionally, effect of CHIT-1 on inducing oxidative stress in these cells were studied by DCF-DA assay. Further, its effect on expression of a proinflammatory cytokine viz. TNF-α and the neurotrophic factors namely, BDNF and GDNF were evaluated via immunoblotting and immunocytochemistry.
Results: Exposure of four increasing concentrations of CHIT-1 to HMC3 cells at different time points resulted in skewing of microglial morphology prominently towards activated phenotypes alongside increased proliferation. Also, CHIT-1 enhanced the expression of TNF-α, a pro-inflammatory cytokine and ROS levels. Meanwhile, the expression of BDNF and GDNF neurotrophic factors were significantly diminished.

Conclusion: This study therefore, provides an insight on the reliable use of HMC3 cells for deeper investigations on the contributions of CHIT-1 to the pathophysiology of sporadic ALS.

Hypoxic U87MG-derived exosomes promote immunosuppressive protumorigenic phenotype of microglia: *In-vitro* study

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Background: GBM, being a highly aggressive grade IV astrocytoma, is known to be highly hypoxic and immunosuppressive surrounded by non-neoplastic glial cells such as microglia, the resident immune cells of the CNS and comprising of 20-50% of total cells in the brain.

Purpose: Growing evidence suggests the significant role of GBM-derived exosomes in microglial activation via transfer of oncogenic biomolecules. Various long non-coding RNAs (lncRNAs) drive GBM tumorigenesis, however, hypoxia driven exosomal lncRNA involvement in microglial M2 polarization is not known.

Methods: Human GBM cells (U87MG) subjected to hypoxic stimulus by cobalt chloride, followed by culture supernatant collection, exosome isolation, quantitative, morphological characterisation by DLS, NTA, TEM and lncRNA profiling by qPCR. Labelled exosome uptake by microglia, microglial phagocytic and morphological changes were visualised by ICC. Pro/anti-inflammatory cytokine, phagocytic gene expression changes via qPCR.

Results: Hypoxia caused an increase in number and size of exosomes released ($9.8*10^7$ particles/ml) as compared to normoxic ($6.0*10^7$ particles/ml). *In-silico* database search and exosomal lncRNA profiling identified the enrichment of exosomal lncRNA H19. Coincubation and uptake of U87MG-derived exosomes caused significant decrease in % of phagocytosis, ADORA-3, IL6 gene expression, increased IL10, STAT-3 gene expression in hypoxic-U87MG exosomes treated microglia. Nuclear colocalization of P2RY12 further demonstrated the microglial morphological changes. U87MG-H19 involvement in microglial activation was demonstrated by U87MG-H19-depleted secretome treatment to CHME-3 that caused decrease in the STAT-3, CD163 suggesting exosomal-H19 mediated regulation of microglial activation.

Conclusion: This study emphasizes the role of hypoxic exosomal lncRNA H19 in microglial M2 polarization in GBM, further paving way for a potential therapeutic target in immunotherapies against GBM tumor.

In Sillico Discovery and Evaluation of *Momordica charantia* L Phytocomponents against DiNP Induced ACHE Associated With Neurodegenerative Diseases in Adult Zebra Fish (*Danio rerio*)

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Background: Neurodegenerative diseases, including Alzheimer's disease (AD), are marked by the progressive loss of cognitive function, often linked to the overactivity of acetylcholinesterase (AChE), which degrades acetylcholine, a neurotransmitter crucial for memory and learning. Natural inhibitors of AChE are sought to mitigate these effects, with *Momordica charantia* (bitter melon) being a promising candidate due to its diverse phytochemical composition.

Purpose: This study investigates the potential of *Momordica charantia* phytocompounds as AChE inhibitors in Zebrafish *(Danio rerio*) using in silico approaches, aiming to identify compounds that could serve as therapeutic agents for neurodegenerative diseases.

Methods: Key bioactive compounds from *M. charantia* were identified through phytochemical analysis and subjected to molecular docking to evaluate their binding affinity with AChE. Molecular dynamics (MD) simulations were performed to assess the stability of the enzyme-inhibitor complexes. The pharmacokinetic properties of the top compounds were predicted using ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling.

Results: Docking results revealed that among the 19 phytocompounds analysed, Ajmalacine, Alkaloid AQC2, Alkaloid SP-K, Steroid U, and quinine exhibited high binding affinities towards AChE. Ligand-protein binding interactions indicated that these selected compounds showed excellent interaction with AChE, with binding scores ranging from −11.0 kcal/mol to −9.1 kcal/mol.

Conclusion: The In silico results suggest that *M. charantia* Quinine, Alkaloid SP-K, Steroid U, and phytocompounds may effectively inhibit AChE activity, offering a natural alternative for managing neurodegenerative conditions. *Momordica charantia* phytocompounds exhibit promising AChE inhibitory activity, highlighting their potential as therapeutic agents against neurodegenerative diseases. Our findings indicate that quinine and Steroid U have potential as therapeutic agents in the development of anti-AChE drugs for neurodegenerative diseases such as Alzheimer's.

Neurotherapeutic Potential of Novel Synthetic Molecule for the Management of Parkinson's Disease

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Background: Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that primarily affects movement. It is marked by the deterioration of dopamine-producing neurons in the substantia nigra, a crucial brain region responsible for regulating motor function. The dopamine loss in PD causes tremors, stiffness, and bradykinesia. As the disease progresses, non-motor symptoms like cognitive decline, mood disorders, and autonomic dysfunction may also occur.

Purpose: L-DOPA is still the gold standard for PD treatment, but no medication currently stops or cures the disease's progression. Many promising neuroprotective compounds face significant hurdles, such as difficulty crossing the blood-brain barrier, toxicity, and instability. To overcome these challenges, we have designed a novel molecule, inspired by natural products and optimized to enhance its therapeutic effectiveness against PD.

Methods: We evaluated the neuroprotective effects of our novel molecule using a rotenone-induced PD model in both *in vitro* (SH-SY5Y cells) and *in vivo* (Wistar rats). To further validate its neuroprotective properties, we conducted behavioral tests, immunohistochemical assays, western blot analysis for dopaminergic neuron markers (TH, DAT), and investigated the underlying pathways.

Results: In our study, the novel molecule we developed effectively reduced ROT-induced ROS generation, prevented mitochondrial dysfunction, and mitigated neuronal apoptosis through the NF-κB and MAPK pathways. Additionally, it demonstrated a significant recovery from ROT-induced behavioral impairments and restored the protein expression of TH and DAT markers.

Conclusion: In conclusion, our investigation demonstrates that our novel molecule offers substantial neuroprotection against behavioral impairments, even surpassing even the effectiveness of L-DOPA. Therefore, this synthesized molecule holds great promise as a potential therapeutic target in the near future.

A mouse model of Parkinson's disease to evaluate sex differences in the progression

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Background: Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic (DA) neurons of the substantia nigra (SN). The pathological hallmark of PD is aggregation of α-synuclein protein in Lewy bodies and their progressive spreading in the brain. 60% of neuronal death occurs before the motor symptoms appear.

Purpose: Successful recapitulation of progressive PD features in animal models is vital to understand disease progression mechanisms. Males have a higher incidence of PD than females. Hence, developing a mouse model replicating these progressive pathological and behavioural changes in both sexes is essential.

Methods: To generate a PD model, we injected AAV-SNCA and α-synuclein pre-formed fibrils into medio-lateral SN. The behavioural outcomes were evaluated using wirehang, cylinder, and openfield tests. We studied the extent of neurodegeneration, α-synuclein aggregation and neuroinflammation at 4 (early), 12 (intermediate) and 24W (late) post-surgery to study stages of disease pathology.

Results: We observed mild motor deficits in mice consistent with other synuclein-based models. Males showed a stronger tendency of motor deficits while females displayed more anxious behaviors. There was a progressive reduction in DA neurons in SN and striatal fibre density, although no sex difference in neurodegeneration was observed. Further, we observed aggregated α-synuclein across time-points at SN that spread trans-synaptically in striatum and cortex. However, the accumulation of aggregates was absent 24W in the striatum and cortex indicating their resistance to aggregation pathology. We also observed a significant increase in activated microglial and astrocytes across at time-point. This activation is strongest at early time-points and attenuates over time.

Conclusion: The model replicated PD pathology with progressive neurodegeneration and striatal fibre loss, accumulation of p-syn. This correlated with increased neuroinflammation in SN. We also observed a differential presentation of behavioural outcomes in male and female mice thus faithfully recapitulating the key features of PD.

MiRNA-135 modulates human neuronal development: Employing 2D human neural stem cells

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Background: The human brain development begins with differentiation of neural stem cells into daughter stem cells and neurons. The genetic, epigenetic and biochemical events make the brain development a highly stochastic and complex process.

Purpose: Though the genetic regulation of human neuronal development has been elaborated yet the post-transcriptional mechanisms of neuronal development still need to unwind. MiRNAs represent one of the most crucial post-transcriptional gene regulators that modulate neuronal development. MiR-135 is a brain specific miRNA and animal studies suggest its involvement in neurotransmission and neurogenesis. How miR-135 regulates human neural development remains elusive. Our study investigates the mechanisms of miR-135 mediated neuronal development using human neural stem cell (hNSC) model.

Method: We derived induced pluripotent stem cells (iPSCs) from human cord blood mononuclear cells using a cocktail of pluripotency transcription factors. 2D differentiation of iPSCs led to the generation of NSCs. We overexpressed miR-135 in hNSCs and assessed hNSCs' proliferation and differentiation.

Results: We observed that miR-135 reduced hNSCs proliferation as it diminishes the expression of NSC marker, Nestin and accelerated the neuronal differentiation by increasing the expression of neuronal marker such as Tuj1 and Map2. MiR-135 also reduced the expression of pluripotency transcription factors such as OCT4 and SOX2 in hNSCs. We further hypothesized that miR-135 might be modulating mitochondrial dynamics to enhance neuronal differentiation. Over expressionof miR-135 enhanced mitochondrial biogenesis by upregulating TFAM. In addition, we also determined the expression of genes involved inmitochondrial fusion and observed an increasing trend of MFN2 and OPA1. Target analysis predicted WNT3 as a target of miR-135. Thus, our study suggests that miR-135 accelerates neuronal differentiation through mitochondrial biogenesis.

Conclusion: Our study provides novel molecular insights into how miR-135 modulates mitochondrial dynamics to boost neuronal development. This may potentiate the design of treatments for neurodegenerative diseases.

Investigating the impact of Pb toxicity on SUMO-associated synaptic proteins in early life Pb-exposure

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Background: Lead (Pb) is a common environmental heavy metal, primarily introduced through human activities. The effects of Pb poisoning on both animals and humans have been extensively studied, particularly its impact on cognition and memory. However, the specific molecular mechanisms by which Pb affects synaptic function remain unclear.

Purpose: This study aims to investigate the relationship between changes in neuronal morphology and the SUMOylation of various synaptic proteins in relation to memory impairment caused by early-life lead exposure in rats.

Methodology: To elucidate these changes, we have employed proteomic, and biochemical approaches on rat pups exposed to lead acetate from postnatal day 0 until weaning.

Results and Conclusion: In the Pb-exposed rats, there was a decrease in the hippocampal neuronal count. Our proteomic analysis of the synaptosomal fraction revealed differential alteration of 289 proteins, out of which 45 are SUMO (Small Ubiquitin-like Modifier) targets. Western blot analysis revealed dysregulation in SUMO-associated proteins for SUMO1, SUMO2, and SUMO4 isoforms. Sequential gel elution and proteomics of specific dysregulated SUMO-associated proteins revealed 11 key proteins (GRIA2, ATP1β3, MAP2, UGP2, EIF3I, PSD95, SUCLG1, CAMK2D, GPM6A, SYN1, PAPPA2). The expression of these proteins was further validated using Western blot. Out of these 11 proteins, we observed a significant downregulation in sodium/potassium-transporting ATPase subunit beta-3 (Atp1β3) ($p<0.005$). We further plan to investigate the role Atp1β3 could play in mitigating the effects of Pb in synaptic neurotransmission.

Unraveling the Variable Penetrance of Inflammatory Gene Signatures into Adjacent Brain Parenchyma in Meningeal Inflammation

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Background: Post-mortem brain tissue from patients with multiple sclerosis (MS) and animal models suggests that the meninges play a crucial part in the inflammatory and neurodegenerative processes that drive the progression of MS pathology. Meningeal inflammation has been identified as a potential risk factor for cortical grey matter damage.

Purpose: Our current understanding of the specific mechanisms that connect meningeal inflammation and grey matter damage is still limited. Therefore, it is critical to comprehend the specific cellular and molecular mechanisms, timing, and anatomical characteristics involved in confining inflammation within the meningeal spaces in MS cases.

Methods: In a mouse model of autoimmune meningeal inflammation, we utilized MRI-guided spatial transcriptomics and RNAscope to analyze the transcriptional signature in areas of meningeal inflammation and the underlying brain parenchyma.

Results: We noticed a widespread rise in the activation of inflammatory signaling pathways in areas with meningeal inflammation, but only a subset of these pathways was active in the neighboring brain parenchyma. Sub-clustering of regions adjacent to meningeal inflammation exposed the subset of immune programs induced in the brain parenchyma, particularly complement signaling and antigen processing/presentation. Analysis using trajectory gene and gene set modeling confirmed varying penetration of immune signatures originating from meningeal inflammation into the adjacent brain parenchyma.

Conclusion: Our study provides valuable data on meningeal inflammation and identifies candidate pathways for grey matter pathology in MS. Additionally, it presents the first detailed spatial transcriptomic characterization in this model.

Understanding the role of Biorientation Defective -1 (BOD-1) in the context of neurodevelopment

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Background: Biorientation Defective -1 (BOD-1) is a novel kinetochore protein required for the biorientation of chromosomes at the metaphase plate. BOD-1 has been implicated in Neurodevelopmental Disorders, with human patients having mutations in BOD-1 showing Intellectual Disability, learning and sensory defects, and schizophrenia. *Drosophila* Bod1 knockdown modes have shown learning defects and *BOD1* knockout in mice causes Ataxia.

Purpose: This study aims to identify the role of BOD-1 function in the neurodevelopment of zebrafish, focusing on its potential regulation of neuronal cytoskeleton elements such as actin and microtubules.

Methods: We have used In Situ Hybridization to study the expression pattern of *zBod1* in zebrafish embryos. Using CRISPR Cas9, we have generated a whole-body knockout model of *zBod1* in zebrafish. We have subjected this mutant model to behavioural assays such as Spontaneous Tail Coiling (STC), Touch Evoked Escape Response (TEER), Acoustic Startle Response (ASR), Optomotor Response (OMR) and Dark Flash Habituation to assess neuronal circuit function. We also use Anti-Acetylated tubulin staining to assess the various axonal tracts.

Results: Through In Situ hybridization, we see that *zBod1* is expressed in the whole body of the developing zebrafish embryo and is especially enriched in the head at 24 hours and 48 hours post fertilization. There is also a significant difference in the Spontaneous Tail Coiling activity of *zBod1* knockouts.

Conclusion: We conclude that *zBod1* is enriched in the nervous system of the developing zebrafish embryo. We have found motor defects in the zBod1 knockout model through the various behavioural screenings, which we shall further study using the Tg(mnx1;gfp) line. Further, we plan to identify interactors of BOD1 through a BioID screen.

Assessing the Impact of Every-Other-Day Fasting on Brain Metabolism in Mouse Model of Aging

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Background: Ageing is a key risk factor for neurodegenerative disorders like Alzheimer's and Parkinson's disease. A reduction in cognition along with impaired synaptic activity has been reported in aged mice. Calorie restriction (CR) has been shown to extend lifespan and reduce disease risk by enhancing neurogenesis, and mitochondrial bioenergetics, while suppressing neuroinflammation. However, the impact of CR on age-related decline in neuronal function *in vivo* is poorly understood.

Purpose: The current study aims to investigate the impacts of every-other-day fasting (EODF) on neuronal functions during ageing.

Methods: All the experimental procedures with mice were approved by IAEC, CSIR-CCMB. C57Bl6 mice were divided into three groups: 6-month *ad libitum* (6-ALY), 18-month *ad libitum* (18-ALO), and 18-month EODF (18-EODF). The last group of mice were subjected to an EODF paradigm from 6 to 18 months. At the end of the EODF paradigm, mice were subjected to various behavioral tests. The neurometabolic activity was evaluated by intravenous infusion of [1,6-$^{13}C_2$]glucose for 7 minutes. The concentrations of ^{13}C labelled metabolites were measured using ^{1}H-[^{13}C]-NMR spectroscopy in brain tissue extracts.

Results: Mice maintained on *ad libitum* diet exhibited significant impairment in grip strength (18-ALO 1.14±0.22N, 6-ALY 1.7±0.17N, $p<0.0001$), latency to fall in the rota rod test (138.9±53.9s *vs* 223.9±32.9s, $p<0.0001$), and number of entry in the Y-maze (14.7±5.0 *vs* 24.0±5.9, $p<0.0001$) when compared with young mice. Restriction of feed improved muscle strength ($p<0.0001$), motor coordination ($p<0.0001$), and locomotion ($p=0.0001$) in mice when compared with those on *ad libitum* diet. There was a significant reduction in the level of GABA (18-ALO 2.3±0.1µmol/g; 6-ALY 2.3±0.1µmol/g, $p=0.04$) and increased glutamine (5.1±0.3 vs 4.6±0.1µmol/g, $p=0.004$) in the cerebral cortex of aged mice, while EODF subjected mice showed improved GABA levels.

Conclusion: Restriction of feed for a year improved muscle strength and motor coordination along with GABA level in mice.

Role of Neuropeptides in the Regulation of Locomotion in *Caenorhabditis elegans*

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Background: Neuropeptides are a class of neuromodulators that are capable of acting at a larger spatiotemporal range than neurotransmitters and can modulate behaviour by binding to G proteincoupled receptors (GPCRs) and causing gene expression changes. Some neuropeptides have the capacity to interact with multiple receptors, and vice-versa.

Purpose: Due to the complexity of their actions, it is difficult to study their functions in organisms with intricate nervous systems. *C. elegans*, with a nervous system of just 302 neurons, exhibits well characterised behaviours and is amenable for genetic manipulation, offering an excellent model system to study the functions of neuropeptides. There are three major families of neuropeptides in *C. elegans*: FMRF-like neuropeptides (FLPs), Neuropeptide-like neuropeptides (NLPs) and Insulin-like neuropeptides (ILPs).

Methods: We performed a preliminary screen of neuropeptide mutant hermaphrodite *C. elegans* for defects in locomotion.

Results: We observed that mutants of an FMRF-amide like neuropeptide, flp-12, exhibit an increase in amplitude of body bends. According to the *C. elegans* Neuronal Gene Expression Map & Network (CeNGEN) database, FLP-12 is highly expressed in SMB neurons. SMB neurons have been previously shown to regulate the amplitude of body bends. A recent study that mapped peptide-GPCR interactions has shown that FLP-12 may bind to FRPR-8, DMSR-1, DMSR-7, DMSR-8 and EGL-6. Consistent with this study, we also found that frpr-8 mutants show an increased amplitude of body bends similar to flp-12 mutants.

Conclusions: These observations lead to the formulation of the hypothesis that FLP-12 is released by SMB neurons and acts through FRPR-8 to control body bend amplitude. To test this hypothesis, we will elucidate the neural circuit through which FLP-12 functions to control body bend amplitude. The results obtained may provide interesting mechanistic insights about how neuropeptides control behaviour.

Effect of bromelain on transgenerational *C. elegans* on high glucose diet

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Background: The increasing prevalence of high-glucose diets has raised concerns about their long-term and transgenerational effects on health, particularly regarding neuropathy linked to hyperglycaemia. *Caenorhabditis elegans* is a widely used model organism for understanding metabolic and genetic adaptations to different diets. This is a free-living nematode inhabiting temperate soil and is chosen due to it is fully annotated genome, short generation time and wellestablished peripheral nervous system. Hyperglycaemia means high blood glucose levels, normally above 130 mg/dL when the patient has not eaten for 8 hours. It is a well-established fact that hyperglycaemia results in oxidative stress and inflammation, which results in neuropathy. Neuropathy, which is a damage to the peripheral nerves, has symptoms that depend on the type of nerve affected.

Purpose: This work aims to unravel the transgenerational consequences of a high glucose diet in *C. elegans* and evaluates the protective role of bromelain, a proteolytic enzyme derived from the pineapple stem, as phytic agent.

Methods: High glucose and bromelain infused diets were given to the F1 and F2 generations of *C. elegans*. Assays performed were glucose toxicity, bromelain toxicity, behavioural and antioxidant estimation. These assays helped to make an attempt to decipher the effects of high glucose diet and bromelain's ameliorative counteracting effect.

Results: Results show cascading effect of high glucose diet on *C. elegans* and subsequent F2 generations. However, bromelain used in combination with the diet, partially reversed some detrimental effects, including indices of neuropathy, raising the possibility of the molecule as an agent for protection against trans generational diet-induced effects.

Conclusion: High glucose diets in *C. elegans* has transgenerational impairments like oxidative stress and reduced lifespan. Bromelain could be a potential ameliorative agent against the damage caused due to high glucose diet.

Decoding the molecular mechanism of endolysosomal trafficking of APP in Alzheimer's Disease

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Background: Alzheimer's disease (AD) is a most general form of dementia, characterized by progressive accumulation of amyloid beta (Aβ) plaques and neurofibrillary Tau protein tangles in the brain owing to defective amyloid precursor protein (APP) metabolism. The membrane expression of APP is regulated by controlled internalization mediated by endocytic machinery. Key genetic risk factors for AD have been identified as regulators of clathrin-mediated endocytosis (CME) such as AP-2, PICALM, BIN1, and APOE4. However, their specific role in APP internalization and amyloid beta (Aβ) production are poorly understood.

Purpose: This study aims to understand the molecular mechanism of endolysosomal trafficking of APP, with a focus on the roles of endocytic adaptors such as AP-2 and PICALM. Particularly, we investigate the role of AP-2 in the clustering of APP into unitary vesicles by recognizing specific $Y_{682}ENPTY_{687}$ motifs on the C-terminus of APP.

Methods: In our study, we will elucidate how PICALM and AP-2 influence the sorting and size of APP unitary vesicles, and how these vesicles direct to recycling endosomes, lysosomes, and autophagosomes by combining nanoscale imaging techniques, genetic modifications, and biochemical interaction studies. Additionally, we will explore how post-translational modifications of AP-2 regulate APP trafficking in both AD transgenic models and under normal conditions.

Results: Our studies pointed out that partial or complete deletion of the $Y_{682}ENPTY_{687}$ motif affects the APP's membrane dynamics and segregation. Additionally, PICALM, a key endocytic risk factor for AD, has been found to interact and colocalize with APP in subsynaptic compartments, highlighting the significance of APP endolysosomal trafficking in AD pathogenesis.

Conclusion: We expect this study will help to reveal the nanoscale morpho-functional features of CME regulators in APP processing within functional synapses and to contribute to the development of potential therapeutic agents for AD by targeting intracellular trafficking of APP.

Development and Validation of a Low-Cost, Arduino-Based Operant Conditioning Chamber

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Background: Operant conditioning involves behavioural learning, where behavioural choices are modified by their consequences. This means that choices followed by positive outcomes tend to be repeated, while those followed by negative outcomes are less likely to be repeated by animals. Operant conditioning chambers have been instrumental in advancing our understanding of functions of brain circuits involved in cognition, perception, addiction, and emotion, among others.

Purpose: Commercially available operant conditioning chambers are often imported and expensive, limiting their accessibility to research and educational institutions. To overcome this hurdle, we designed and constructed a low-cost, Arduino-based operant conditioning chamber.

Method: Using an Arduino IDE interface, we designed a model of an Arduino-based operant chamber. The chamber was constructed at an in-house workshop using infrared sensors, LED lights, sound speakers, a stepper motor, and Arduino MEGA and UNO microcontrollers, followed by optimization, dry runs, and wet runs using Sprague-Dawley rats. The training sessions were hierarchically structured based on task complexity. Progression to subsequent training levels was contingent upon achieving a predetermined performance criterion of correct responses over three consecutive days.

Results: The effectiveness of the chamber was validated through multiple experimental trials. The total construction cost of the chamber was approximately 15,000 INR. In dry runs, there was 98% accuracy. We found successful trial completion in wet runs with an accuracy rate of 75-85%. Animals that consistently failed to achieve the criterion number of correct consecutive choices (70% correct choices) were excluded from further analysis.

Conclusion: The Arduino platform offers a practical and cost-effective solution for conducting behavioural experiments. We anticipate that the design and construction details of the operant chamber shared here will enable accessibility to researchers and educators.

Investigating the Amyloid Precursor Protein as a Risk Factor for the Development of Alzheimer's Disease

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Background: Alzheimer's disease (AD) is the leading cause of neurodegeneration worldwide. Predominantly, resources are directed to efforts targeting the amyloid-beta peptide in the hope of treating AD. Using super-resolution microscopy, we have shown that the APP is distributed heterogeneously in the functional zones of the synapse. These domains, which are on the order of a few tens of nanometres – nanodomains - are dynamically modulated over time. Our observation has also highlighted the discrete association of the APP nanodomains with that of secretases. The heterogeneous distribution of the amyloidogenic proteolytic machinery and the stochasticity in product formation provide new evidence of factors possibly regulating the pathogenesis of AD.

Purpose: The lack of a cure and the high failure rate of anti-Alzheimer drugs in various stages of clinical trials points to the voids in our understanding of the onset of AD and the need to explore the key variables possibly involved in the origin of the disease. We are primarily interested in understanding the role of the Amyloid-beta precursor protein (APP) in causing AD. Currently, there is a lack of detailed biochemical and biophysical studies that characterize this nano-organization. The rules governing this nano-organization are unclear. It remains to be seen whether it's a spontaneous nucleation or limited structures determining the packing density. We have studied the phase-separation kinetics of APP using an in-vitro and a data-driven approach. I'll be presenting the results of our understanding of the thermodynamics of the organization of APP.

Methods: Immunocytochemistry, Super-resolution Microscopy, Image Analysis, Subcloning, Protein Purification

Results: Data driven analysis of super-resolution images of APP suggests a first-order mechanism for phase separation of APP molecules.

Conclusion: Spontaneous nucleation plays a role in the heterogenous organization of APP on the neuronal membrane.

Deciphering the Interactions of Caspr1 and Nav1.6 in Retinal Neurons: Insights from In-Silico to In-Vitro Investigations and Ex-Vivo Analysis of Diabetic Retina

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Background: Diabetic retinopathy (DR), a leading cause of vision loss, is characterized by early neurodegenerative changes that precede vascular abnormalities. The axon initial segment (AIS), a key site for action potential initiation in retinal neurons, is highly enriched in proteins such as Caspr1 and Nav1.6, both of which play crucial roles in maintaining neuronal function. Disruptions in the molecular organization of the AIS under hyperglycemic conditions could contribute to early neuronal dysfunction in DR. This study investigates the interaction between Caspr1 and Nav1.6 in retinal neurons, with a focus on understanding the effects of high glucose (HG)-induced stress on these proteins using both in-silico and experimental approaches.

Purpose: The primary goal of this study is to elucidate the molecular interactions between Caspr1 and Nav1.6 in retinal neurons and to determine how these interactions are affected under diabetic conditions. We aim to identify potential mechanisms through which hyperglycemia-induced stress may disrupt AIS integrity, potentially contributing to neurodegeneration in DR.

Methods: In-silico docking studies were performed using HADDOCK to predict Caspr1-Nav1.6 interactions. 661W retinal cells were treated with siRNA targeting Caspr1, followed by coimmunoprecipitation (Co-IP), immunofluorescence, and Western blotting to assess protein protein interactions and expression levels. Retinal tissue sections from diabetic and control mice were subjected to immunostaining for Caspr1 and Nav1.6 to examine changes in their colocalization. Quantitative PCR (qPCR) was used to assess mRNA expression levels of Caspr1 and Nav1.6, while protein expression was analyzed via Western blotting.

Results: Docking studies identified significant interactions between Caspr1 and Nav1.6 in retinal neurons. Co-immunoprecipitation and Western blotting confirmed this interaction, while immunofluorescence revealed their colocalization in the AIS. Under hyperglycemic conditions, Caspr1 and Nav1.6 mRNA levels increased, but their protein levels were downregulated, suggesting post-transcriptional modifications or degradation. In diabetic retinal tissues, colocalization of these proteins was disrupted, indicating structural changes in the AIS.

Conclusion: The interaction between Caspr1 and Nav1.6 is crucial for maintaining neuronal function in retinal ganglion cells, with implications for understanding the pathophysiology of diabetic retinopathy. The observed discrepancies between mRNA and protein levels under hyperglycemic conditions highlight the need for further investigation into regulatory mechanisms affecting these proteins. Future studies will focus on the electrophysiological properties of Caspr1 knockout models and validation of these findings in diabetic retinopathy animal models to enhance our understanding of early neurodegenerative processes in diabetes.

Inhibition of GSK-3β by Kenpaullone Ameliorates Controlled Cortical Impact-Generated Neurological Deficits in Mice

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Background: There is no promising treatment for the management of traumatic brain injury (TBI) generated complications. Apparently, exaggerated oxidative and inflammatory elements are attributed to post-TBI neuronal loss and disruption of neural circuits. Activation of glycogen synthase kinase-3β (GSK-3β) signaling plays a key role in neuronal death in several neurodegenerative diseases.

Purpose: To study the effects of kenpaullone, a selective GSK-3β inhibitor, in a controlled-cortical impact (CCI) mouse model of TBI.

Methods: Male C57BL/6 mice were subjected to CCI surgery using the Impact One instrument. The kenpaullone (1 mg/mL, peroral) treatment was given daily for 2 weeks post-CCI. Rotarod and beam walker tests were employed to assess motor functions, and anxiety-like phenotype was assessed with the elevated zero maze (EZM). At the end of treatment, we collected brain and plasma samples for western blotting and RT-PCR assays.

Results: Early immediate treatment with kenpaullone prevented the CCI-generated neurological aberrations in rotarod and beam walker tests. The anxiety-like traits remained unaffected at 14 dpi, as open-arm activity in EZM test remained similar between CCI and kenpaullone-recipient groups. In the immunoblotting assay, we observed increased levels of phosphorylated β-catenin and phosphorylated GSK-3β in the ipsilateral brain region of CCI mice, which were restored to normal following kenpaullone treatment. However, total β-catenin and GSK-3β levels remained unchanged across the groups. Administration of kenpaullone after CCI surgery also decreased the elevated levels of malondialdehyde, nitrite, Superoxide dismutase, and catalase in the plasma samples at 3 dpi. While kenpaullone treatment positively modulated the altered levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-18, and IL-1β), anti-inflammatory cytokines (IL-10 and IL-22), IBA-1, doublecortin and BDNF in CCI mice, these effects were not significant.

Conclusion: We suggest that the GSK-3β inhibition by kenpaullone improves CCI-generated neurological deficits and suppresses neuroinflammatory processes in the brain.

Unveiling Marine Bacteria as a Source of Novel Neuroprotective Agents for Parkinson's Disease

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Background: While current therapies for Parkinson's disease (PD) offer symptomatic relief, they often come with limitations such as side effects, diminishing efficacy over time, and inability to halt disease progression. Therefore, it's imperative to seek new therapies to address these shortcomings and provide more effective, sustainable treatments. The marine environment harbors a wealth of unique chemical compounds with potential biological functions.

Purpose: In the present study, we investigated whether exposure to marine bacterium, CDMP6 could ameliorate PD phenotypes.

Method: Three distinct strains of *Caenorhabditis elegans* were used in this study: BY250 expressing GFP in dopaminergic neurons; UA44, PD model expressing human α-synuclein and GFP in the dopaminergic neurons specifically; and NL5901 expressing human α-synuclein in body wall muscle cells. Worms were fed on either *E. coli OP50* or CDMP-6 from L1 to day 3 of adulthood, followed by fluorescence imaging, RT-PCR, and behavioural assays.

Result: The exposure to CDMP-6 displayed neuroprotective effects in the PD models of *C. elegans.* It also resulted in reduced aggregation and expression of α-synuclein, improved motility, pharyngeal pumping & olfactory sensitivity. The transcriptomics data additionally revealed genes exhibiting differential expression after feeding CDMP-6, suggesting potential molecular mechanisms underlying its neuroprotective effects.

Conclusion: Our results highlight the potential of investigating marine-derived compounds as promising candidates for Parkinson's disease therapy, paving the way for the development of improved and enduring treatment options for patients facing this challenging condition.

Structural Insights into Fyn-SH3 and Tau Interaction: Implications of AD-Specific Phosphorylation on NMDAR Dysregulation

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Background and Purpose: Alzheimer's disease (AD) is marked by amyloid-β plaques and Tau neurofibrillary tangles. Fyn kinase, a multidomain protein, facilitates crosstalk between amyloid-β and Tau by interacting with Tau through its SH3 domain and Pro-X-X-Pro (PXXP) motifs. The 5th and 6th PXXP motifs in Tau are critical for Fyn binding. Evidence suggests that the Fyn-Tau interaction plays a significant role in AD pathogenesis, making it a promising therapeutic target. However, there is a gap in understanding the structural details of this interaction. In AD, Tau becomes hyperphosphorylated, particularly at sites around the PXXP motifs. The impact of phosphorylation in the PRD region on Tau's interaction with Fyn-SH3 remains unclear. Additionally, Tau recruits Fyn to the postsynaptic density (PSD), where Fyn phosphorylates the GluN2B subunit of N-methyl D-aspartate receptors (NMDARs), affecting their function. Since Tau's interaction with Fyn is mediated through the 5^{th}-6^{th} PXXP motifs, examining the effects of these motifs with and without AD-specific phosphorylation could enhance our understanding of NMDAR regulation. This study aims to elucidate the pathophysiology of the Fyn-Tau interaction and its impact on NMDAR regulation through structural and electrophysiological studies.

Methods: X-ray crystallography elucidated the Fyn-Tau complex structure. Biophysical techniques studied Fyn-Tau interaction with/without AD-specific phosphorylation. Electrophysiology assessed the impact of Fyn-Tau interaction on NMDAR function in single neurons.

Results:

1. We determined the structure of the Fyn-Tau complex at 1.01 Å resolution using X-ray crystallography.
2. Biophysical studies revealed that Tau with AD-specific S214-phosphorylation abolishes Fyn interaction.
3. Electrophysiology showed that S214-phosphorylation delays NMDAR desensitization, leading to excitotoxicity.

Conclusions: This study provides the first crystal structure of the Fyn-Tau complex, revealing its implications for AD-pathology and NMDAR function. Our findings suggest that AD-specific S214-phosphorylation alters Fyn recruitment to NMDARs, contributing to abnormal activity and offering insights for potential therapeutic strategies.

Investigating Mitochondrial Dysfunction in Early-Life Pb-Exposed Rats

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Background*:* Lead (Pb) is a cumulative hazardous heavy metal that enters the body through drinking water, ingestion, and inhalation. Pb toxicity affects almost all the systems in the body, of which the nervous system is the most affected. Pb exposure during childhood affects brain development and leads to neurodevelopmental disorders. It is seen that Pb exposure affects the mitochondria, leading to changes in mitochondrial mass, membrane potential, mitochondrial DNA, electron transport chain, and oxidative stress.

Purpose*:* This study aims to decipher the alterations in the molecular mechanisms of mitochondrial dysfunction in the hippocampus of early-life Pb-exposed rats.

Methods: Rat pups were exposed to 100 ppm lead acetate from postnatal day 0 until weaning through lactation. Oxidative phosphorylation (OXPHOS) was conducted to assess the function of the electron transport chain (ETC) and the mass spectrometric analysis (LC-MS/MS) for identifying dysregulated mitochondrial proteins in the isolated adult rat hippocampal fractions. Additionally, Western blotting and qPCR were utilized to validate the proteomics data.

Results and Conclusion*:* The isolated hippocampal lysate from Pb-exposed rats demonstrated a significant reduction in mitochondrial Complex I activity ($p=0.0022$), indicating the harmful effects of Pb toxicity on the electron transport chain and ATP production. The mass spectrometric analysis identified 59 highly dysregulated mitochondrial proteins, further characterized by their localization and function. Western blotting of several dysregulated proteins, including Hspd1, Idh3a, and Dlst, confirmed our mass spectrometric findings. These results strongly suggest that early-life Pb exposure in rats disrupts mitochondrial function and protein dynamics, paving the way for further exploration of cellular pathways for potential therapeutic interventions.

High-affinity binding of celastrol to monomeric α-Synuclein mitigates *in vitro* aggregation

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Background: Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by the accumulation of Lewy bodies, which predominantly consist of aggregates of α-synuclein (αSyn). Increased accumulation of Lewy bodies causes neurotoxicity in the substantia nigra pars compacta resulting in neuronal death.

Purpose: Strategies aimed at inhibiting the aggregation of αSyn may confer neuroprotective effects. Research has identified specific residues within αSyn that play critical roles in its aggregation. Notably, residues 36 to 42 function as the nucleation 'master controller,' while residues 1 to 12 serve as a 'secondary nucleation site'. These sites drive monomeric αSyn to aggregation. Therefore, small molecules targeting these motifs are promising for disease-modifying therapy.

Methods: In our study, we employed computational methods to screen phytochemicals for their potential binding affinity to αSyn. We investigated their drug-likeness and assessed their pharmacokinetic properties. We then docked the ADMET-qualified candidates with the Non-Amyloid Component region of αSyn: the region implicated in amyloid fibril formation. To further investigate the dynamics of protein conformation upon ligand binding, we conducted molecular dynamics simulations, identifying the key residues contributing to binding interactions. The binding affinity for top three compounds demonstrating stable interactions with αSyn were further evaluated *in vitro* using Microscale thermophoresis (MST) assay, Thioflavin-T (Th-T) aggregation assay and Nuclear Magnetic Resonance (NMR) techniques.

Results and conclusions: Amongst the top identified compounds, celastrol derived from the Chinese herb *Tripterygium wilfordii* demonstrated a particularly high binding affinity. NMR studies indicated that celastrol interacts extensively with the critical motifs driving αSyn oligomerization and fibrillization. Additionally, Th-T assays revealed that celastrol effectively reduced the rate of αSyn aggregation, exhibiting a similar efficacy to levodopa. Therefore, our findings suggest that celastrol represents a promising lead compound for drug development aimed at attenuating αSyn aggregation in the context of PD.

Depression-associated induction of gasdermin D and gasdermin E exacerbates neurovascular and cognitive dysfunction in Alzheimer's disease

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Background: Depression is one of the major risk factors and one of the most prevalent psychiatric symptoms of Alzheimer's disease (AD) with an unclear mechanism. Patients with neuropathologically confirmed AD with comorbid depression exhibit much higher levels of cognitive dysfunction.

Purpose: We hypothesized that Aβ produced in AD and inflammasomes generated in depression together triggers gasdermin D and E, leading to pyroptosis and exacerbation of AD pathology.

Methods: We conducted studies using microvessels isolated from postmortem human brains. To recapitulate the Aβ produced in AD and depression-induced IL1β, we developed an *in vitro* blood-brain barrier model utilizing human brain vascular endothelial cells and pericytes. To mimic Alzheimer's dementia with comorbid depression, we developed a rat model by injecting Aβ into the brain and inducing chronic unpredictable stress-induced depression.

Results: The analysis of microvessels isolated from the human postmortem brains exhibited induction of NLRP3 inflammasomes, gasdermin D and gasdermin E in patients with AD. Using *in vitro* model of blood-brain barrier, the concurrent exposure with Aβ and IL1β resulted in transendothelial barrier leakage, which was attenuated by treatment with gasdermin inhibitors. The analysis of anterior cingulate cortex and hippocampus from rats with comorbid depression and AD, showed enhanced activation of gasdermin D and E, as well as pyroptosis, synaptic dysfunction, neuroinflammation and blood-brain leakage. Inhibition of NLRP3, gasdermin D and E attenuated the neurovascular pathology and improved the cognitive function in rats with comorbid depression and AD.

Conclusion: Our *in vitro* and *in vivo* studies strongly suggest that gasdermin D and gasdermin E mediate blood-brain barrier and synaptic dysfunction, thus leading to neurovascular and cognitive impairment in AD comorbidity with depression. Our studies provide compelling evidence that Aβ produced in AD and inflammasomes generated in depression exacerbate pyroptosis and neuroinflammation leading to aggravation of AD pathology.

Age-related changes in fractal dimension and their dependence on periodic and aperiodic activity

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Background: The human brain, a complex network of interconnected neurons, generates electrical signals that reflects the intricacies of cognition and motor function. These signals exhibit dynamic patterns characterized by nonlinearity, making them challenging to decipher. The non-linear dynamics in brain has been explored using various tools such as fractal dimension (FD). However, change of FD with age has been disputed in literature, potentially due to differences in computational techniques and frequency ranges employed across studies. Moreover, alpha and gamma band oscillatory power has been shown to decreases with healthy aging, alongside a flattening of the power spectral density (PSD) slope. While these changes could potentially influence FD, their exact relationship with FD remains unclear.

Purpose: To address these gaps, we investigated the frequency-dependent changes in Higuchi's Fractal Dimension (HFD) during aging and its correlation with PSD oscillations and slope.

Methods: We analysed 64-channel electroencephalogram (EEG) data from 217 individuals aged 50-88 under baseline condition (eyes open) and during the presentation of gammainducing visual stimulus.

Results: Our results revealed an age-related increase in HFD up to 150 Hz, followed by a decrease at higher frequencies. Interestingly, this pattern is opposite to the age-related changes of the PSD slope. Furthermore, stimulus-induced HFD changes were inversely correlated with alpha and gamma oscillatory power reductions.

Conclusion: These findings suggest that HFD effectively captures changes in oscillatory dynamics and the 1/f slope of the PSD, both linked to the brain's excitatory-inhibitory (E-I) balance. Consequently, HFD can be used as a biomarker for age-related neural changes and other neurological disorders which may be due to modulation of E-I balance.

Investigating the role of the antagonist MTEP in metabotropic glutamate receptor 5 (mGluR5) trafficking and mGluR5-mediated AMPA receptor endocytosis

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Background: Group I mGluRs have been implicated in various neuropsychiatric disorders like autism, fragile X syndrome and also in various synaptic plasticity including learning and memory formation. Trafficking of these receptors plays the critical role in regulating the spatiotemporal localization and signaling of these receptors and any alterations can lead to severe pathological consequences. Some amount of work has been done in understanding the underlying cellular and molecular mechanisms of desensitization and rapid internalization of group I mGluRs post agonist treatment. Some GPCRs could also be desensitized, internalized and downregulated by antagonists. Indeed, there are reports of antagonist-mediated internalization of few GPCRs, but the mechanisms of such phenomena and their physiological significance have not been studied.

Purpose: The aim of this study is to unravel the basic cellular and molecular mechanisms of antagonist (MTEP)-mediated trafficking of mGluR5 and what are the roles of various postsynaptic density proteins like Norbin, Tamalin, PICK1 in the trafficking pathway. Finally, the role of antagonists in the mGluR-mediated AMPA receptor trafficking, which is the cellular correlate for mGluR-dependent synaptic plasticity, will also be investigated.

Methods: To unravel the cellular and molecular mechanisms behind the antagonist-mediated trafficking of mGluR5, we have used the elegant techniques like the dual antibody-feeding assay, molecular replacement approach, confocal microscopy, western blotting assay.

Results: Till now, we have found that 100μM concentration of MTEP induces maximum amount of internalization of the mGluR5 in a clathrin and dynamin dependent mechanism at 30 minutes post MTEP-treatment. The endocytosed receptors recycle back to the cell surface 60 minutes post MTEP-treatment, through dephosphorylation by PP2A and PP2B.

Conclusion: Further detailed studies need to be done to understand the role of the post-synaptic density proteins in this MTEP-mediated endocytosis of mGluR5 and also whether MTEP has any effect in the mGluR5-mediated AMPA receptor endocytosis.

Cell-to-cell transfer of mitochondria in the modulation of senescence-like phenotype upon α-synuclein treatment

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Background: α-synuclein, a pathogenic aggregate released from degenerating neurons can be taken up by surrounding neurons and glial cells. α-synuclein protofibrils induce oxidative stress and facilitate the biogenesis of f-actin-based intercellular membrane nanotubes (TNTs), and these TNTs promote the inter-cellular transfer of organelles such as lysosomes and mitochondria.

Purpose: To evaluate actin remodeling in the biogenesis of α-synuclein-induced TNTs and their role in neurodegeneration and premature senescence.

Methods: Actin-membrane stress modulation in the biogenesis of TNTs was evaluated by the nucleus flatness index and isometric scale factors from quantitative microscopy. TNT biogenesis was correlated to mitochondrial membrane potential by measuring JC1 and lysosomal toxicities, senescence markers by immunocytochemistry and western blots.

Results: Oxidative stress modulates the stability of nuclear lamina and contributes to cellular senescence. We have shown that FAK-mediated regulation of actin cytoskeleton networks plays a significant role in protecting nuclear structural integrity by stabilizing Lamin A/C in cellular mechanical homeostasis. α-synuclein protofibrils induced premature senescence is transient and reversible, which stems from the loss of ROCK-mediated actin-cytoskeleton tension. The senescence cells promote transient biogenesis of TNTs at reduced cytoskeleton stress. TNT-mediated cell-to-cell transfer not only eliminates toxic mitochondria and curbs ROS levels, but it also helps to accelerate the degradation of α-SYN protofibrils.

Conclusion: We hypothesize that the clearance of defective mitochondria through TNTs aids in reversing premature cellular senescence by remodeling actin cytoskeleton stress in α-synuclein protofibrils treated astroglia cells. Our study delineates the significance of interactions between modulation of cytoskeleton networks and nuclear structural integrity via Lamin A/C in α-synuclein protofibrils induced senescent cells.

Ethnicity- and gender-based differences in hematological parameters: A case study of Siddi adolescents in Mundgod, Karnataka

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Background: Ethnic groups have been shown to demonstrate variations in blood parameters and immune cells. Our ongoing work shows that adolescents of an African-origin ethnic group called the Siddis, demonstrate increased perceived discrimination, which is positively correlated with cortisol levels and negatively correlated with achievement motivation and dopamine levels.

Purpose: The purpose of this study was to investigate hematological differences between Siddi and non-Siddi adolescents, focusing on effects of gender and age.

Methods: Blood samples were collected from 142 subjects, of which 77 were Siddis and 65 were nonSiddis, aged between 12-19 years, both males and females. RBCs, hemoglobin levels, WBCs, granulocytes, lymphocytes, mid cell fraction cells, and platelets were assessed.

Results: Significant ethnic differences were observed, with Siddi males demonstrating lower RBCs ($p < 0.01$), hemoglobin ($p < 0.01$), WBCs ($p < 0.001$), granulocytes ($p < 0.001$), and lymphocytes ($p < 0.001$) as compared to non-Siddi controls. Siddi females too had lower RBCs ($p < 0.05$) and WBCs ($p < 0.05$) as compared to non-Siddi controls. Gender-based differences were observed with increased granulocytes ($p < 0.001$) in Siddi females. Siddi males of 12-16 years had lower RBCs ($p < 0.01$), and granulocytes, while those between 1719 years had reduced WBCs ($p < 0.05$), variations not observed in non-Siddi controls. Granulocyte to lymphocyte ratio (GLR) was reduced in Siddi males as compared to non Siddi controls ($p < 0.001$) and Siddi females ($p < 0.05$). ROC curve analysis indicated that GLR moderately distinguishes between Siddi and non-Siddi (AUC = 0.676).

Conclusion: The study reveals the hematological profiles of Siddi adolescents, highlighting the influence of ethnicity, age and gender. While variation in RBC and WBC whole and differential counts and hemoglobin levels in Siddis is reflective of ethnicity, the implications for health and disease outcomes needs to be considered.

Association between Serum Folic Acid and Cognitive Functioning Among Rural Aging Indians: A Cross-Sectional Study

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Background: There is a dearth of studies assessing this association among the rural Indian population.

Purpose: To assess the association between serum folic acid and cognitive functioning among rural aging Indians.

Methods: We cross-sectionally analysed the baseline data of participants aged 45+ years without dementia(N=4990) from the Centre for Brain Research- Srinivaspura Aging, Neuro Senescence and COGnition (CBR-SANSCOG) study. General linear model was used to examine the relationship between folic acid levels (ng/ml, continuous) and cognitive performance, assessed by Hindi Mental State Examination (HMSE, continuous) score, adjusting for age, sex, education, hypertension, diabetes mellitus, physical activity, depression score (Hamilton Depression Rating Scale), tobacco and alcohol use, and homocysteine levels. Voxel based morphometry (VBM) analysis was performed in a subset who underwent brain MRI (Siemens 3T Magnetom Prisma) using SPM12 in MATLAB 2023a.

Results: In our study sample (mean age- 59.65±9.8 years, 51.82% female), we found that folic acid levels were not significantly associated with HMSE scores (β=0.02,95% CI [0.01,0.04], p=0.13). However, upon sex-stratification, increasing folic acid levels were associated with better HMSE scores only in females (β= 0.04,95%CI [0.01,0.07], p=0.02). Upon further age-stratifying females, increasing folic acid levels were associated with better HMSE scores (β=0.07,95%CI [0.01,0.14], p=0.03) only in those aged 65+ years. In the MRI analysis, we found that females with deficient(<3ng/ml) folic acid levels had lower gray matter volumes particularly in right cuneus, supra-marginal gyrus, insula and inferior parietal area than those in the sufficient group(≥3ng/ml).

Conclusion: Our study found a sex-specific association between folic acid levels and cognitive performance, wherein older females with higher folic acid levels had better cognitive performance. Females with folic acid deficiency had lower brain volumes in specific areas as compared to the non-deficient group. Older rural women with lower folate levels could comprise a high-risk group for developing dementia.

40 Hz audio-visual stimulation improves sleep architecture in β-amyloid oligomers (oAβ) induced rat model of AD

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Background: Sleep disturbances are common at early stages of Alzheimer's disease (AD) along with β-amyloid pathology. Existing therapies only offer symptomatic relief but do not stop progression of the disease. While non-pharmacological therapies, such as 40 Hz audio-visual (AV) stimulation have shown promise, their impact on sleep remains to be explored.

Purpose: To examine the effect of 40 Hz AV stimulation on sleep alterations in oligomeric $A\beta_{25-35}$ ($oA\beta_{25-35}$) induced rat model of AD

Methods: A non-transgenic Aβ model was developed by intraventricular (AP: -1.0 and ML: ±1.6 to bregma, and DV: -3.8mm) injection of oligomeric beta-amyloid$_{25-35}$ peptide fragments (80µg/kg) in 6-8 months old female Sprague-Dawley rats. Electrodes were stereotaxically implanted into the hippocampus (AP: - 3.3, ML: -2.5 to bregma, and DV: -2.4mm) and medial prefrontal cortex (AP: +3.2, ML: +0.6 to bregma and DV: -3.6mm), nuchal muscles for electromyogram (EMG), external canthus of the eyes for electrooculogram (EOG), and scalp electrodes for reference and ground. Polysomnography recordings were performed at two time points, three and four weeks post injections from 10:00 AM to 4:00 PM and scored manually to assigning different sleep stages. AV stimulation consisted of LED flickering at 40Hz (12.5ms light on and 12.5ms off, 55W), and speakers fitted above the chamber programmed to present a 10KHz tone of 60 decibels, switched on for 1ms during light on period once in every 25ms, one hour per day for seven consecutive days. Polysomnography recordings were performed post stimulation.

Results: $oA\beta_{25-35}$ injection increased wakefulness, reduced sleep duration and induced sleep fragmentation characterized by increased wake after sleep onset (WASO). 40 Hz AV stimulation reduced wakefulness and WASO.

Conclusion: 40 Hz AV stimulation reverses $oA\beta_{25-35}$ induced sleep disruption and sleep fragmentation. 40 Hz AV stimulation can be further explored as a potential therapeutic strategy to target sleep alterations in AD.

Bisphenol F-induced neurobehavioral transformation is associated with oxidative stress and neurodegeneration in zebrafish brain

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Background: Nowadays, plastics have become an inseparable part of our life and its ever-increasing use has resulted in unchecked disposal into the environment, leading to significant health hazards. Bisphenol F (BPF) is one such pollutant which is extensively used in the production of plastics; however, its neurodegenerative potential is elusive in literature.

Purpose: Earlier reports revealed the basic understanding towards neurotoxic potential of BPF through altered neurobehavioral response, increased oxidative stress, motor dysfunction, etc. However, literature is limiting with respect to the underlying mechanism of BPF-persuaded transformed neurobehavioral response in zebrafish and our current study was aimed to understand the same.

Methods: The present study was designed to unravel the temporal response of zebrafish following duration dependent exposure to BPF in zebrafish. The native neurobehavioral response (bottom dwelling and scototaxis), brain biochemistry (oxidative stress indices) and neuromorphological study (chromatin condensation) were conducted.

Results: The neurobehavioral studies showed a gradual alteration in bottom dwelling and scototaxis behaviour. These observations support the notion that oxidative stress is linked to neuromorphological changes in periventricular grey zone (PGZ) of zebrafish brain. Notably, BPF exposure leads to apoptotic neuronal death as shown through increased chromatin condensation and cleaved caspase 3 expression. Downregulation in expression of NeuN, a marker of post-mitotic mature neuron, suggests significant neurotoxic potential of BPF though induction of neurodegeneration in PGZ region of zebrafish brain.

Conclusion: Concisely, the findings of our study demonstrated the role of BPF as a potent neurotoxicant by altering natural neurobehavioral response by increasing oxidative stress levels and triggering neuromorphological changes in zebrafish brain.

Extracellular vesicles-mediated Temozolomide resistance and Epithelialmesenchymal transition in Glioblastoma cells: An *In Silico* and *In Vitro* analysis

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Background: Extracellular vesicles (EVs) play a critical role in cell communication and are gaining attention in complex diseases. Glioblastoma (GBM) is a highly aggressive brain tumor associated with poor prognosis due to its mesenchymal phenotype and resistance to Temozolomide (TMZ). The involvement of EVs in GBM progression, especially in TMZ resistance and epithelial-mesenchymal transition (EMT), is not well understood.

Purpose: Our study examines the contribution of EVs in GBM progression, focusing on TMZinduced resistance and EMT by establishing an *in vitro* model to study the mesenchymal phenotype and degree of TMZ resistance of U87 MG cells in the presence and absence of the EV inhibitor GW4869, further validated by *in silico* approaches.

Methods: We employed both *in vitro* and *in silico* approaches in our study. Initially, we conducted *in vitro* assays, including cell viability assays, migration assays, and gene expression studies using qPCR. Following this, we utilized the TCGA-GBM online dataset and various bioinformatics tools (GEPIA2, UALCAN, EXOCARTA, DAVID DB and STRING) for detailed *in silico* analysis.

Results: *In vitro*, TMZ treatment alone led to a 30% reduction in cell survival, while the addition of GW4869 resulted in an 80% reduction, indicating that inhibiting EV release significantly impairs TMZ resistance. Furthermore, GW4869 treatment also altered various EMT regulatory elements, suggesting a link between EV activity and EMT dynamics in GBM. *In silico* analysis revealed significant upregulation of EV biogenesis markers like CAV1, RAB31, and TSG101, as well as EV tetraspanins like CD63, CD81, and RHOA in GBM, highlighting their role in tumor progression. We also found positive correlations between EV biogenesis, MGMT, and STAT3 expression, implicating these factors in TMZ resistance.

Conclusion: Our findings provide new insights into EV-mediated TMZ resistance and EMT in GBM, suggesting novel druggable targets within the EV biogenesis pathway to overcome therapy resistance.

Caveolin-1 protects neurons during excitotoxicity and in Epilepsy

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Background: Temporal lobe epilepsy (TLE), a prevalent neurological disorder is associated with excessive glutamate release that overactivates glutamatergic receptors, leading to sustained neuronal depolarisation and elevated intracellular calcium $[Ca^{2+}]i$. This cascade triggers increased reactive oxygen species (ROS) formation, mitochondrial dysfunction, and activation of apoptotic pathways. Caveolins, a family of integral membrane scaffolding proteins within membrane lipid rafts (MLRs), play a key role in cell signaling by interacting with various signaling molecules. Impaired Cav-1 expression is linked to Alzheimer's disease, ageing, cancers, Huntington's disease, ALS, schizophrenia, and cerebral ischemia. However, the role of Cav-1 in glutamatergic excitotoxic signaling in neurons and epilepsy is not well understood.

Purpose: To investigate the role of Cav-1 expression in neuronal glutamate signalling and *in-vitro* and *in-vivo* models of TLE.

Methods: Hippocampal neuronal cultures were prepared from postnatal day-1 Wistar rat pups. Fluorescence imaging was performed to study the $[Ca^{2+}]i$, ROS, and mitochondrial membrane potential in Cav-1 overexpressed and knocked down primary rat hippocampal neurons. Cav-1 expression and its molecular associations were analysed via Western blot and co-immunoprecipitation.

Results: Cav-1 overexpression (Cav-1 OE) reduced ionotropic glutamate receptors (NMDA, AMPA and Kainate) induced Ca^{2+} influx and Cav-1 knockdown (Cav-1 KD) did not affect Ca^{2+} influx, on the other hand, it caused Ca^{2+} dyshomeostasis. Cav-1 OE inhibits ROS formation, and mitochondrial membrane potential depolarisation upon excitotoxic glutamate application. In contrast, loss of Cav-1 significantly increased depolarisation of mitochondrial membrane potential, and ROS formation upon excitotoxic glutamate insult. Furthermore, Cav-1 OE reduced the CTZ-induced epileptiform activity and Cav-1 KD increased the same in cultured hippocampal neurons. Cav-1 association with synaptic proteins and iGluRs are not altered in the Lithium-Pilocarpine model of epileptic rats.

Conclusion: Cav-1 regulates iGluRs and protects neurons from CTZ-induced epileptiform activity and excitotoxicity.

Evaluation of the efficacy of IM-1725-RS-109 against Citicoline as a probable stroke therapeutic

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Background: Stroke, considered the second leading cause of death, is a neurological condition caused by a partial or total lack of blood flow to any specific region of the brain. The two major types of cerebral stroke are Hemorrhagic (ruptured blood vessel causing a thrombus) and Ischemic (reduced blood flow due to compressed blood vessel). Insufficient blood supply in the damaged brain region(s) trigger hypoxia and associated complications.

Purpose: Currently, tissue plasminogen activator (tPA) therapy is the only Food and Drug Administration (FDA) approved treatment available for stroke patients irrespective of their origin. Similarly, Citicoline is the only presently used psychostimulant with a significant neuroprotective effect included in post-stroke treatment. However, due to restricted medical access and very limited capacity of regeneration within the Central Nervous System (CNS), there is a dearth of effective treatment for the fast recovery of the impaired neurons post-stroke. In context to these facts, our study is designed to suggest an augment to the stroke therapeutics.

Methods: In the present study, we are keen to evaluate the therapeutic efficacy of a candidate compound IM-1725-RS-109 in the alleviation of post-stroke neural deficits in Ferric Chloride-Induced thrombus stroke mouse model. Starting with the *in vitro* models, here we propose to perform a comparative study of a patented drug (IM-1725-RS-109) with citicoline by evaluating their neuroprotective potentials.

Results: A comparative evaluation through behavioral and molecular characterizations in details may pave us the way to provide further insights in future stroke therapeutics. Additionally, it may also give us an idea if our novel compound along with tPA has a better prospect in synergistic neuroprotection than citicoline.

Conclusion: The overall study may help us increase the pool of cost-effective and better neuroprotective agents in the treatment of cerebral stroke.

Visual search asymmetries are explained by visual homogeneity

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Background: Visual search is often asymmetric. Searching for a Q among Os is often easier than searching for O among Qs. But what image property causes asymmetry in visual search? The most popular explanation is that searching for the presence of a feature is usually easier than searching for its absence – but even this does not explain many asymmetries where no obvious feature can be named.

Purpose: Here, we report a novel and empirically measurable image property – visual homogeneity – that explains visual search asymmetries. For each image, its visual homogeneity is the reciprocal of the time it takes to confirm the absence of an oddball target in a search array containing this image. We hypothesized that a search target is easy to find when the distractors are visually homogeneous. More generally, the visual homogeneity of the target and distractor would determine whether a given visual search is asymmetric.

Methods: To investigate this hypothesis, we asked human participants to search for an oddball target that could be present or absent among an array of distractors. We selected 40 popular search asymmetries reported in the literature.

Results: Search times were highly consistent, as evidenced by a high split-half correlation across participants ($r = 0.92$, $p < 0.00005$). Search asymmetries, measured as the difference between the search times of the hard and easy targets, were also likewise consistent across participants (split-half correlation: $r = 0.64$, $p < 0.0005$). Importantly, search asymmetry was accurately predicted by a weighted sum of the visual homogeneity of the target and distractor ($r = 0.56$, $p < 0.0005$). These predictions were driven primarily by the distractor, suggesting that search is asymmetric when the distractor is visually homogeneous.

Conclusion: Taken together, our findings demonstrate for the first time, an empirically measurable image property that can explain visual search asymmetry.

Celastrus paniculatus: A therapeutic approach for rotenone-induced neurotoxicity

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Background: Parkinson's disease (PD), a common neurodegenerative disorder, is marked by various motor and non-motor impairments. Rotenone exposure impairs Complex I in the mitochondrial electron transport chain of dopaminergic neurons, reducing antioxidant levels and triggering oxidative stress. *Celastrus paniculatus* (CP), a medicinal plant, is known for enhancing learning, memory, and its antioxidant properties.

Purpose: In the next thirty years, Parkinson's disease (PD) is projected to double in prevalence and current medications mainly alleviate motor symptoms but tend to lose effectiveness over time, prompting interest in herbal remedies. This study examines the neuroprotective properties of CP against rotenone-induced neurotoxicity in rats, focusing on its impacts on motor functions, oxidative stress, and cognitive impairments to enhance PD treatment options.

Methodology: Rats received rotenone (1.5 mg/kg s.c.) every other day and CP (200 and 400 mg/kg i.p.) daily for 28 days. Behavioral tests were conducted from days 15 to 28. On day 29, after the tests, the rats were sacrificed, and hippocampal BDNF and striatal dopamine levels were measured using ELISA kits. Additionally, oxidative stress markers (SOD, GSH, CAT, and MDA) in the hippocampus and striatum were assessed.

Results and Discussion: Rotenone exposure led to significant behavioral deficits, such as reduced sucrose preference, locomotion, exploratory behavior, muscle strength, motor coordination, balance, and recognition memory, all linked to oxidative stress with lower antioxidant levels and higher lipid peroxidation. Rotenone also lowered hippocampal BDNF and striatal dopamine levels. CP treatment improved these behaviors, increasing sucrose preference, locomotion, muscle strength, motor coordination, balance, and recognition memory. These improvements were associated with higher antioxidant levels, reduced lipid peroxidation, and increased hippocampal BDNF and striatal dopamine levels.

Conclusion: The results emphasize CP's therapeutic benefits in mitigating the behavioural and biochemical disturbances triggered by rotenone in rats, mediated by its antioxidant and neuroprotective properties.

Effect of Oleic acid on neurite outgrowth

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Background: Neuroblastoma, is a sympathetic nervous system tumour occurring in neural crest cells, resulting in the loss of the ability to differentiate into mature neurons. Prescribed treatment includes a combination of chemotherapy, immunotherapy, and antibody-targeted therapy; however, the rate of cure significantly varies. Plant-derived compounds are being considered for cancer treatment because of selective toxicity and immune system modulation. For example, Oleic acid, an unsaturated omega-9-fatty acid found predominantly in olive oil, has been used to induce differentiation in neonatal human epidermal keratinocytes, but its effect on neuroblastoma remains uncertain.

Purpose: The present study aims to decipher neuronal differentiation induced by Oleic acid.

Methods: Neuroblastoma cell line, N2a, was used in the study. Cell viability at different concentrations of Oleic Acid was studied using MTT assay. Morphological changes such as neuronal projections and nucleus-to-cytoplasm ratio were observed using Giemsa stain. RT-PCR was performed using gene-specific primers to quantify gene expression related to differentiation.

Results: Increased concentration of Oleic acid did not exhibit a significant difference in cell viability. Post-treatment with Oleic acid, demonstrated the beginning of neurite outgrowth after 24h, interestingly proper projections were observed after 48h. Further validation was observed by differential expression of Beta3 Tubulin, Nestin, in oleic acid-treated N2a cells when compared with untreated cells. Additionally, the effect of neurotrophic factors, BDNF, was studied using gene-specific primers. Differential expression of BDNF was indicative that an activated cascade of signaling pathways may be involved in neuronal differentiation with oleic acid treatment.

Conclusion: Based on the results, it is indicative that Oleic acid holds the potential to induce neuronal differentiation in N2a cells. This can increase the efficacy of treatment strategies used for curing neuroblastoma. To validate the likelihood of the promising effects of Oleic acid on Neuroblastoma, more studies must be done in this area.

Dental Pulp Stem Cell Secretome Protects Motor Neurons Against Excitotoxicity and Oxidative Stress: An *In Vitro* Analysis

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder. It is characterized by the loss of both upper and lower motor neurons. Although the pathophysiology of ALS remains obscure, several studies have demonstrated the role of glutamate toxicity and altered free radical scavenging systems in the pathogenesis of motor neuron diseases (MND).

Purpose: To date, no effective treatment for ALS has been available. Stem cell therapy is emerging as an alternative therapeutic approach to treat neurodegenerative diseases. Of note, recent studies highlight the neuroprotective potential of secretome derived from adult mesenchymal stem cells.

Methodology: In the present study, we evaluated the neuroprotective effect of secretome obtained from dental pulp stem cells (DPSC) in an *in-vitro* model of MND. We assayed its antioxidant properties, anti-apoptotic and anti-necrotic properties, and its gene expression.

Results: NSC-34 cells, when exposed to kainic acid and hydrogen peroxide for 24 hours, resulted in significant cell death that was corroborated with increased activities of caspase-3 and lactate dehydrogenase, suggesting apoptotic and necrotic mode of neuronal death. In contrast, NSC-34 cells exposed to kainic acid and hydrogen peroxide, when treated with DPSC secretome for 24 hours, resulted in increased cell viability. DPSC secretome protected NSC-34 cells through anti-apoptotic mechanisms by decreasing pro-apoptotic caspase 3 activity and by enhancing the expression of anti-apoptotic factor BCL-2. We also observed a significant decrease in lactate dehydrogenase activities suggesting the anti-necrotic properties of DPSC secretome as well.

Conclusion: Our results suggest that the DPSC secretome could be a potential therapeutic agent to prevent motor neuron degeneration in MND, such as amyotrophic lateral sclerosis.

Treatment with *Mucuna pruriens* effectively alleviates acute neuronal injury by inhibiting neuroinflammation and improves motor function in ischemic reperfusion injury

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Background: Cerebral ischemia is a cause of mortality and morbidity globally. Its pathophysiology encompasses a complex interplay of several factors such as excitotoxicity, neuroinflammation, oxidative stress, and blood-brain barrier disruption, ultimately culminating in neuronal damage.

Purpose: The current study assessed the neuroprotective efficacy of *Mucuna pruriens(MP)* and its potential against treating ischemic reperfusion injury associated functional deficits.

Methods: Sprague Dawley male rats (3-4 months) were divided into Sham, right middle cerebral artery occlusion(rMCAO), and MP+rMCAO. The rMCAO group had their middle cerebral artery occluded for 1.5 hours, while the MP+rMCAO group received orally administered MP at 200mg/kg body weight for 15 days before occlusion with treatment continuing for 24 hours and 7 days after occlusion. Assessments were conducted at 24 hours and 7 days, including evaluations of modified neurological severity scoring, infarct volume, blood-brain barrier integrity, motor behaviour, and inflammatory marker levels.

Results: The intervention with MP led to a significant reduction in the mNSS score in the MP+rMCAO group compared to the rMCAO group. Furthermore, the infarct volume was significantly reduced, and the integrity of the blood-brain barrier was well-preserved in the MP+rMCAO group. Additionally, a significant decrease in proinflammatory cytokines and an effective increase in the levels of tight junctional proteins was observed in the MP+rMCAO group compared to the rMCAO group. Moreover, there was a substantial improvement in motor function in the MP+rMCAO group.

Conclusion: The possibility of preventing the occurrence of acute ischemic stroke serves the need for prophylactic therapy in populations that are at high risk. This study implies that MP treatment could mitigate the pathogenesis of neural degeneration evoked by rMCAO by attenuating neuroinflammatory markers and improving neurobehavioral functions. MP as a prophylactic therapy elevates the ischemic tolerance levels of neurons to sudden metabolic damage simultaneously accelerating their functional recovery following cerebral ischemia.

Energy State dependent prioritization of defensive circuits through a CART neuronal projection

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Background: Living organisms face competing motivations that influence their survival, especially the need to meet the energy requirement. These internal states modulate various survival behaviors, with neuropeptides playing a crucial role in this regulation. One such neuropeptide is Cocaine and Amphetamine Regulated Transcript (CART), which has established functions in both satiety and anxiety or innate fear responses. The interaction between hunger and defensive behaviors is critical for understanding survival strategies.

Purpose: The primary aim of this research is to investigate how hunger and satiety act as a master circuit that modulates other survival circuits. Specifically, the study focuses on the role of CART in modulating defensive behaviours in rodents under different energy states.

Methods: The research utilized chemogenetic approaches in CART transgenic mouse lines. This allowed for the manipulation of CART neuronal circuits projecting from the arcuate nucleus (Arc) to the central amygdala (CeA). The study compared the behavioral responses of fasted animals to those of control animals, assessing freezing responses to the noxious predator odor TMT and anxiety-like behaviors.

Results: Starvation led to decreased levels of CART in both the Arc and CeA, suggesting an energy state dependent role of CART in both feeding and innate fear. When the CART neuronal circuit was activated in fasted animals, these subjects exhibited increased freezing responses and heightened anxiety-like behaviors, similar to those of ad-libitum fed animals. Furthermore, fasted animals displayed reduced risk-taking when the circuit was activated, reinforcing the idea that CART plays a significant role in prioritizing defensive behaviors based on energy states.

Conclusions: The findings highlight the importance of CART in modulating behavioral states related to hunger and satiety. To further elucidate the specific role of CART, CART heterozygous and knock-out transgenic lines will be used to dissect the relationship between circuit function and neuropeptide release in behavior prioritization.

Identification of Key Signaling Pathways in Women with Major Depressive Disorder: A Transcriptomic Study

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Background: Major depressive disorder (MDD) is a highly complex psychiatric disorder with high morbidity and disability rate. Clinically, MDD has heterogeneous features involving disturbances of mood and cognitive function. But in-spite of the high prevalence and seriousness of the disorder, there are no biological indicators for the diagnosis and treatment of MDD. The diagnosis of MDD is subjective in nature and depends on the selfreports from patients and clinical observations. Therefore, there is an urgent requirement of exploring the underlying mechanisms of MDD and identifying effective biomarkers to facilitate efficient diagnosis and treatment. The major limitation in understanding the intricacy of the disease is the almost unknown pathophysiology of MDD.

Method: In the present study, using RNA-sequencing technique, we identified the differentially expressed signaling pathways contributing to the pathophysiology of MDD in women. Briefly, we used whole blood of the women suffering with MDD (n=6) and their well-matched healthy counterparts (HC, n=4) to develop transcript profile data of differentially expressed genes from the Peripheral Blood Mononuclear Cells (PBMC). Further, utilizing robust bioinformatic tools we identified the significant differentially expressed genes with a high fold change and performed network analysis for getting insights into their corresponding signaling pathways and potential biological mechanisms associated with MDD.

Result: Our result suggests that the Neuroactive ligand-receptor interaction pathways with ion channel activity, inflammatory mechanisms could be important in the pathophysiology of MDD in women.

Conclusion: Examining these pathways could offer crucial insights into the etiology of major depressive disorder in women and potentially identify diagnostic markers.

An electrophysiological study to investigate fight-flight defense responses in humans using 3D virtual reality simulation

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Background: Predatory imminence continuum displays the psychological perception of the imminence of the threat. The defense responses alter as the psychological perception of the threat's imminence increases.

Purpose: The study explores the fight/flight responses and underlying neural correlates using EEG in a virtual reality (VR) environment.

Methods: The experiment (N=16,_Mean age (SD)=23.94(3.45)) consisted of a desktop VR environment including the training and the experimental phase (5 conditions). Conditions 1 to 4 included a threat avatar, whereas condition 5 did not. The conditions differed based on threat proximity (distal/proximal) and the participant's escapability (escape/no-escape). Twenty trials were presented, with each condition presented four times. Participants responded with a Fight/Flight response to the threat, followed by a rest scene of 10s and a fixation of 5s.

Results: Chi-square test indicated no significant difference between fight/flight responses across four conditions. A paired sample t-test indicated significant difference between Fight (M=2.94, SD=1.39) and Flight (M=1.00, SD=1.37), t(15)=2.82, p=0.01 of 'Proximal threat noescape' condition only. A rmANOVA for reaction-time indicated significant difference across 4 conditions, $F(3,45)=3.26, p=0.03, \eta^2=0.18$. Time-frequency analysis of 8-channel EEG (N=9) over frontal regions showed peaks in delta-power across conditions however an overall low power was assessed for all the frequency bands.

Conclusion: Heightened fight responses were observed across conditions as the VR environment involved no consequences compared to real life. A significant difference in reaction-time indicates distinction based on threat proximity and escapability. The delta-power observed across conditions may indicate an involvement of emotional (threat) and cognitive (fight/flight) components and an underlying neural distinction for threat and no threat conditions.

Characterisation of Impact of Noise-Induced Hearing Loss on Mental Health and Cognition

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Background: According to the WHO report, 10% of the global population is affected by hearing loss. In India, it is estimated that approximately 6.3 crore individuals have hearing loss. Individuals with hearing loss are shown to have mental health/cognitive deficits. An altered functional connectivity between auditory and non-auditory pathways that regulates the emotional and cognitive processes is hypothesized as the reason.

Purpose: However, the impact of hearing loss due to acute sound exposure (DJ party) vs. chronic sound exposures (work environment) on mental health and cognition is not characterized. It is essential to reveal these differences as these may underlie the pathophysiology in different cases.

Methods: Adult male Wistar rats were noise-exposed (white noise at 110dB SPL) either acutely or chronically, followed by an assessment of hearing function using an auditory brainstem response test. The anxiety/depression was studied using open field and elevated plus maze test, while the novel object recognition test and morris water maze tests were used to study cognition. The genes involved in the excitatory and inhibitory neurotransmission, such as serotonin, NMDA and GABA, were analysed using the qRT-PCR technique at pre-identified structures.

Result: The auditory brainstem response test confirmed that acute and chronic noise exposure negatively affected auditory processing in rats. The behavioral analysis illustrated deficits in measures of mental health and cognition. Also, an altered level of excitatory and inhibitory gene expression was observed at the emotional and cognitive centers. These findings demonstrated that the changes in gene expression post-noise exposure at critical emotional and cognitive brain regions led to deficits in their function.

Conclusion: Hearing loss disrupts a complex network of brain regions involved in emotional and cognitive function. Understanding the interdependence of these circuits and their functions is essential to devise therapeutics towards sensory deficit-led anxiety/depression and cognition.

Human iPSC-derived astrocytes reveal Functional and Metabolic deficits in Fragile X Syndrome

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Background: Fragile X syndrome (FXS), a leading inherited cause of autism spectrum disorder and intellectual disability, has been studied extensively using rodent models. More recently, human stem cell-derived model systems have also been used to gain mechanistic insights into the pathophysiology of FXS. However, these studies have focused almost exclusively on neurons. Further, despite growing evidence for a key role for glia in neuronal function in health and disease, little is known about how human astrocytes are affected by FXS.

Purpose: This study aims to highlight the role of astrocytes in brain development and their significance in disease conditions.

Methods: In this study, we patterned the human induced pluripotent stem cells into the neuroectodermal lineage with dual SMAD inhibition and small molecules approach. Subsequently, we utilized specific growth factors and cytokines to generate control and FXS patient-derived astrocytic progenitor cells (APCs). Treatment of APCs with CNTF, a differentiating cytokine, regulated and drove the progenitor cells towards astrocytic maturation.

Results: With this protocol we successfully generated forebrain-specific GFAP-expressing astrocytes. We found that these astrocytes are functional, as evidenced by their calcium responses to ATP application, and they exhibit dysregulated glycolytic and mitochondrial metabolism in FXS astrocytes.

Conclusion: Taken together, these findings provide a human platform for the investigation of cell-autonomous and non-cell autonomous consequence of astrocyte mutations in neurodevelopmental disorders.

Role of glia in amyloid beta-induced cholinergic degeneration in the rat brain

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Background: Abnormal amyloid-beta (Aβ) deposition is a hallmark of Alzheimer's disease (AD), predominantly affecting brain regions such as the hippocampus and cerebral cortex, which are heavily innervated by basal forebrain cholinergic neurons. However, the striatum and other brain areas are largely spared. The regional specificity of AD and the role of cholinergic vulnerability in disease progression remain poorly understood.

Purpose: This study aims to investigate the pathological effects of aggregated Aβ1-42 in the hippocampus and striatum, focusing on the regional vulnerability and structural reorganization of cholinergic innervations in the rat brain.

Methods: Male Wistar rats underwent stereotactic injections of aggregated Aβ1-42 into the hippocampus and striatum. Histological analysis was performed using Nissl staining and Immunohistochemistry for Choline Acetyltransferase (ChAT), Iba-1 (microglia), and GFAP (astrocytes). Morphometric analysis was conducted to quantify cellular changes, with statistical analysis to determine significance.

Results: Aβ treatment caused significant morphological disruptions, especially in the hippocampus, where the granule cell layer showed increased glial cell density and signs of neuroinflammation. Cholinergic fibers exhibited axonal fragmentation and network disruption near the Aβ injection site. In the striatum, while overall architecture remained intact, there was increased gliosis and signs of neuronal degeneration.

Conclusion: Aβ1-42 treatment caused significant morphological disruptions, in the hippocampus exhibited increased glial density, neuroinflammation, and disrupted cholinergic fibers, while the striatum showed gliosis and early neuronal degeneration. These observations suggest that Aβ1-42 may have region-specific effects, influencing both inflammatory and neurodegenerative processes.

Efficacy of Narasimha rasayana on altered cognitive functions in an animal model of epilepsy

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Background: Previous studies have shown that seizures can cause cognitive disorders. On the other hand, polyherbal formulation Narasimha Rasayana (NS) has beneficial effects on the nervous system. However, there is little information on the possible effects of the NR on seizures.

Purpose: The aim of this study was to investigate the possible effects of NR on cognitive impairment, acetylcholinesterase (AChE) activity and oxidative stress induced by epilepsy in rats.

Methods: Rats were randomly divided into different groups. In all rats, except the control group, kindling was induced by intraperitoneal injection of pentylenetetrazol (PTZ) at a dose of 35 mg/kg every 48 h for 20 days. Standard group received 5 mg/kg escitalopram + PTZ; treatment groups received PTZ or 10 or 20 mg/kg NR + PTZ for 15 days. Open field test (OFT) and elevated plus maze (EPM) tests were used to measure anxiety, T-maze and novel object recognition test (NORT) used to evaluate memory and learning. On the last day of behavioural experiment, animals were sacrificed; the hippocampus, frontal cortex and septum were removed and subjected to biochemical estimation.

Results: Statistical analysis of the data showed that the kindling increased anxiety in EPM, impaired memory in T-maze and NORT. Interestingly, the NR showed marked increase in spontaneous alterations and decline in the anxiety in T-maze and EPM, respectively. NR treatment enhanced object recognition memory, showed better recognition and discrimination memory compared to PTZ animals. Furthermore, neither kindling nor treatment affected the AChE activity in the hippocampus, frontal cortex and septum.

Conclusion: The findings of the current investigation demonstrated that treatment with Narasimha Rasayana avoids cognitive deficit and cures behavioural abnormalities in kindled rats without affecting cholinergic transmission.

Alterations in kynurenine precursor and product levels and its link to Inflammation in post-mortem brain tissue of schizophrenia patients in Indian population

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Background: Schizophrenia (SCZ) is characterized by a complex array of symptoms, as heterogeneous as its overall clinical presentation. While classical neurotransmitters have been extensively studied in SCZ, the role of neuromodulators, particularly the kynurenine pathway (KP) metabolites from tryptophan catabolism, remains less understood in its pathophysiology

Purpose: Dysregulation in this pathway alters kynurenine metabolite levels, contributing to neuroinflammation, neurodegeneration, and cognitive deficits. Our study examines KP enzymes at both mRNA and protein levels and cytokines at the transcriptional level within the Indian population to identify potential biomarkers and novel therapeutic targets for SCZ

Methods: Post-mortem dorsolateral prefrontal cortex tissue from 10 SCZ patients and 17 HCs was obtained from NIMHANS. Gene expression was analyzed using RT-qPCR for mRNA of KP enzymes and cytokines, Western blotting for protein levels of key KP enzymes, and LCMS/MS for measuring KP metabolites.

Results: TDO gene expression was significantly elevated (2.5-fold) in SCZ patients compared to healthy controls ($p < 0.001$), along with an increase in KAT II gene expression ($p < 0.05$). SCZ patients also showed higher mRNA levels of pro-inflammatory cytokines IL-1β ($p < 0.005$) and TNF-α ($p < 0.05$). Protein levels of IDO ($p < 0.01$) and KAT II ($p < 0.005$) were elevated in SCZ patients. Additionally, tryptophan was lower, while Kynurenine intermediates were higher in SCZ patients than controls ($p < 0.05$).

Conclusion: Our study reveals a derivative association between KP metabolites and cerebral inflammation in Asian Indian SCZ patients. Differences in KP enzymes and inflammatory cytokines between SCZ and HC suggest potential alterations in brain kynurenine levels, influencing symptom severity and cognitive function. These findings may offer insights into the cognitive deficits associated with SCZ.

INTERACTIONS OF AICD, ZINC, AND COPPER WITH DNA REVEAL CONFORMATIONAL CHANGES THAT CAUSE ALZHEIMER'S DISEASE (AD).

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Background: Neurofibrillary tangles and Amyloid plaques are central to the progression of Alzheimer's Disease (AD). It has been well substantiated that the Amyloid precursor protein is cleaved enzymatically at its C terminal end yielding the APP intracellular domain (AICD). It has been shown that AICD is an intrinsically unstructured molecule involved in AD pathology and appears to be a potential candidate for understanding the complexity of this disease. **Purpose:** It is however known that the relevance of the AICD mechanism in neurodegeneration is poorly understood. Recent evidence reveals that AICD is localized in the nucleus, and upon binding to DNA, gene expression appears to get altered and thus could be regarded as the third hallmark of AD. Reports have highlighted those higher concentrations of copper induce a neurotoxic effect, which could enhance AD pathogenesis. Methods: Hence, our work focuses on the interactions of AICD with copper and DNA via circular dichroism and computational studies.

Results: Our results reveal that the AICD-Cu and AICD Zn complex, interacts with the DNA and triggers conformational perturbations leading to AD.

Conclusion: In conclusion, our Circular dichroism studies serve the evidence Zn, Cu, and AICD bind to DNA and cause the conformational change from B-DNA to altered B-DNA and A-DNA conformation. Our in-silico studies provide valuable information on DNA conformational changes of secondary structures with the binding to some specific residues of AICD, Zn, and Cu.

Untargeted Plasma Metabolomics in Kerala Cohort Identifies Severity-Linked Biomarkers for Alzheimer's Disease Diagnosis

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Background: Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide. As life expectancy increases and pre-onset diagnostic markers remain elusive, the assessment and management of AD are projected to become increasingly challenging. The number of affected individuals is expected to surge to 150 million by 2060, significantly exacerbating the global economic burden. This highlights the urgent need to discover reliable biomarkers to facilitate early diagnosis and improve management strategies for AD.

Purpose: This study investigates the plasma metabolite profile of an unexplored Southwest Indian cohort. Using untargeted metabolomics, it aims to uncover distinct and unique pathways and metabolite signatures with biomarker potential.

Methodology: Plasma samples from healthy controls (HC), mild dementia Alzheimer's (MDA), and Moderate-Severe Dementia Alzheimer's (MSDA) groups were analyzed using the LC-MS/MS platform following solvent extraction under standard conditions. The mass spectrometric raw data were processed, and detected spectral identifiers were mapped against publicly available metabolite databases to identify putative metabolites. The assigned metabolite data were normalized and analyzed using MetaboAnalystR (version 6.0) and R (version 4.3.1).

Results: Metabolite set enrichment analysis identified significantly dysregulated metabolite sets and pathways relevant to MDA and MSDA conditions. Pathway analysis further highlighted key metabolites within these enriched sets, particularly those involved in Taurine and Hypotaurine metabolism, Arachidonic acid metabolism, energy metabolism, and amino acid metabolism.

Conclusion: This study underscores the potential of metabolomic profiling to differentiate between disease states and healthy conditions. The identified metabolites are associated with processes implicated in AD, such as oxidative stress and inflammatory responses. These findings offer valuable insights into the underlying biochemical changes in AD and suggest potential biomarkers for diagnosis and monitoring of treatment efficacy.

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