



ANNUAL SCIENTIFIC REPORT

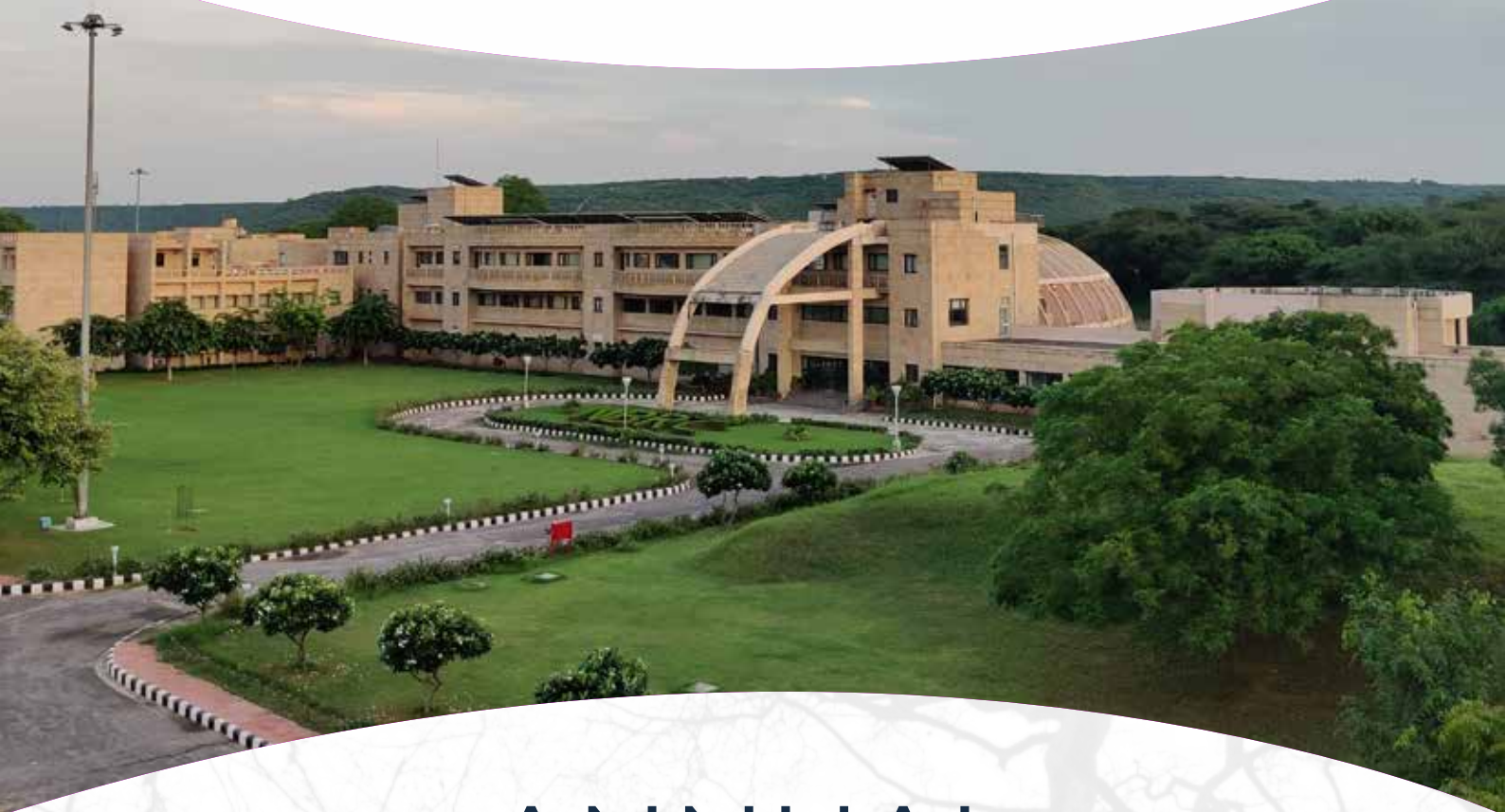
2024 - 2025



BIOTECHNOLOGY RESEARCH AND INNOVATION COUNCIL (BRIC)
A DEPARTMENT OF BIOTECHNOLOGY ORGANIZATION



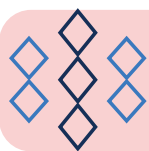
2024-2025



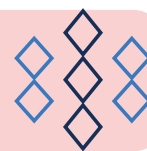
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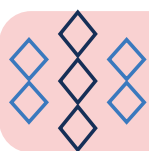
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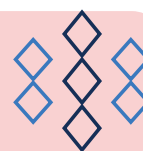
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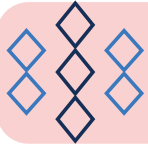
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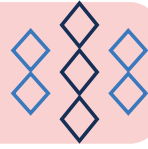
Annual Scientific Report Compilation Committee 2024-25



- ◆ Dr. Anirban Basu, Chairperson
- ◆ Dr. Anindya Ghosh Roy, Member
- ◆ Dr. Bhavani Shankar Sahu, Member
- ◆ Ms. Seepika, Convener



Mission, Vision & Mandate



Mission & Vision

- ◆ Develop a world-class Centre for Brain Research and network with local researchers.
- ◆ Understand brain function and apply the knowledge for societal benefit.

Research Mandate

- ◆ Pursue research to understand physiology of brain in health, neurodevelopmental and neurodegenerative disorder.
- ◆ Generate trained human resources with the capability to carry out interdisciplinary research in neuroscience.
- ◆ Promote neuroscience in India through networking among institutions across the country.

From Director's Desk...



Sagar Sengupta

Director (Additional Charge)

Director's Report

National Brain Research Centre (NBRC), Manesar

It gives me immense pleasure to present the Director's Report of the National Brain Research Centre (NBRC), Manesar, for the year 2024–2025. Over the past year, NBRC has continued to strengthen its role as India's premier neuroscience research and training institute, combining cutting-edge basic and clinical neuroscience research with national coordination efforts, infrastructure development, and public engagement. This report provides an overview of our achievements, significant scientific contributions, grants received, the challenges we face, and our vision for the future.

Growth and Activities at NBRC

NBRC's mandate is to pursue research across multiple domains of neuroscience—molecular, cellular, systems, computational and clinical—while also providing advanced education and training. In 2024–25, NBRC made significant advances in several spheres:

- 1. The Dementia Cohort Programme:** NBRC scaled up its multimodal dementia initiative, combining MRI-based imaging, cognitive assessment, sociodemographic profiling and caregiver perspectives. This unique cohort emphasizes rural and monolingual populations, aiming to fill critical gaps in global dementia datasets.
- 2. Infrastructure Strengthening:** The NBRC Neuroimaging and Neurospectroscopy Laboratory continued to provide high-quality MRI/MRS capabilities, serving both internal investigators and national collaborators. Computational neuroscience and bioinformatics pipelines were further enhanced to deal with large datasets.
- 3. Basic and Translational Neuroscience:** Our laboratories published pioneering work in non-coding RNA regulation of neural development, host-pathogen interactions in neurotropic

viruses, and epigenetic modulation of memory. These outputs demonstrate NBRC's strength in bridging mechanistic insights with translational potential.

4. **Education and Training:** NBRC successfully ran its PhD and MSc programmes, admitted a new cohort of students, and organized the Regional Young Investigators' Meeting (Delhi NCR), fostering inter-institutional collaborations. Workshops, summer schools and public seminars further enhanced NBRC's profile as a centre for training the next generation of neuroscientists.
5. **Outreach:** Engagement with schools, clinicians, and community organizations continued, with a special emphasis on raising awareness about dementia, mental health, and the importance of brain research.

Significant Research Publications

NBRC scientists published a range of impactful research papers in the last year. A few significant contributions include:

1. Bindu, Hriday Shanker Pandey, Pankaj Seth. Interplay Between Zika Virus-Induced Autophagy and Neural Stem Cell Fate Determination. *Molecular Neurobiology* PMID: 37910284. The helps to advance the understanding of ZIKV-induced neuropathogenesis and suggests autophagy as a potential target for anti-ZIKV therapeutic intervention.
2. Atreye Majumdar, Indira Priya Siva Venkatesh, Vivek Swarup, Anirban Basu. Short-chain fatty acids abrogate Japanese encephalitis virus-induced inflammation in microglial cells via miR-200a-3p/ZBTB20/IK β a axis. *mBio*. PMID: 38869276. Findings of this study pave the way to a better understanding of Short-chain fatty acids mechanisms that can be used to develop strategies against viral neuroinflammation.
3. Swati Singh, Kirti Lathoria, Sonia B Umdor, Jyotsna Singh, Vaishali Suri, Ellora Sen. A gain of function mutation in AKT1 increases hexokinase 2 and diminishes oxidative stress in meningioma. *Cytokine*. PMID: 38325141. Investigates the AKT1-E17K gain-of-function mutation in meningioma models and reports increased hexokinase 2 (HK2) expression coupled with reduced markers of oxidative stress and altered inflammatory mediator profiles, suggesting metabolic rewiring associated with this driver mutation.
4. Nisha Chetana Sastry, Arpan Banerjee. Dynamicity of brain network organization & their community architecture as characterizing features for classification of common mental disorders from whole-brain connectome. *Translational Psychiatry*. PMID: 38951513. Presents whole-brain connectome analyses showing that dynamic network reconfiguration and community architecture features can distinguish common mental disorders; provides computational markers that may improve neuroimaging-based classification.
5. Mohima Mukherjee, Chandramouli Mukherjee, Vinayak Ghosh, Aamna Jain, Souren Sadhukhan, Sushma Dagar, Bhavani Shankar Sahu. *Journal of Cell Science*. PMID: 38348894. This study elucidates how endoplasmic reticulum stress disrupts regulated secretion by modulating key exocytotic and granulogenic molecular switches.
6. Nisha, Deepti Thapliyal, Bhavya Gohil, Mayanglambam Dhruba Singh. *Molecular Neurobiology*. PMID: 40042729. This research highlights the neuroprotective role of PTEN downregulation in ameliorating Huntington's disease phenotypes in *Drosophila* models.

7. Harjot Kaur Brar, Swagata Dey, Pallavi Singh, Devashish Pande, Anindya Ghosh-Roy. eNeuro. PMID: 38548333. This study demonstrates that dendrite regeneration can restore lost sensory function due to injury in adulthood using the PVD neuron model in *C. elegans*.
8. Dipanjana Banerjee, Sania Sultana, Sourav Banerjee. Gas5 Regulates Early-Life Stress-Induced Anxiety and Spatial Memory. PMID: 38960403. This research identifies the long non-coding RNA Gas5 as a key regulator in early-life stress-induced anxiety and spatial memory deficits.

Together, these publications represent NBRC's strength in combining molecular mechanisms with translational neuroscience.

Major Research Grants and Programs

During 2024–25, NBRC received significant external funding to support its mission:

- ◆ DBT/BRIC National Dementia Science Programme: NBRC has been identified as a coordinating institution for this nationwide initiative. The project focuses on multimodal imaging and biomarker discovery in dementia, positioning NBRC at the forefront of dementia research in India.
- ◆ DBT Research Grants to individual laboratories supported work in diverse areas including non-coding RNA biology, neuroinflammation, auditory system development, and computational neuroscience.
- ◆ Infrastructure Support: Continued DBT investment allowed NBRC to maintain and enhance the national neuroimaging platform, which serves researchers across India.

These grants underscore NBRC's ability to attract competitive funding and its alignment with national research priorities.

Challenges Faced by NBRC

Despite its many achievements, NBRC faces several challenges that must be addressed to ensure sustained growth:

1. **Recruitment and Retention:** Attracting and retaining top scientific talent remains a challenge, given global competition.
2. **Infrastructure Expansion:** While the neuroimaging and spectroscopy platforms are strong, there is a need for next-generation technologies such as high-field MRI, advanced PET, and multi-omics integration platforms.
3. **Translational Pipeline:** Moving discoveries from bench to bedside requires deeper engagement with clinical centres, industry, and regulatory bodies.
4. **Public Awareness:** Neuroscience research in India must contend with low levels of awareness and stigma around mental health and neurological disorders.

Addressing these challenges will require strategic planning, enhanced funding, and stronger partnerships with national and international institutions.

Societal Impact and the Road Ahead

NBRC's research directly addresses some of the most pressing public health challenges in India. The dementia cohort initiative will create resources for early detection, culturally appropriate diagnostics, and potentially more affordable interventions. Research in neuroinflammation, memory modulation, and host-pathogen interactions has implications for treating neurodegeneration, cognitive decline, and viral encephalitis, all of which disproportionately affect the Indian population.

Looking forward, NBRC aims to:

- ◆ Strengthen its role as a national hub for neuroimaging and multi-omics integration.
- ◆ Develop translational pipelines for diagnostics and therapeutics in dementia, neurodegeneration, and neuroinflammation.
- ◆ Expand partnerships with hospitals, universities, and industry to accelerate clinical translation.
- ◆ Continue training the next generation of neuroscientists, with a focus on diversity and inclusion.
- ◆ Enhance public outreach to improve awareness of brain health in society.

In sum, NBRC is well-positioned to make transformative contributions to neuroscience in India, ensuring that our discoveries benefit society at large and strengthen India's global standing in brain research.

I would like to acknowledge the dedication of NBRC's faculty, students, staff, collaborators, and funding agencies for their continued support. Together, we will continue to push the frontiers of neuroscience and contribute meaningfully to human health.

Scientific Report



Ahmad Raza Khan

Scientist-IV

Dr. Ahmad joined National Brain Research Centre, Gurgaon in August, 2024, as a Scientist-IV. His research interests are microstructural and metabolic imaging in radiologically subtle brain disorders. He is a Ramalingaswami Fellow (DBT-2019) and before that he served as an Assistant Professor at Aarhus University, Denmark (2017-19). He completed his Postdoc from Aarhus University (2013-17), Denmark and the first year of postdoc at Oregon National Primate Research Centre (ONPRC), Oregon Health and Science University (OHSU), Portland, USA (2013-14).

PhD Students

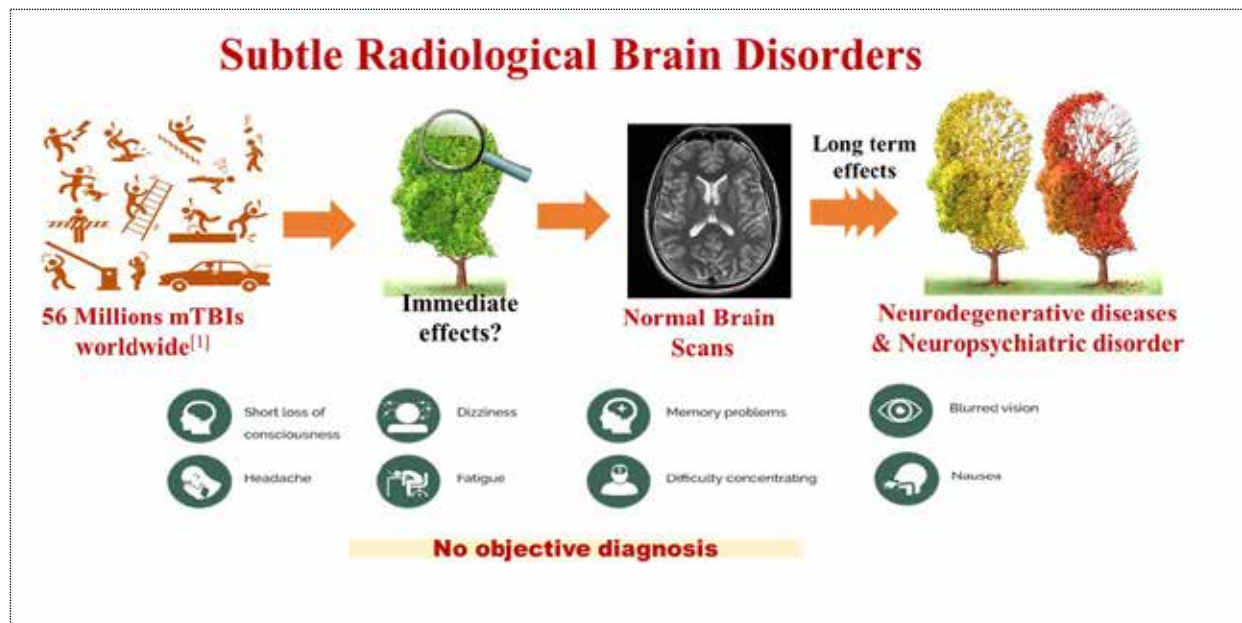
◆ Nudrat Jahan

◆ Vaishnavi Sharma

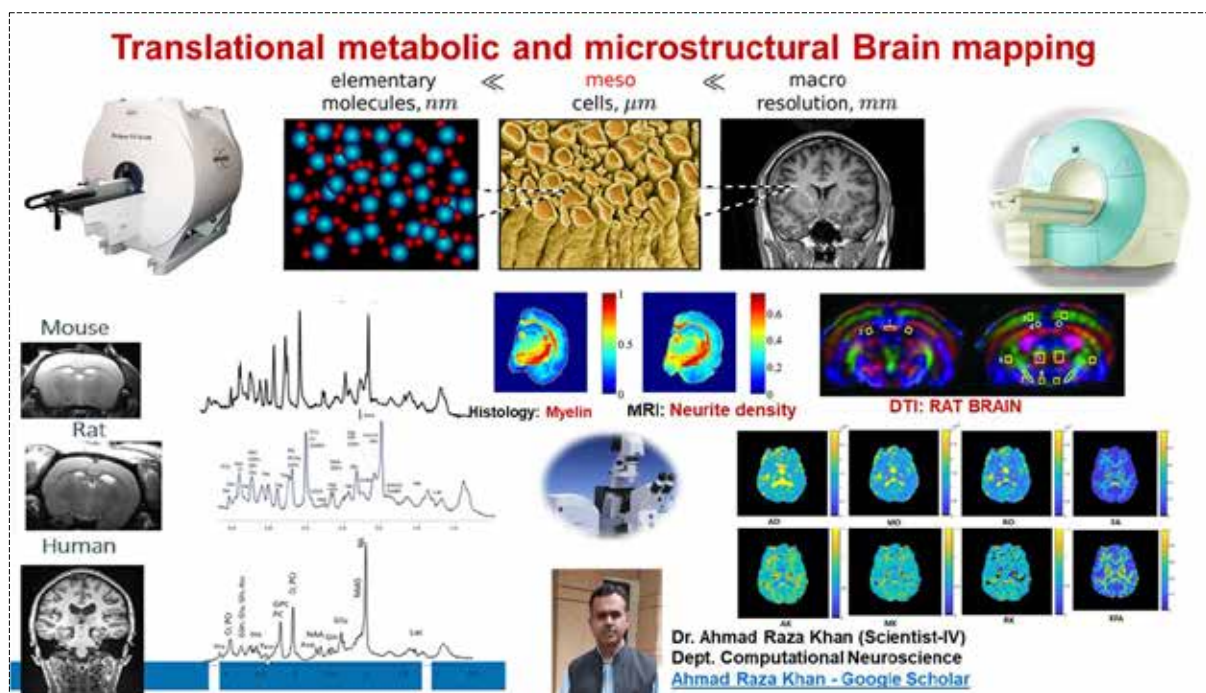
Microstructural and Metabolic Mapping of Subtle Radiological Brain Disorders

Advanced neuroimaging methods, particularly micro-structural and metabolic imaging of radiological modest brain illnesses, including depression, mild traumatic brain injury, and sleep abnormalities, are the core focus of our lab. This involves using modalities such as diffusion MRI and MR spectroscopy to explore the tissue micro-architecture and metabolic processes within the brain. We are also interested in identifying the cellular underpinnings of MR signals. To validate/ corroborate the MRI findings. Our lab is employing cutting-edge quantitative immunohistochemistry based on 2D and 3D microscopic data to determine the cellular basis of MR signals. The overarching goal is to enhance knowledge of neurodegenerative disorders, brain pathology, and function, thereby supporting clinical diagnosis and treatment approaches

Project 1: Translational neurospectroscopy and microstructural markers for mild traumatic brain injury



Project 2: Microstructural and neurometabolic alterations in treatment resistant depression model.



Presentation

Invited Talks

- Khan AR.** MRS principle and applications at NMR based Metabolomics and in vitro Diagnostic Research Workshop: 25 Feb 2025, CBMR, SGPGIMS campus, Lucknow.

2. **Khan AR.** Diffusion MRI principle and applications, at NMR based Metabolomics and in vitro Diagnostic Research Workshop: 26 Feb 2025, CBMR, SGPGIMS campus, Lucknow.

Poster Presentation

3. **Khan AR.** et al. Microstructural Alterations in Mild & Repetitive Mild Close Head Injuries at ISMRM Workshop on 40 Years of Diffusion: Past, Present & Future Perspectives. 15-20 (17th) February 2025 at Kyoto, Japan.

Funding

- ◆ The project works are supported by NBRC Core funds.
- ◆ Ramalingaswami Re-entry Fellowship: Department of Biotechnology.

Collaborators

- ◆ Prof. Senthil Kumaran, NMR Research Centre, AIIMS, Delhi
- ◆ Prof. Deepak Gupta, Department of Neurosurgery, AIIMS, Delhi
- ◆ Prof. (Major) Mamta Sood, Department of Psychiatry, AIIMS, Delhi
- ◆ Prof. Anirban Basu, NBRC, Gurgaon
- ◆ Dr. Dinesh Gupta, CBMR, SGPGIMS Campus, Lucknow
- ◆ Prof. Zafar Neyaz, Department of Radiodiagnosis, SGPGIMS, Lucknow
- ◆ Prof. Zia Hashim, Department of Pulmonary Imaging, SGPGIMS, Lucknow

Scientific Report



Anindya Ghosh Roy

Scientist-VI

Research Associates / Post-doctoral Fellows

- ◆ Swagata Dey (India Alliance Early career fellow)
- ◆ Sibaram Behera (Wellcome-DBT Funded)
- ◆ Sunanda Sharma

PhD Students

- ◆ Pallavi Singh
- ◆ Dhyey Vyas
- ◆ Chakshu Mangal
- ◆ Dikshalee Bassi
- ◆ Ashish Singh
- ◆ Panchal
- ◆ Astha Sharma
- ◆ Sukriti Aggarwal

MSc Students

- ◆ Vibha
- ◆ Arya Patil

Project Assistant

- ◆ Mydhiy Vasudevan (Funded by Wellcome Trust DBT)

Technical Assistant

- ◆ Sumit Mahapatra

Development and repair of neural circuit

Background

The goal of our research team is to understand how neurons and neuronal circuits develop and maintain normal function and regenerate. We are using a variety of approaches to study the development and function of neural circuits in vivo, including genetics, genomics, sub-cellular imaging, laser neurosurgery and optogenetics. Since *C. elegans* is transparent and has a simple nervous system, we can manipulate and observe individual neurons in a living animal.

We are interested in understanding how neurons are polarized during the initial stages of development, how neural circuits respond to injury in adulthood; and how molecular mechanisms such as cytoskeleton dynamics, RNA based mechanisms, and intracellular signalling affect these processes. One major focus is axon regeneration.

Research Outcome during 2024-25

1) Regulation of neuronal microtubule cytoskeleton

Microtubules play an important role in the development and maintenance of the nervous system. It is not clear how microtubules are differentially organized in the dendritic and the axonal compartments of the neuron. We are using *C. elegans* mechanosensory neurons to address these questions. We previously showed that loss of KLP-7, a kinesin-13 family microtubule depolymerizing protein, leads to ectopic neurite extensions in touch neurons, which can be suppressed by the pharmacological destabilization of microtubules (Puri et al., 2021, Dey et al 2024).

To uncover relevant factors involved in the biological pathways governing microtubule regulation in neuron, we conducted a suppressor screen using the neuronal ectopic extension phenotype caused due to loss of kinesin-13 family microtubule depolymerizing protein KLP-7 in *C. elegans*. Interestingly, apart from eleven variants of α (mec-12) and β (mec-7) tubulins, we isolated a variant of cytokinesis associated protein, W02B8.2/citk-1, the kinase-less worm orthologue of mammalian citron-rho interacting kinase (CIT). Little is known about the role of CITK in microtubule regulation in post-mitotic neurons. In this study, we found that the kinase-less worm orthologues of CIT, citk-1 and citk-2 redundantly modulate microtubule stability in the axon-like anterior process and maintain the population of plus-end-out microtubules in the dendrite-like posterior process of the PLM mechanosensory neurons in a cell autonomous manner (Figure 1). In the absence of citk-1, PLM neurons exhibit variable morphological defects including defects in migration, growth, and guidance. Moreover, the neuronal and microtubule phenotypes of loss of both citk-1 and citk-2 were phenocopied by the mutant animals of aspm-1, the worm homolog of abnormal spindle-like microcephaly-associated protein (ASPM), suggesting a genetic association, similar to their association in dividing mammalian cells. These observations suggest that the cytokinesis associated citron kinase and ASPM-1 have non-mitotic roles in *C. elegans* mechanosensory neurons in the regulation of microtubules (Sharma et al 2025/ Manuscript under review).

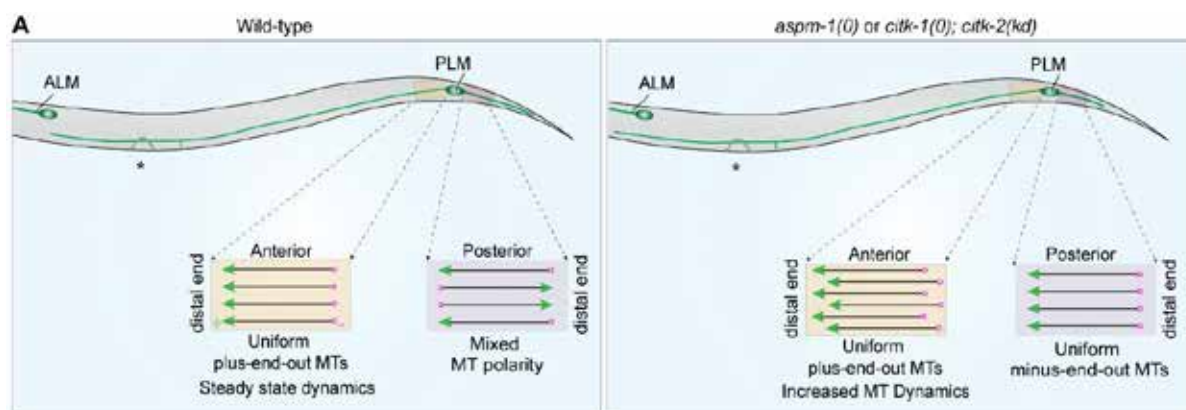


Figure 1: Schematic representation of microtubule dynamics in the anterior and posterior processes of PLM mechanosensory neurons in the wild-type *C. elegans* animals (left panel) and the mutant animals (right panel). The 30 µm ROI in the anterior process (orange rectangular selection) and posterior process (pink rectangular selection) are zoomed-in to illustrate microtubule dynamics in these processes. The black lines represent microtubules, the green arrowhead depicts the plus-ends of microtubules, bound by plus-end-binding proteins and the circular ring depicts the minus-ends of microtubules. The direction of arrowhead shows the direction of microtubule growth. (A) In the wild-type animals the anterior process exhibits a plus-end-out steady-state microtubule dynamics, while the posterior process displays a mixed microtubule polarity. (B) Similar ROI in mutant animals shows increased microtubule dynamics in the anterior process, schematized as increased number of growing microtubules, and a minus-end-out microtubule polarity in the posterior process.

2) Neuronal Regeneration

A) Independent control of functional rewiring after axon injury by let-7 miRNA and Insulin signalling (IIS) pathways

The capability of neurons to regenerate after injury becomes poor in adulthood. Previous studies indicated that loss of either let-7 miRNA or components of Insulin signalling (IIS) can overcome the age-related decline in axon regeneration in *C. elegans*. In this study, we wanted to understand the relationship between these two pathways in axon regeneration. We found that the simultaneous removal of let-7 and the gene for insulin receptor *daf-2* parallelly increased the functional recovery involving posterior touch sensation following axotomy of PLM neuron in adulthood. Conversely, the loss of let-7 could bypass the regeneration block due to the loss of DAF-16, a transcriptional mediator of DAF-2. Similarly, the loss of *daf-2* could bypass the requirement of LIN-41, a transcriptional co-factor of the let-7 pathway. Our analysis revealed that these two pathways independently control targeting of the regenerating axon to the ventral nerve cord, which leads to functional recovery. The computational analysis of the gene expression data revealed a large number of genes, their interacting modules, and hub genes under let-7 and IIS pathway are exclusive in nature. Our study highlights a potential to promote neurite regeneration by harnessing the independent gene expression program involving the let-7 and Insulin signalling pathways. (Figure 2: Ravivarma et al 2025, Journal of Biosciences/ <https://link.springer.com/article/10.1007/s12038-025-00525-3>)

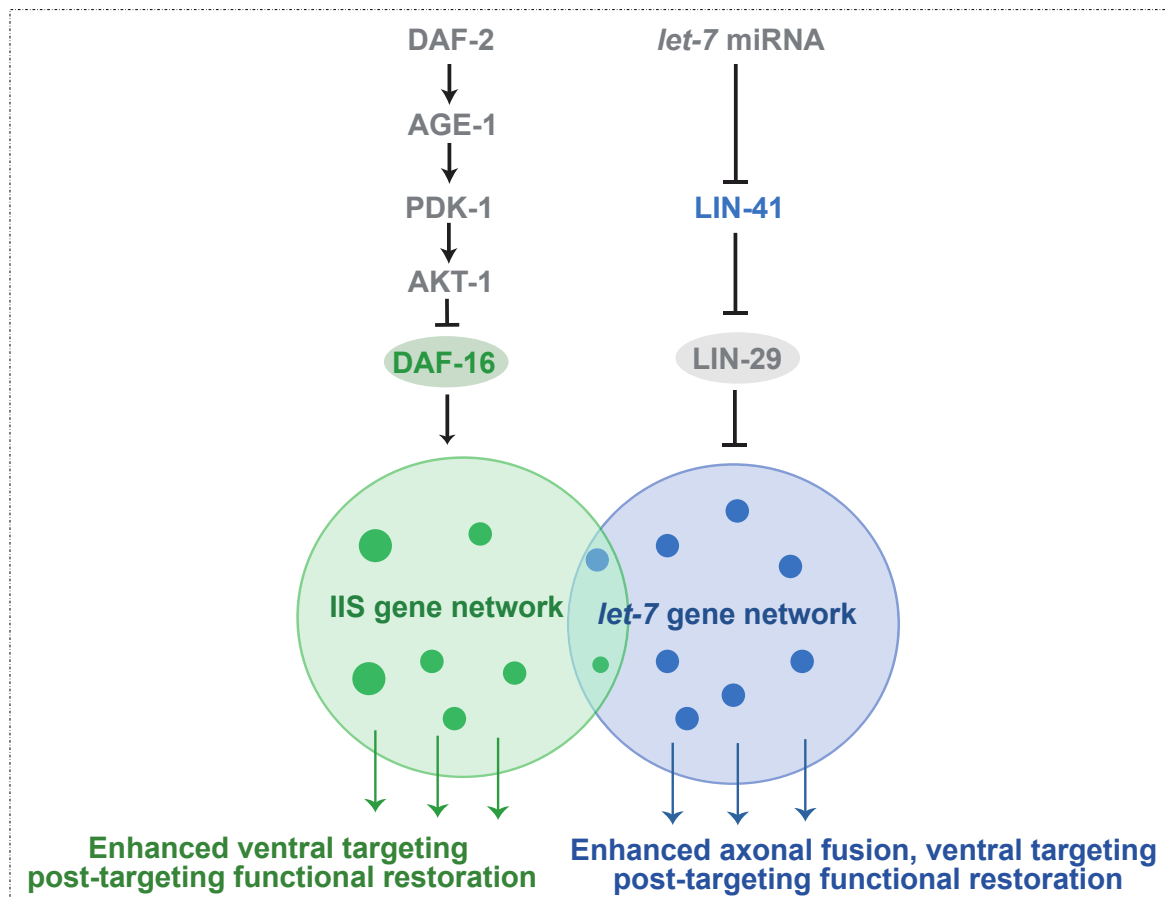


Figure 2: The illustration of Insulin signaling and let-7 pathway controlling differential gene targets and their interacting modules which in turn control various aspects of axon regeneration and associated functional recovery. Filled circles within let-7 and IIS gene network depicts the individual regulatory modules.

B) Exercise-induced differential transcriptional output of AMPK signalling improves axon regeneration and functional recovery

In adulthood, the regenerative capacity of the injured brain circuit is poor, thereby preventing functional restoration. Rehabilitative physical exercise is a promising approach to overcome such functional impairment, and the metabolic sensor AMPK has emerged as a critical mediator for this paradigm. However, the mechanistic understanding of upstream and downstream components of AMPK signalling in the physical exercise-mediated enhancement of axon regeneration is still unclear. In this project, we addressed the question by combining swimming exercise with laser axotomy of *Caenorhabditis elegans* posterior lateral microtubule (PLM) neurons. We found that AICAR-mediated AMPK activation is sufficient to promote axon regeneration and functional recovery. The PAR-4/Liver kinase B1 (LKB1) acts upstream of AMPK to improve functional recovery following swimming exercise. Using genetics, tissue-specific RNAi, and AICAR treatment, we found that the transcriptional regulators DAF-16 and MDT-15 mediate the beneficial effects of swimming by acting downstream of AMPK. MDT-15 functions within neuron to mediate the benefit of AMPK activation in axon regeneration, whereas DAF-16 acts both in neuron and muscle to promote regrowth. Additionally, we demonstrated that swimming exercise induces nuclear localization of DAF-16 in an AMPK-dependent manner. Our results showed that neuronal and non-neuronal arms of AMPK signalling play an integrative role in response to physical exercise to promote functional

recovery after axon injury (Figure 2/ Behera et al 2025/ Manuscript under revision/ doi: <https://doi.org/10.1101/2024.12.08.627390>).

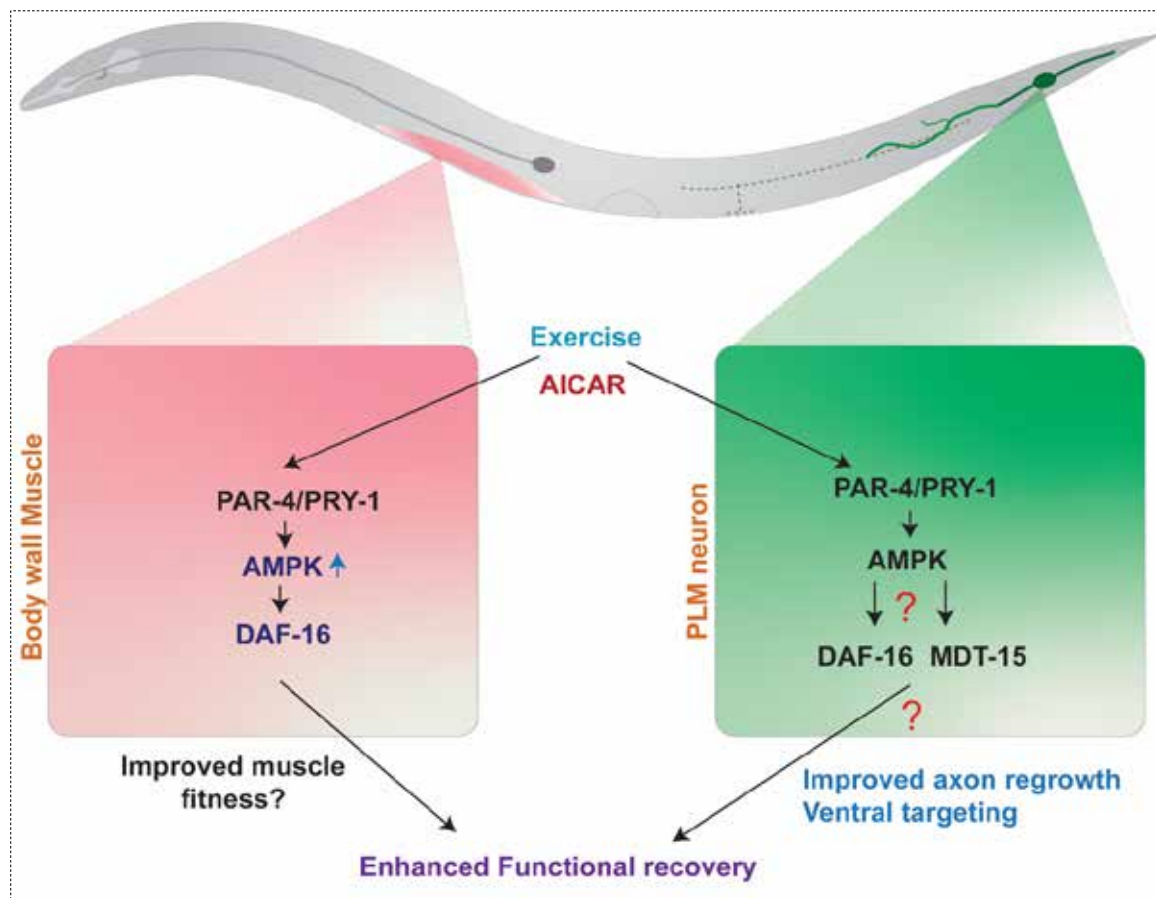


Figure 3: Schematics showing the summary of the AMPK signalling components required in body wall muscle and neuron for enhanced functional recovery after swimming exercise.

C) Study of Dendrite Regeneration using PVD neuron as Model

The information-receiving units of a neuron, dendrites are equally vulnerable to physical insults. However, less is known about dendrite regeneration (Ramón y Cajal, 1991, Thompson-Peer et al., 2016). To understand the mechanisms of dendrite regeneration, we used PVD neurons, having branched dendrites. The PVD neurons are responsible for harsh touch sensation. After the primary dendrite was severed near the cell body, we observed that the regrowth started from the injured tip and continued following a similar trajectory with complex branching patterns. We found that neither initiation of regrowth nor branching is affected by the axon injury pathways. Surprisingly, we found that a small GTPase CED-10 (RAC) and an upstream GEF TIAM-1 is essential for dendrite regeneration. Our work provides a framework for understanding the cellular mechanism of dendrite regeneration using PVD neuron (Brar et al., 2022, PLOS-Genetics).

Over last two years, we developed a high-throughput approach to selectively induce dendrite injury in the PVD neuron, enabling systematic analysis of regenerative mechanisms. We combined this efficient injury method with RNAi to screen through 825 genes that are highly expressed in PVD. We identified key regulators of dendrite regeneration, including the Fibroblast Growth Factor Receptor (FGFR) EGL-15 and its downstream signaling components, regulators of F-actin dynamics, and transcription factors. Moreover, we found that FGFR/EGL-15 is necessary and sufficient within the neuron at an early point after injury to initiate the branching from the

broken dendrite tip, while it is also required in the epidermal tissue to prevent the distal dendrite degeneration. Further analysis revealed that the FGF ligand, EGL-17 functions within the surrounding epithelia for the neuron specific role of EGL-15. Downstream of EGL-15, the GRB2/SEM-5 adaptor dependent signaling arm involving GEF/SOS-1, RAS/LET-60, and MAPK-1/MPK-1 are required for dendrite regeneration. In vivo imaging of GFP::Moesin revealed that FGFR is required for the rapid upregulation of F-actin turnover near the injured dendrite tip. However, this signaling pathway is not required for axon regeneration. In summary, our study identified the conserved FGFR signaling that responds to dendrite injury to initiate the dendrite regeneration through F-actin cytoskeleton and this mechanism is distinct from the signaling pathways, which respond to axon injury (Figure 4/ Singh et al 2025, Manuscript under review).

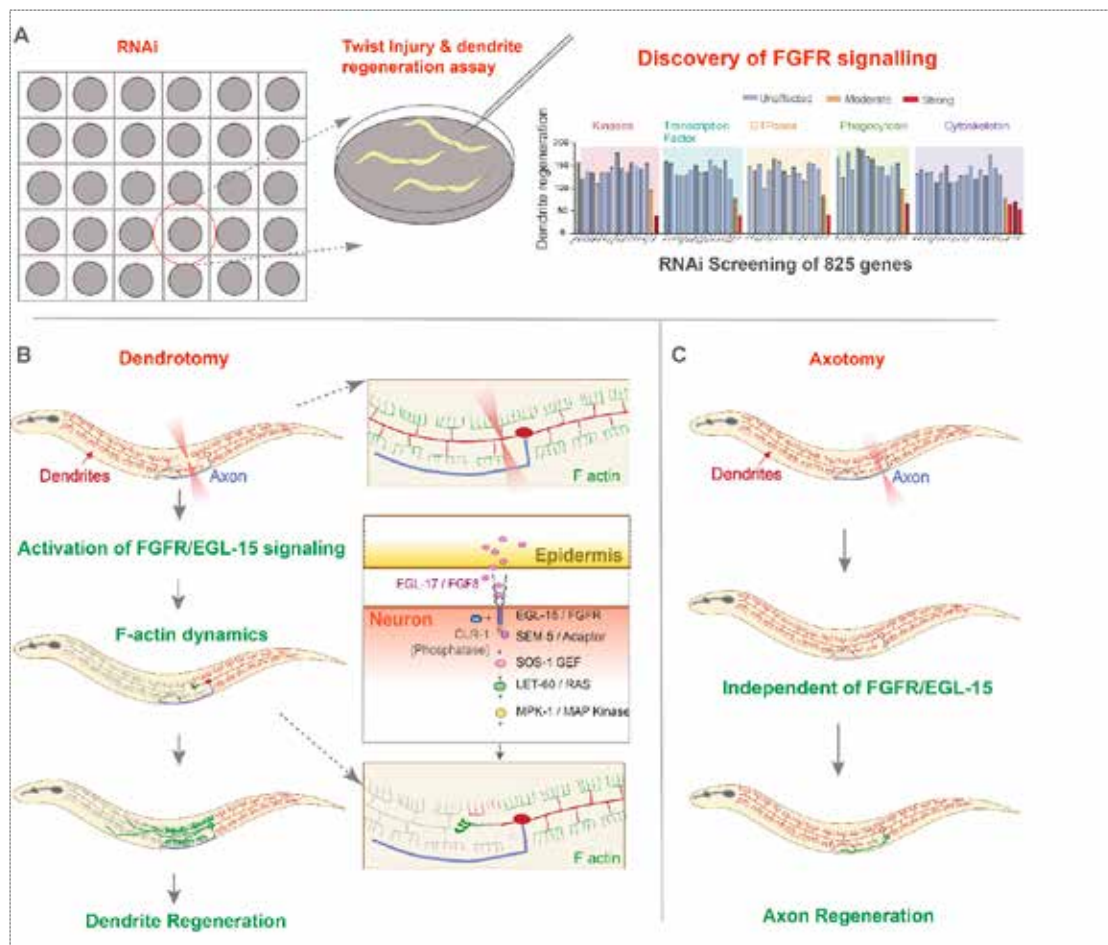


Figure 4: A) Scheme for the discovery of egl-15/FGFR pathway in dendrite regeneration process. This discovery was made in an RNAi screening combined with a new neurosurgery method developed in this study. B) Details of the ligand (EGL-17) dependent activation of FGFR/EGL-15 cascade in the PVD neuron after dendrite injury, which upregulates F-actin polymerization at the broken dendrite tip. This process is essential for dendrite regeneration. C) Axon injury of PVD leads to successful axon regeneration independent of FGFR.

3) New Initiative: Understanding the basis of mental health disorders in behavioural addictions (internet addiction, gaming disorder, eHealth)

Our lab, along with Khushbu Aggarwal (NBRC), Dipanjan Roy (IIT-Jodhpur), and Yatana Pal Singh Balhara (AIIMS New Delhi) has initiated a comprehensive multi-modal research project investigating the neurobiological, neurocognitive, and epigenetic correlates of Problematic Digital Behaviour (PDB) in Indian emerging adults (18-24 years). This investigation employs a

multi-dimensional approach combining behavioral assessment, standardized cognitive testing, multimodal neuroimaging, and epigenetic analysis to establish biological signatures of PDB across multiple levels. The project specifically examines how excessive digital engagement affects brain structure and function in regions responsible for reward processing, impulse control, and emotional regulation during this critical neurodevelopmental period when the prefrontal cortex is still maturing. This research addresses urgent public health concerns, as meta-analyses reveal alarmingly high prevalence rates of internet addiction in India. The findings will contribute to evidence-based screening tools, intervention strategies, and digital wellness policies tailored specifically to the Indian context.

Publications

- 1) Dey S, Kumar N, Balakrishnan S, Koushika SP, Ghosh-Roy A. KLP-7/Kinesin-13 orchestrates axon-dendrite checkpoints for polarized trafficking in neurons. *Mol Biol Cell*. 2024 Sep 1;35(9):ar115. doi: <https://doi.org/10.1091/mbc.E23-08-0335>
- 2) Ravivarma S, Behera S, Roy D, Ghosh-Roy A. Independent control of functional rewiring after axon injury by let-7 miRNA and insulin/insulin-like growth factor signaling pathways. *J Biosci*. 2025;50:24. <https://link.springer.com/article/10.1007/s12038-025-00525-3>
- 3) Brar H K, Bassi D, and Ghosh-Roy A. Analysis and Quantification of Functional Regeneration of Dendrite and Axon of PVD Neuron After Laser Injury in *Caenorhabditis elegans*. *Bio-Protocols*. Vol 15, Iss 8, Apr 20, 2025 DOI: 10.21769/BioProtoc.5280
- 4) S Behera, and Ghosh-Roy A. Exercise-induced differential transcriptional output of AMPK signalling improves axon regeneration and functional recovery, doi: <https://doi.org/10.1101/2024.12.08.627390>
- 5) Pranita Ray, Pallavi T Rao, Mintu Nandi, Afreen Haque, Samrat Mitra, Raychaudhuri, Anindya Ghosh-Roy, and Smarajit Polley. Activation and regulation of a p38 α MAPK by its downstream MAPKAP kinase through feedback phosphorylation and LLPS-driven condensate formation. doi: <https://doi.org/10.1101/2024.08.01.606155>

Presentations

- 1) 2024 Apr 26th, Invited seminar at the Department of Genetics, Delhi University South Campus, Title: "Functional rewiring of neural circuits".
- 2) 2024 June 13th to 16th, Invited seminar at the Asia Pacific Worm meeting-24 (APWM24) at the Indian Institute of Science-Bangalore, Title: "Neural Circuit Repair".
- 3) 2024 June 17th, Invited seminar at the National Centre for Biological Science (NCBS) -Bangalore, Title: "Functional rewiring of neural circuits".
- 4) 2024 Aug 14th Invited seminar at the Centre for DNA Footprinting (CDFD) -Hyderabad, Title: "Regenerating and Reconnecting Neural Circuits".
- 5) 2024 Aug 27th, Invited seminar at the conference "Intracellular Quality and Metabolic Control from E. Coli to Homo Sapiens" at MAHE-MIRM, Bangalore, Title: "Functional rewiring of injured neural circuits".
- 6) 2024 Sept 10th to 14th Presentation at the Cold Spring Harbor meeting: Molecular Mechanisms of Neuronal Connectivity, New York-USA. Title: 'RNAi screening using a new neurite injury protocol reveals FGFR receptor tyrosine kinase signalling underlying dendrite regeneration'

- 7) 2025 Jan 20th, to 22nd Invited talk in the 49th Annual Meeting of ISHG and International Conclave on Neurogenetics at NIMHANS, Bengaluru, India for the session "Modelling of Human Diseases/Regenerative Medicine", Title: "Regenerating and Reconnecting Neural Circuits".
- 8) 2025 Feb 14th to 17th Invited speaker at the Molecular Motors Transport & Tracks (M2T2-2025) at IIT Jodhpur from 17th -19th February. Title: "The conserved Fibroblast Growth Factor Receptor based signaling is required for dendrite regeneration"

Funding

- ◆ India Alliance Wellcome-DBT (IA/S/22/1/506243) - 4.5 Crore - Project title: ""Study of neuronal regeneration using *C. elegans*".
- ◆ NBRC Core

Collaborators

- | | |
|--|---|
| ◆ Sourav Banerjee, NBRC, India | ◆ Khushbu Agarwal, NBRC, India |
| ◆ Smarajit Polley, Bose Institute, Kolkata | ◆ Sandhya Koushika, TIFR, Mumbai, India |

Award

- ◆ Fellow of the National Academy of Sciences, India (NASI)

Degrees Awarded

- | | |
|--------------------------------|-----------------------|
| ◆ Arkaprabha Bhattacharya, MSc | ◆ Sunanda Sharma, PhD |
|--------------------------------|-----------------------|

Meetings/Conferences Organized

Co-organized along with Sourav Banerjee the 21st NBRC Foundation Day Symposium

I helped organize a conference to brainstorm the frontier areas of Neuroscience by bringing scientists inside and outside the country and across various stages of their careers. It was a 3 days conclave engaging renowned experts to invigorate the Brain-research community in this country. The theme was 21st NBRC Foundation Day Symposium was Brain & Society.

Scientific Report



Anirban Basu
Scientist-VII

Doctoral work from the CSIR-Indian Institute of Chemical Biology (IICB), Kolkata & post-doctoral work from Pennsylvania State University College of Medicine, Hershey, Pennsylvania. Dr. Basu's research is primarily directed towards discovering therapeutic strategies to develop disease-modifying therapy by abrogating inflammation in CNS disorders. His recent work indicates the importance of the gut-brain axis, a bi-directional communication network, which is a key area of interest in understanding the process of neuroinflammation and other disease conditions.

Research Fellows

- ◆ Indira S Priya
- ◆ Akasmika Priyadarshini
- ◆ Anirudh S

MSc Student

- ◆ Aashi Makhija
- ◆ Mayghaa Chatterjee
- ◆ Rajyasree Basu

Research Associate:

- ◆ Atreye Majumdar
- ◆ Meenakshi Bhaskar
- ◆ Kamalika Roy

Technician - C

- ◆ Kanhaiya Lal Kumawat

Technician - B

- ◆ Manish Dogra

The Gut-Brain Axis in CNS Inflammation: Molecular Mechanisms and Pharmacological Implications

Japanese Encephalitis Virus (JEV) initiates its infection by entering the host, followed by viral replication in peripheral tissues, which in turn triggers the activation of both innate and adaptive arms of the immune system. Our laboratory has been at the forefront of unraveling the molecular intricacies of the various stages of the JEV life cycle, making significant contributions to the understanding of host-virus interactions. As a member of the flavivirus family, JEV is the leading cause of arthropod-borne human encephalitis across Asia. Similarly, other viruses like West Nile Virus (WNV) and Chandipura Virus (CHPV), which are also vector borne diseases, have also been implicated in causing severe neurological disorders. These viruses primarily replicate in myeloid and lymphoid cells, as well as vascular endothelial cells. JEV, in particular, can persist in the human nervous system in about 5% of cases, and this persistence might explain the neurological sequelae observed in roughly 70% of survivors. Understanding the host's response to these viral infections is crucial for controlling and clearing these pathogens, emphasizing the need for a comprehensive understanding of viral pathogenesis to prevent long-term neurological damage caused by these encephalitic viruses.

Short-chain fatty acids (SCFAs) synthesized in the gut serve as crucial mediators of the intricate gut-brain axis. Our research has illuminated the microRNA-mediated mechanisms by which SCFAs influence an in vitro model of Japanese Encephalitis Virus (JEV) infection. In this study, N9 microglial cells were pre-treated with an SCFA cocktail prior to JEV infection. A comprehensive analysis, including cytokine bead analysis (CBA), immunoblotting, and PCR, was employed to assess key inflammatory markers. microRNA sequencing was conducted using the Illumina HiSeq platform, and bioinformatic tools were utilized for the identification of differentially expressed (DE) miRNAs and Weighted Gene Co-expression Network Analysis (WGCNA). miRNA mimic/inhibitor experiments, coupled with luciferase assays, were performed to explore miRNA-target interactions. Notably, a significant reduction in MCP1 and TNF α levels, alongside decreased phospho-NF- κ B expression, was observed under SCFA treatment. Furthermore, a marked attenuation in HDAC activity and protein expression was recorded. miRNA sequencing revealed 160 DE miRNAs in SCFA+JEV treated cells at 6 hours post-infection (HPI). WGCNA highlighted miR-200a-3p as a hub miRNA, significantly upregulated in SCFA-treated conditions. Through bioinformatic predictions and subsequent validation, the transcription factor ZBTB20 was identified as a target gene for miR-200a-3p. Further miRNA mimic/inhibitor assays confirmed that miR-200a-3p regulated ZBTB20, as well as I κ B α , thereby potentially dampening NF- κ B signal activation downstream.

We have further explored the prophylactic potential of short-chain fatty acids (SCFAs) in JEV-infected animals. Post-natal day 10 BALB/c mice were intraperitoneally injected with either a SCFA mixture (acetate, propionate, and butyrate) or PBS for a period of seven days, followed by JEV infection. The mice were closely monitored for the onset and progression of symptoms. Upon reaching terminal illness, brain tissue was harvested for further analysis. Remarkably, SCFA-supplemented JEV-infected mice (SCFA+JEV) exhibited a delayed onset of symptoms, lower hindlimb clasping scores, reduced weight loss, and improved survival compared to their PBS-treated JEV-infected counterparts (JEV). A significant downregulation of inflammatory cytokines—TNF- α , MCP-1, IL-6, and IFN- γ —was observed in the SCFA+JEV group relative to the JEV-infected control group. Tissue section analysis revealed reduced glial activation in animals receiving SCFA supplementation prior to infection, as evidenced by morphometric analysis of astrocytes and microglia. Furthermore, caspase-3 immunoblotting and TUNEL assays demonstrated a reduction in cellular death post-JEV infection. Our study significantly contributes to the growing body of

evidence supporting SCFAs as potent anti-inflammatory and neuroprotective agents, while expanding their potential application as a supplementary intervention in mitigating JEV-mediated neuroinflammation.

Flaviviruses, transmitted by mosquitoes, are arthropod-borne pathogens that pose a significant global threat to both human and animal health, with the potential to cause widespread public health crises. While various endocytic pathways have been identified for flaviviral entry, the precise role of cellular factors in viral replication and entry remains an area of ongoing investigation. In our study, we have uncovered the crucial role of the Low-Density Lipoprotein Receptor (LDLR), a protein long known for its function as a cholesterol carrier in neurons, yet previously unexplored as an essential host factor for the replication of Japanese Encephalitis Virus (JEV) and West Nile Virus (WNV). To explore this, we employed 10-day-old BALB/c pups and two neuronal cell lines, NSC34 and HT22, of distinct origins, as experimental models. The transient knockdown of the LDLR gene in vitro, via siRNA-mediated gene silencing, drastically reduced viral-specific transcripts and proteins upon viral incubation. Furthermore, flaviviral binding and internalization were significantly impaired in LDLR-transfected cells compared to non-specific eGFP-transfected controls. Antibody neutralization experiments using an LDLR-specific polyclonal antibody further corroborated the essential role of LDLR in viral entry, as it markedly reduced viral uptake in vitro. Additionally, ectopic expression of LDLR through plasmid transfection led to a notable increase in virus replication, reinforcing the receptor's pivotal role not only in viral attachment but also in flaviviral replication. Collectively, our findings establish LDLR as a novel host factor integral to both flaviviral entry and replication, positioning it as an attractive target for future antiviral research.

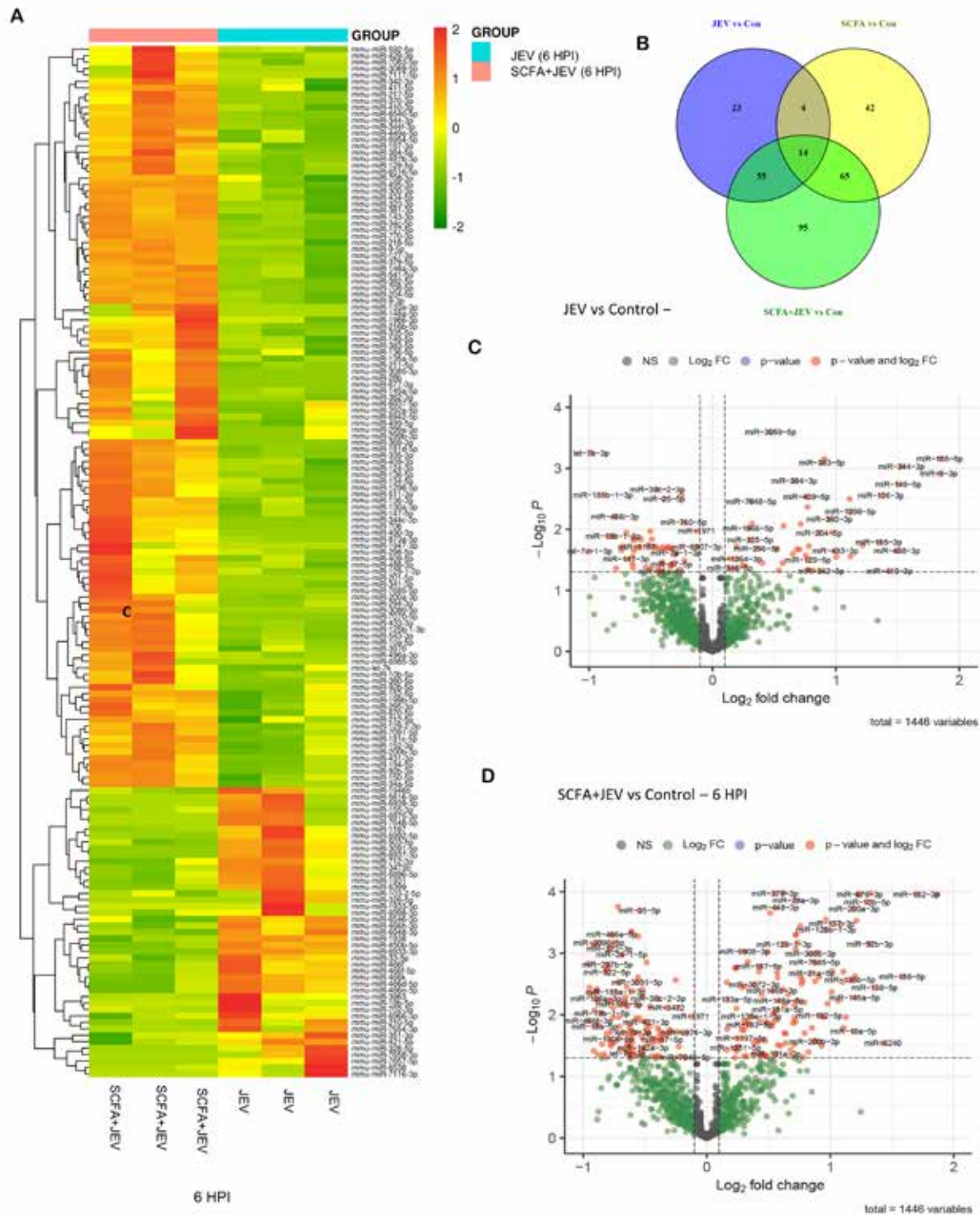


Figure 1: Differential expression analysis of microRNAs post SCFA pre-treatment and/or JEV infection. Small RNA sequencing was performed post SCFA pre-treatment and JEV infection at 3 MOI (A) represents heat map depicting differentially expressed microRNAs in JEV group and SCFA+JEV group 6 HPI (B) Venn diagram showing the number of miRNAs differentially expressed across different conditions (C) Volcano plot showing the differentially expressed miRNAs in JEV group versus control group (D) Volcano plot showing the differentially expressed miRNAs in SCFA+JEV group versus control group.

Publications

1. M Bhaskar, A Satheesan, and A Basu (2025) Low-density Lipoprotein Receptor is an important host factor in flaviviral entry and replication in neurons. *Biophysical Biochemical Research Communication* 443:151160.
2. A Majumdar, I P S Venkatesh, V Swarup, and A Basu (2024) Short-chain fatty acids abrogate Japanese encephalitis virus-induced inflammation in microglial cells via miR-200a-3p/ZBTB20/IK β a axis. *mBio* 15(7):e0132124
3. I P S Venkatesh, A Majumdar, and A Basu (2024) Prophylactic administration of gut microbiome metabolites abrogated microglial activation and subsequent neuroinflammation in an experimental model of Japanese encephalitis. *ACS Chemical Neuroscience* 17;15(8):1712-1727

Presentations

1. A Basu Emerging and Re-emerging Viral Diseases: Host Immunity and Therapeutic Interventions. Durgapur Govt College, 21st August, 2024; DBT Star College event.
2. A Basu The Gut-Brain Axis in Viral Infections: How the Microbiome Affects Brain Inflammation. SIRCON-2024, MGM Institute of Health Sciences, Navi Mumbai. 7th December, 2024. Society of Inflammation Research India, (Oration lecture of Society of Inflammation Research-India)
3. A Basu The Gut-Brain Connection: Unlocking Potential to Revolutionize CNS Disorder Treatment ICCNS-2M- 2025, NIPER, Ahmedabad, 17th-19th February, 2025 (Plenary lecture)
4. A Basu Reimagining Therapeutics: Repurposed Drugs for Emerging Viral Diseases. INSA, science academies lecture workshop, 24th and 25th FEB, 2025, Department of Biotechnology, Dhanalakshmi Srinivasan University, Trichy
5. A Basu Gut Feelings: How the Gut-Brain Axis Influences Brain Health. 24th and 25th FEB, 2025, INSA, science academies lecture workshop, Department of Biotechnology, Dhanalakshmi Srinivasan University, Trichy.
6. A Basu The Gut-Brain Axis Explained: Why What You Eat Matters. Microbes: Miracle or menace "Innovation for health, environment & industry" Dept. of microbiology, Ram Krishna Mission Vivevekananda Centenary College, Rahara, 18-19th March, 2025. (Keynote speaker)
7. A Basu The Microbiome-Gut-Brain Axis: Mechanisms, Nutrition, and Disease Implications. Institute of Health science, Presidency University, Kolkata, 21st March, 2025. (Colloquium speaker)

Funding

- ◆ J C Bose Fellowship (SERB), Starting from November 2021 for five years. (JCB/2020/000037)

Collaborators

- ◆ Vivek Swarup, School of Biological Sciences, UC Irvine, California
- ◆ Vivek Sharma, Department of Biological Sciences, Birla Institute of Technology and Science Pilani, Hyderabad Campus, Hyderabad
- ◆ Ugir Hossain Sk, Senior Scientific Officer, Chittaranjan National Cancer Institute, Kolkata

Degrees Awarded

- ◆ Indira S Priya, PhD

Scientific Report



Arpan Banerjee

Scientist-VI

Post-doctoral Fellows

- ◆ Suman Saha
- ◆ Rashmi Dhamija
- ◆ Dhrubajyoti Biswas

PhD Students

- ◆ Pratika Siwatch
- ◆ Ankit Yadav
- ◆ P. V. Vinitha
- ◆ Medha Bhinwar
- ◆ Dr Prateek

Integrated MSc-PhD Students

- ◆ Ritu Moni Borah
- ◆ Kirti Saluja
- ◆ Vinsea AV Singh
- ◆ Shahswati Tripathi
- ◆ Azman Akhtar
- ◆ Rishabh Bapat
- ◆ Tanmay Singhal

MSc Students

- ◆ Mahima Elsa Joji
- ◆ Atharva Parolekar
- ◆ Austin Varghese

Using network neuroscience to understand disorders of mental health, emotion arousal and brain ageing

Cognitive Brain Dynamics Lab (CBDL) is engaged in basic and translational research using non-invasive neuroimaging tools EEG, MEG, TMS & fMRI. We have primarily two themes of research: 1) Exploring and innovating novel research designs and analysis tools for MEG/ EEG & fMRI recordings and 2) Studying the relationships between in structure and function in the context of whole brain macroscopic neural networks related to various cognitive functions using empirical

and theoretical approaches. Here we outline the major project updates from the period April, 2024 - March, 2025. The overarching goal of these projects is to develop and implement network neuroscience approaches for neurobiological understanding of mental health, ageing related brain functions and emotion arousal.

Project 1: Dynamicity of brain network organization and their community architecture as characterizing features for classification of common mental disorders from the whole-brain connectome.

The urgency of addressing common mental disorders (bipolar disorder, attention-deficit hyperactivity disorder (ADHD), and schizophrenia) arises from their significant societal impact. Developing strategies to support psychiatrists is crucial. Previous studies focused on the relationship between these disorders and changes in the resting-state functional connectome's modularity, often using static functional connectivity (sFC) estimation. However, understanding the dynamic reconfiguration of resting-state brain networks with rich temporal structure is essential for comprehending neural activity and addressing mental health disorders. This study proposes an unsupervised approach combining spatial and temporal characterization of brain networks to classify common mental disorders using fMRI timeseries data from two cohorts (N = 408 participants). We employ the weighted stochastic block model to uncover mesoscale community architecture differences, providing insights into network organization. Our approach overcomes sFC limitations and biases in community detection algorithms by modelling the functional connectome's temporal dynamics as a landscape, quantifying temporal stability at whole-brain and network levels. Findings reveal individuals with schizophrenia exhibit less assortative community structure and participate in multiple motif classes, indicating less specialized network organization. Patients with schizophrenia and ADHD demonstrate significantly reduced temporal stability compared to healthy controls (Figure 1). This study offers insights into functional connectivity (FC) patterns' spatiotemporal organization and their alterations in common mental disorders, highlighting the potential of temporal stability as a biomarker.

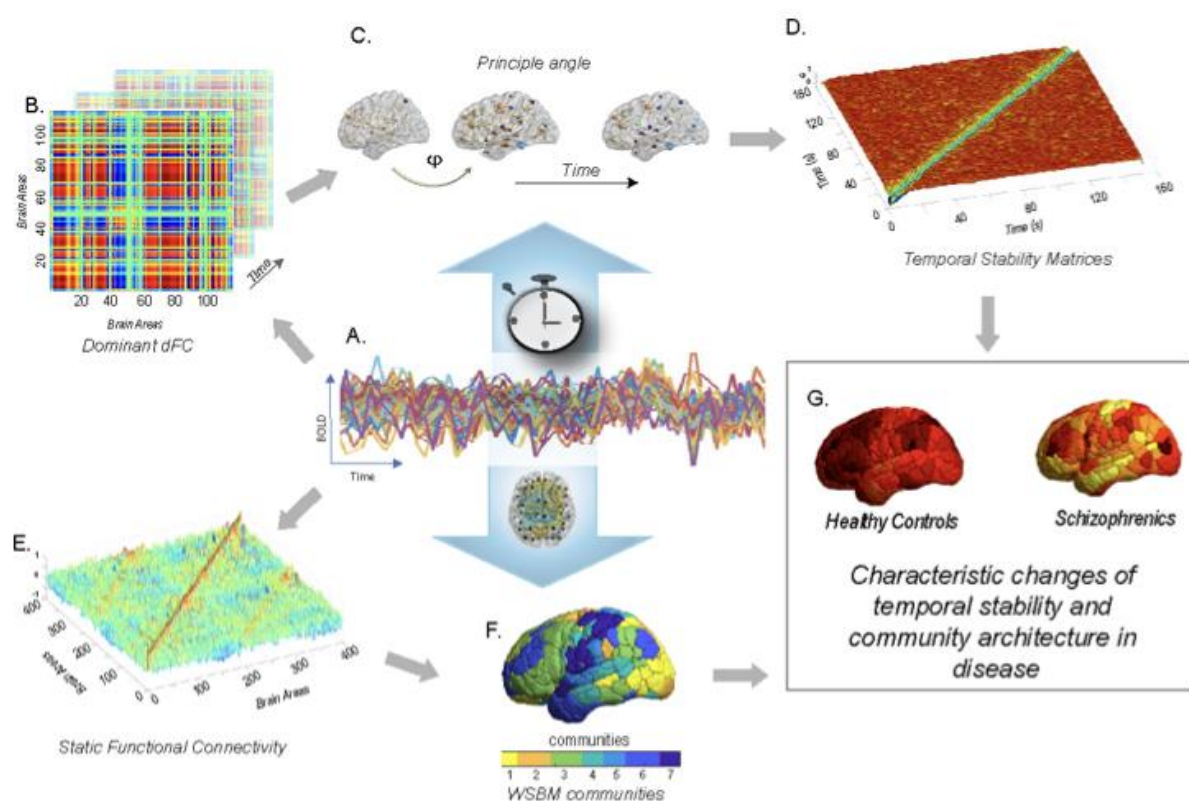


Figure 1: Capturing the dynamicity of brain networks in disorders of mental health using dynamic functional connectivity approaches. A) Shows the BOLD time series data, B) illustrates the estimation of static functional connectivity using Pearson correlation, which is then transformed using the *r*-to-*z* method, C) displays topographic representation of the WSBM communities. The subject-wise undirected, signed, weighted adjacency matrix serves as the input for the Weighted Stochastic Block Model (WSBM), a data-driven generative community detection algorithm that groups brain areas into $K=7$ communities based on their stochastic equivalence. D) Presents the matrix representation of the reduced dominant dynamic functional connectivity (dFC) patterns, denoted as $D(t)$, computed at each time point. E Demonstrates the calculation of similarity between dominant dFC subspaces using angular distance or principal angle ($\angle$). F) Showcases the Time X Time temporal stability matrix, where each entry represents the principal angle between dominant dFC subspaces at time points and. This matrix visualizes the temporal landscape, with the principal angle ranging from 0 (indicating low angular distance) to $\pi/2$ (indicating high angular distance). Constructing a Time X Time temporal stability matrix allows us to visualize the temporal “landscape” for the entire duration of the scan. G) We calculate the temporal stability of the dynamic functional connectome using two measures: entropy and global temporal distance. We investigated changes in community architecture in common mental health disorders such as schizophrenia, bipolar disorder, and ADHD.

Project 2: Contributions of short and long-range white matter tracts in dynamic compensation with aging.

Optimal brain function is shaped by a combination of global information integration, facilitated by long-range connections, and local processing, which relies on short-range connections and underlying biological factors. With aging, anatomical connectivity undergoes significant deterioration, which affects the brain's overall function. Despite the structural loss, previous research has shown that normative patterns of functions remain intact across the lifespan, defined as the compensatory mechanism of the aging brain. However, the crucial components in guiding the compensatory preservation of the dynamical complexity and the underlying mechanisms remain uncovered. Moreover, it remains largely unknown how the brain readjusts its biological parameters to maintain optimal brain dynamics with age; in this work, we provide a parsimonious mechanism using a whole-brain generative model to uncover the role of sub-communities comprised of short-range and long-range connectivity in driving the dynamic compensation process in the aging brain. We utilize two neuroimaging datasets to demonstrate how short- and long-range white matter tracts affect compensatory mechanisms. We unveil their modulation of intrinsic global scaling parameters, such as global coupling strength and conduction delay, via a personalized large-scale brain model. Our key finding suggests that short-range tracts predominantly amplify global coupling strength with age, potentially representing an epiphenomenon of the compensatory mechanism. This mechanistically explains the significance of short-range connections in compensating for the major loss of long-range connections during aging. This insight could help identify alternative avenues to address aging-related diseases where long-range connections are significantly deteriorated.

Project 3: Inhibition of thalamic relay nuclei scales the aperiodic and alpha band oscillations associated with arousal during naturalistic stimulus viewing.

Existing psychological theories posit valence and arousal as two dimensions along which subjective emotions' states are represented. The present study sought to determine whether the emotional ratings projected along the valence–arousal axis during naturalistic stimulus viewing are further mapped in the neurodynamical attributes observed from noninvasive electroencephalography (EEG) in humans and their potential biophysical causes (Figure 2). While

several studies have explored the periodic features of EEG dynamics of emotion processing, very few studies have previously explored the aperiodic (1/f) components vis-à-vis emotion arousal. Recent signal processing developments have established that segregating EEG time series into aperiodic and periodic components provides fundamental insights underlying neural computations, specifically excitatory-inhibitory balance. In this study, we identified that there is a significant increase in exponent and offset of aperiodic background during arousal. In contrast, there were no discernible variations between the aperiodic components during the differential valence scenarios. Reduction in periodic alpha power was observed with high arousal in line with previous studies. Finally, implementation of a biophysically realistic corticothalamic model of neural field activity allowed us to mechanistically explain that both the empirical observations of heightened arousal represented as higher slope of aperiodic background and decrease in power of the periodic alpha oscillations emerge from an increased inhibitory influence to relay nuclei of the thalamus.

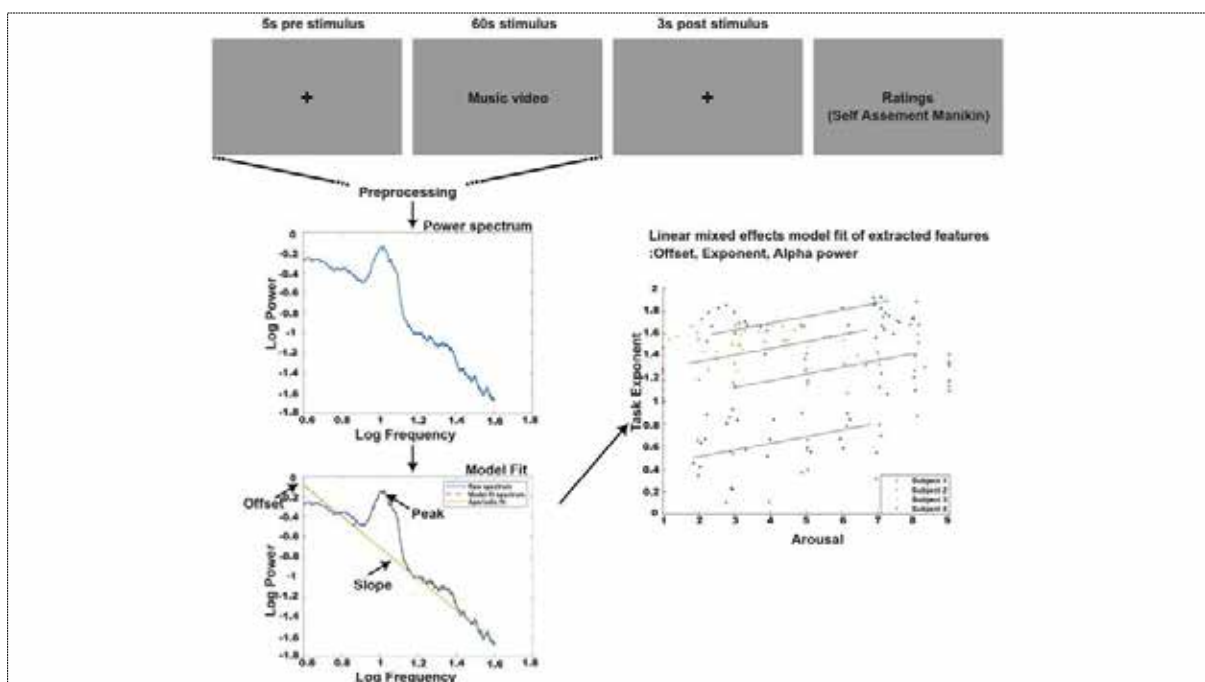


Figure 2: Representation of the stimulus presentation and methodological workflow to study role of aperiodic and periodic signal components in emotion arousal. Each trial consists of a 5-s prestimulus fixation, followed by a 60-s music video, and ends with a 3-s fixation window. After each trial, participants rate Arousal and Valence; additional ratings for Dominance, Liking, and Familiarity were collected but are not included in the current study (see Supplementary Fig. S1 (Koelstra et al., 2012)). The methodological process includes power spectral analysis applied to the EEG data, followed by FOOOF to separate aperiodic and periodic components. Extracted features, such as offset, exponent, and power within specific bands, are then subjected to a linear mixed model analysis to investigate their relationship with the emotional ratings.

Publications

1. Borah, R. M., Pathak, A. & Banerjee, A. (2025) Inhibition of thalamic relay nuclei scales the aperiodic and alpha band oscillations associated with arousal during naturalistic stimulus viewing. *Imaging Neuroscience*.
https://direct.mit.edu/imag/article/doi/10.1162/imag_a_00451/127395

2. Chakraborty, P., Saha, S., Deco, G., Banerjee, A. & Roy, D (2025) Contributions of short and long-range white matter tracts in dynamic compensation with aging. *Cerebral Cortex* 35 (2). <https://doi.org/10.1093/cercor/bhae496>
3. Koshy, B., Thilagarajan, V. V., Berkins, S., Banerjee, A., Manikandan, S., Livingstone, R. S., Mohan, V. R., Scharf, R., Jasper, A., Kang, G. (2025) Childhood brain morphometry in children with persistent stunting and catch-up growth. *PLOS One* 20(2): e0306500. <https://doi.org/10.1371/journal.pone.0306500>
4. Singh, S.S.#, Mukherjee, A#, Raghunathan, P., Ray, D. & Banerjee, A. (2024): High segregation and diminished global integration in large-scale brain functional networks enhances the perceptual binding of cross-modal stimuli *Cerebral Cortex* 34 (8). IF 3.7 <https://academic.oup.com/cercor/article/34/8/bhae323/7728942>.
5. Sorrentino, P., Pathak, A., Ziaemehr, A., Troisi, L.E, Cipriano, L, Romano, A, Sparaco, M, Quarantelli, M, Banerjee, A, Sorrentino, G, Jirsa, V, Hashemi, M, (2024) The virtual multiple sclerosis patient, *ISCIENCE*, doi:<https://doi.org/10.1016/j.isci.2024.110101>.
6. Sastry, N. C. and Banerjee, A. (2024) Dynamicity of brain network organization and their community architecture as characterizing features for classification of common mental disorders from the whole-brain connectome. *Translational Psychiatry* 14 (268). <https://www.nature.com/articles/s41398-024-02929-5>.
7. Ghosh, P#. Talwar, S# & Banerjee, A (2024) Unsupervised characterization of prediction error markers in unisensory and multisensory streams reveal the spatiotemporal hierarchy of cortical information processing *eNeuro*. 11 (5) ENEURO.0251-23.2024. DOI: <https://doi.org/10.1523/ENEURO.0251-23.2024>

Award

- ◆ Elected fellow, National Academy of Sciences of India (NASI, Prayagraj)

Invited Talks

- ◆ Feb 2025: Invited talk at AAIC 2025, AI based connectomics for ageing disorders
- ◆ Feb 2025: Invited talk in CMC Vellore, Whole brain connectomics platform to gain insights to health and disease.
- ◆ August 2024: Invited talk at IISER Berhampore, Whole brain connectomics platform to track health and disease.

Funding

1. Early diagnosis and structural and functional decline of the brain and associated injuries in professional athletes playing contact sports. Department of Sports, Ministry of Youth Affairs & Sports, Feb 2023- Feb 2026 67 lakh INR) on no cost extension
2. AI tools in low MRI settings. Bill and Melina Gates Foundation, Aug 1, 2023 – Aug 2025, 113922 US\$)
3. Co-PI DBT Dementia Programme

Collaborations

- ◆ **Anirban Basu**, NBRC
- ◆ **Ellora Sen**, NBRC
- ◆ **Dipanjan Roy**, IIT Jodhpur
- ◆ **Beena Koshy**, CMC Vellore
- ◆ **Mohammad Dastjerdi**, Loma Linda University

Degrees Awarded

- ◆ Mahima Elsa Joji, MSc

Scientific Report



Bhavani Shankar Sahu

Scientist-IV

PhD Students

- ◆ Chandramouli Mukherjee
- ◆ Shashank Saxena
- ◆ Mohima Mukherjee
- ◆ Krittika Biswas
- ◆ Palki Choukshey
- ◆ Tamanna Saini
- ◆ Shreya Kumari (iBRIC PhD student)

MSc Students

- ◆ Sanchari Banerjee
- ◆ Sourav Chatterjee
- ◆ Upasana Mohapatra

Research Associates

- ◆ Sushma Dagar
- ◆ Puyam Milan Meitei

Lab Technician

- ◆ Mahender Singh

Technical Assistant

- ◆ Ankit Parashar

Cell biology and biochemistry of nerve cells- Implications in health and disease.

Project: Dense core vesicle exocytosis is impaired in obesity associated metabolic stress.

Obesity that disrupts metabolic homeostasis is a major health challenge and a significant risk factor for many diseases, including those associated with the brain. Metabolic homeostasis regulates a wide range of biological processes. Dense core vesicles are specialized organelles in neurons/neuroendocrine cells which release their cargo in response to external stimuli mediated by calcium, and the phenomenon is called regulated secretion. The release of cargo such as neuropeptides and catecholamines during regulated secretion controls adipose, brain, heart, and other organ functions. Defective-regulated DCV exocytosis has been reported in many pathophysiological conditions, including diabetes, obesity, and mental health disorders. In this project, we aim to understand the effect of obesity-associated metabolic stress on regulated exocytosis in neuroendocrine cells by using the diet-induced obesity mice model and mimicking the obesity-associated metabolic stress in PC12 and INS-1 cells.

Eight-week-old C57BL/6J mice (N=22 males) were fed a high-fat diet and the control group received a standard chow diet. All the animals were kept on a 12-hour dark light cycle in the animal house facility of the National Brain Research Centre. We measured the weight changes every once a week and after the 8th week on the high-fat diet, the mouse became obese and gained considerably more weight. After 16 weeks on High-fat diet, we observe a prominent weight gain as shown in Fig 1a (16.09 ± 1.25) high-fat diet group mice as compared to the control group (2.02 ± 0.25).

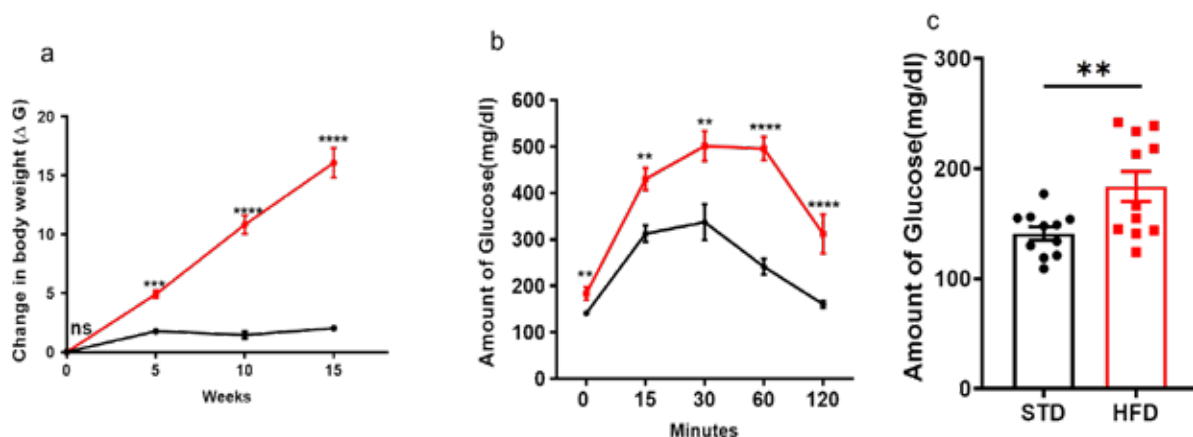


Figure 1: Establishment of diet-induced obesity model in C57BL6/J mice, red traces represent mice fed with 60% calories from High fat diet (HFD), and black traces represent mice fed with standard chow diet (STD). (a) Change in body weight " ΔG " over 15 weeks. (b) Glucose tolerance test performed after 15 weeks of mice fed with HFD and STD indicating establishment of glucose insensitivity. (c) Blood glucose levels after 8 hours of fasting in mice fed with HFD and STD for 15 weeks. Number of mice N=22 (STD=11 and HFD=11)

Next, we studied the change in plasma membrane dynamics in cultured adrenal chromaffin cells by using FM4-64 staining. FM4-64 binds to the plasma membrane of the cells and upon induction of exocytosis using high KCl, there is a fusion of vesicles with the plasma membrane leading to an increase in the surface area of the plasma membrane. FM present in the solution binds to added extra-added membrane. Interestingly, we observed a reduced FM fluorescence

in chromaffin cells from obese mice when compared with control cells (Fig 2) indicating a plausible defect in the fusion of various vesicles (DCVs and SLVs) present in the chromaffin cells.

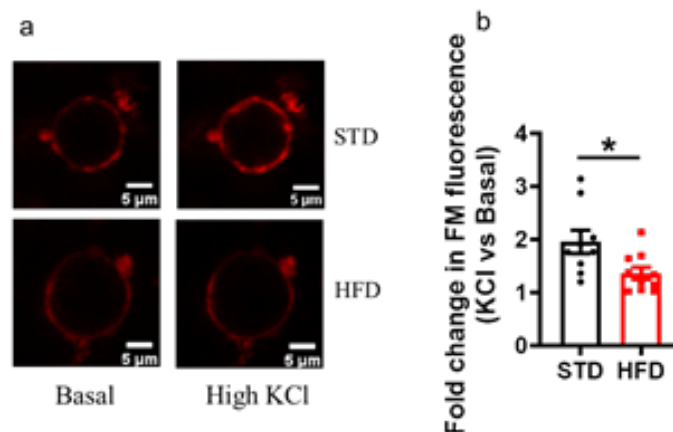


Figure 2: HFD induced metabolic stress reduces exocytosis with respect to STD. (a) Adrenal chromaffin cells isolated from HFD and STD fed mice were labeled with 5 μ M FM4-64 dye for 1 min basal Tyrode solution and then imaged in spinning disk confocal microscopy. Regulated exocytosis was imaged by the addition of an equal volume of 100 mM K⁺ Tyrode's solution (50 mM K⁺ final) after 2 min. Scale bar indicates 5 μ m. (b) Traces represents change in intensity with respect to time. Number of mice, N= (STD=3 and HFD=4); (n = 12 cells from HFD fed mice and n = 8 cells from STD-fed mice). *p < 0.05

Next, we studied the release of synaptic like vesicle (SLV) and used Synaptophysin, a v-SNARE tagged to pH-sensitive GFP (SyphHy). Our initial SyphHy results show a non-significant release as shown (Fig 3c) by maximum SyphHy fluorescence intensities (2.4 ± 0.45) in chromaffin cells from obese mice as compared to the STD mice chromaffin cells (2.4 ± 0.68). This increased SyphHy fluorescence from obese chromaffin cells also showed a trend towards slower decay (Fig 3d) than control cells indicating slower endocytosis. High KCl is a strong secretagogue leading to the release of most of the available vesicles that might be obscuring any changes in exocytosis that can be quantified using pHluorin imaging. This indicates that during metabolic stress, DCVs and SLVs in chromaffin cells are likely to have slower endocytosis as compared to control chromaffin cells, which is shown in Figure 3.

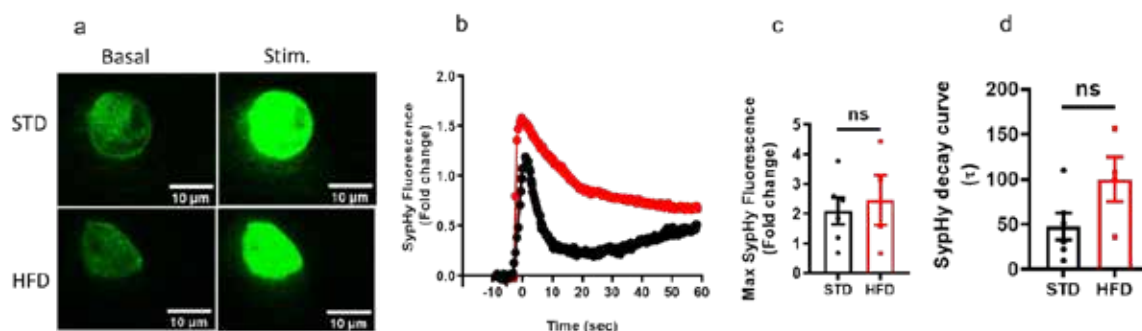


Figure 3: Synaptic like-vesicular dynamics in isolated Adrenal chromaffin cells from mice fed with HFD and STD for 15 weeks using SyphHy (Synaptophysin-pHluorin) live cell imaging. (a) Adrenal chromaffin cells isolated from HFD and STD fed mice were transfected with SyphHy and then imaged live by spinning disk confocal microscopy for 10s in basal Tyrode's solution. Regulated exocytosis was triggered by the addition of an equal volume of 100 mM K⁺ Tyrode's solution (50 mM K⁺ final) and imaged for an additional 1min. Scale bar indicates 10 μ m. (b) Traces represent fold change in intensity with respect to time.

to time. (c) Bar graph shows the maximum fluorescence intensity after stimulation for each cell. (d) Bar graph shows the half-life of synaptic like vesicles tagged with SyPhy by decay curve fit analysis. Multiple comparison statistical analysis was performed by non-parametric student *t*-test, ns: non-significant relative to stimulated exocytosis from isolated adrenal chromaffin cells. Number of mice $N=6$ (STD=3 and HFD=3); ($n = 4$ cells from HFD fed mice and $n = 6$ cells from STD fed mice).

Cytosolic calcium influx in chromaffin cells: Cytosolic calcium is one of the key components determining the release of vesicles. Therefore, next we examined the levels of cytosolic calcium in chromaffin cells using Fluo 4 AM. High KCl-induced membrane depolarization resulted in a large calcium influx leading to an increase in fluorescence intensity of Fluo 4 AM on binding with cytosolic Ca^{2+} (Fig.4). Maximum fold change in Fluo 4 AM fluorescence for chromaffin cells from obese animals is (fold change is 3.7 ± 0.75) as compared to control chromaffin cells (fold change is 3.3 ± 0.81) and were not significantly affected suggesting that calcium dynamics is not affected in metabolic stress condition.

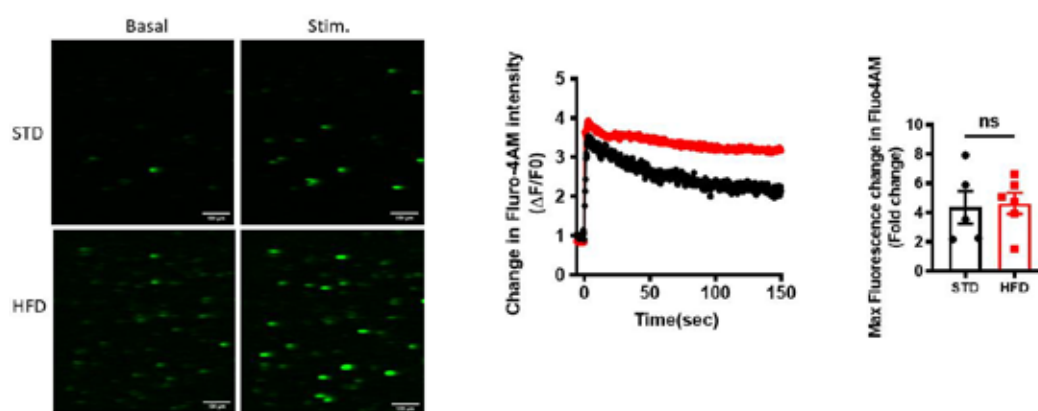


Figure 4: Intracellular Calcium flux of isolated Adrenal chromaffin cells from HFD and STD mice for 15 weeks, which shows non-significant changes. (a) Adrenal chromaffin cells isolated from HFD and STD fed mice were labelled with Fluo-4, AM dye for 30 mins followed by de-esterification basal Tyrode solution and then imaged live by spinning disk confocal microscopy for 1 min in basal Tyrode's solution. Regulated exocytosis was triggered by the addition of an equal volume of 100 mM K^+ Tyrode's solution (50 mM K^+ final) and imaged for an additional 2 mins. Scale bar indicates 100 μm . (b) Traces represents change in intensity with respect to time. (c) Bar graph shows the maximum fluorescence intensity after stimulation for each experiment. Multiple comparison statistical analysis was performed by non-parametric student *t*-test, ns: non-significant relative to stimulated exocytosis from isolated adrenal chromaffin cells. Number of mice $N=6$ (STD=3 and HFD=3) ;($n = 6$ experiments from HFD fed mice and $n = 5$ experiments from STD fed mice).

Dextran

FM labels all forms of regulated exocytosis and cannot differentiate various modes of exocytosis. Therefore, we used another fluorescence-based method to differentiate the formation of various types of the fusion pore and the resulting endocytosis events. Chromaffin cells were loaded with fluorescent Dextran (10 kDa or 40 kDa), a large inert fluid-phase marker dissolved in high K^+ . Kiss and Run (KAR) result in the uptake of 10kDa dextran into the vesicles while the uptake of large dextran (40 kDa) happens via full fusion events. Our initial results showed a similar 10 kDa dextran uptake in chromaffin cells from obese mice and control mice (Fig 5b). Interestingly, we observed a trend towards reduction in the number of 40 kDa dextran puncta in chromaffin

cells from HFD induced obese mice as compared to control mice (Fig 5d), indicating a defect in endocytosis/ DCV recycling.

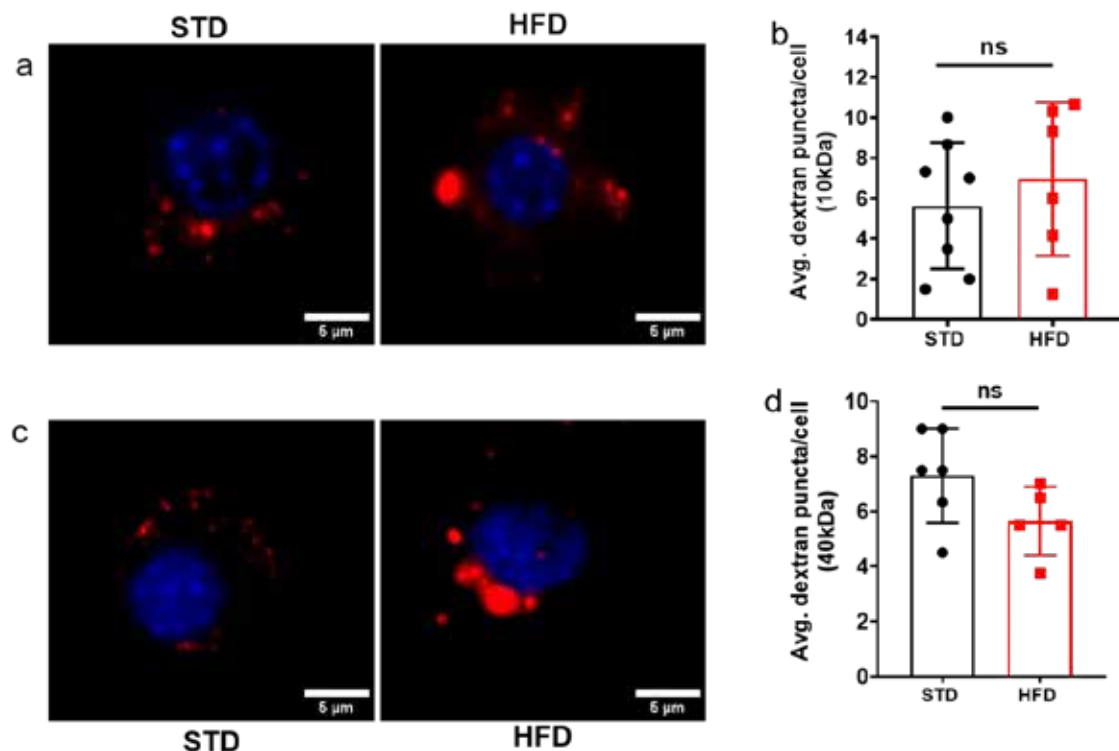


Figure 5: Obesity induced metabolic stress reduced the endocytic uptake of 10 kDa dextran in Adrenal chromaffin cells. (a) Representative images showing the uptake of 10 kDa TMR-dextran (red) during 100 mM KCl stimulation for 5 mins in cells isolated from STD fed mice and HFD fed mice (b) Bar graph shows average puncta density of 10 kDa dextran/cell, both STD mice and HFD mice isolated Adrenal chromaffin cells showed similar 10kDa dextran uptake. Number of mice, N= (STD=3 and HFD=4); (n = 8 cells from HFD fed mice and n = 6 cells from STD fed mice). (d) Representative images showing the uptake of 40 kDa TMR-dextran (red) during 100 mM KCl stimulation for 5 mins in chromaffin cells from STD mice and HFD fed mice. DAPI (blue) is used to label the nucleus. (d) Average puncta density of 40 kDa dextran/cell. Chromaffin cells from HFD-fed mice showed a reduced uptake of large dextran (40 kDa) indicating a defect in full fusion events (exocytosis). Number of mice, N= (STD=3 and HFD=4); (n = 5 cells from HFD fed mice and n = 6 cells from STD fed mice); ns = non-significant.

Electron microscopy

To evaluate the changes in DCVs at the ultrastructure level during metabolic stress conditions, we performed electron microscopy on adrenal medulla samples from obese and control mice and found a significant increase in DCV diameter in obese chromaffin cells as compared to STD chromaffin cells. This increase in vesicle diameter is likely caused by the recycling defect of DCVs in metabolic stress conditions.

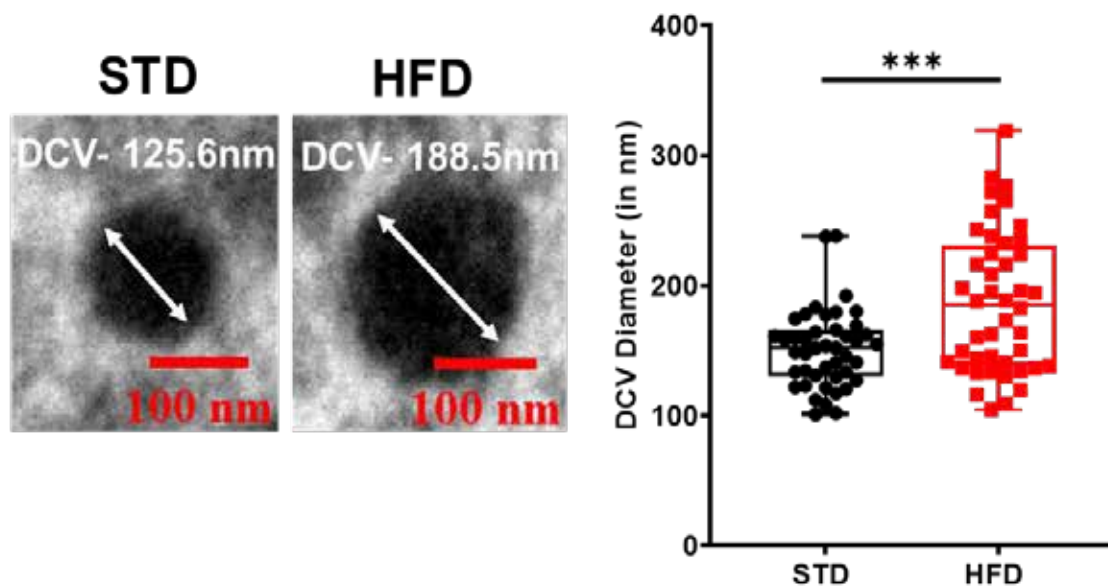


Figure 6: Electron microscopy of adrenal medulla from STD (control) and HFD (obese) mice. (a) Representative images showing a single dense-core vesicle from STD and HFD adrenal medulla samples. Scale bar: 100 nm. (b) Quantification of the dense-core vesicle diameter indicating larger vesicle diameter in case of HFD fed obese mice chromaffin cells as compared to control. Data is represented as mean $\pm$ SEM; Number of adrenal glands $n=4$; STD =3 and HFD=3)

Conclusion

Obesity has emerged as a global health threat and is strongly associated with an increased risk of metabolic disorders such as diabetes and cardiovascular dysfunction. High-fat diet (HFD)-induced obesity animal models effectively recapitulate the features of human obesity. In this study, we investigated the effect of obesity-induced metabolic stress on regulated exocytosis in chromaffin cells. We observed a significantly higher weight gain in HFD-fed animals as compared to standard chow diet animals. Fasting glucose levels were significantly higher in HFD-fed animals indicating a defect in glucose clearing capability of these animals. We performed FM-staining to study the change in plasma membrane dynamics in chromaffin cells. FM labels both dense-core vesicles and synaptic-like vesicles. The change in FM fluorescence levels in response to high KCl were significantly lower in the chromaffin cells from HFD-fed animals as compared to control indicating a defect in regulated exocytosis. We performed SypHy imaging to study the synaptic-like vesicle cycling and Initial data shows that SypHy exocytosis seems not be affected however we observed a trend towards slower endocytosis as shown by tau. Additionally, analysis of different modes of exocytosis showed a selective decrease in the 40 kDa band, indicating a specific impairment in the full fusion mode of exocytosis (Figure 5). Calcium plays an important role in vesicle exocytosis and we found that calcium dynamics was not significantly different in chromaffin cells from both control and HFD-fed animals. Electron microscopy revealed a significant change in the DCV diameter in the chromaffin cells isolated from HFD-fed animals as compared to the control chromaffin cells isolated from STD animals. All these results indicate that HFD-induced metabolic stress leads to the defects in the regulated exocytosis.

Publications

1. Protective role of Pten downregulation in Huntington's Disease models. Nisha, Deepti Thapliyal, Bhavya Gohil, Aninda Sundar Modak, Sanchi Ahuja, N. Tarundas Singh, Sahu BS, Dhruva M Singh. Mol Neurobiol (2025)
2. Sida cordifolia, a medicinal plant, is efficacious in models of Huntington's disease by reducing ER stress. Prasanna K Simha, Chandramouli Mukherjee, Karishma Bhatia, Vikas Kumar Gupta, Neerav M Sapariya, Padmanabhi Nagar, ZA Azim Nazeer, Ashwini Godbole, Sahu BS, Sanjeev K Upadhyay. Front. Mol. Biosci. Sec. Cellular Biochemistry Volume 12 - 2025 (Joint corresponding author with equal first author contribution of PKS and CM)
3. Razzoli M, McGonigle S, Sahu BS, Rodriguez P, Svedberg D, Rao L, Ruocco C, Nisoli E, Vezzani B, Frontini A, Bartolomucci A. A key role for P2RX5 in brown adipocyte differentiation and energy homeostasis. Adipocyte. 2024 Dec;13(1):2421745.

Funding

- ◆ Pratikhsa Trust (Infosys), ICGEB Grant from Trieste, IBRO, Paris.
- ◆ SERB Startup grant.

Collaborators

- ◆ Sanjeev Upadhyay MSU Baroda
- ◆ Ashwini Godbole TDU Bangalore

Award

- ◆ Ignite Research Foundation

Degrees Awarded (MSc)

- ◆ Aamna Jain
- ◆ Mohima Mukherjee
- ◆ Shivam Malviya
- ◆ Aninda Sundar Modak
- ◆ Ankita Roy

Meetings/Conferences Organized

Regional Young Investigator Meeting (RYIM)-jointly organized with Ashoka University, 19-21st March 2025

Scientific Report



Dhananjay Huilgol

Scientist-IV

Dr. Dhananjay Huilgol started his laboratory at NBRC as Scientist IV (Associate Professor) in January 2025. He received his PhD training at the Tata Institute of Fundamental Research, Mumbai for studying novel neuronal migrations in the olfactory system. His postdoctoral training was at Cold Spring Harbor Laboratory and Duke University in cortical development, before he joined NBRC as a faculty.

PhD Student

◆ Sumit Singh

Developmental basis of cell type diversification and forebrain circuit assembly

Cells of our body execute varied and specialized functions such as physical contraction, hormone secretion and sensory perception. Across the body, they can be grouped based on their structural and molecular properties, the function they serve, and their evolutionary history, thereby allowing a systematic study of 'cell types' of the physiological system they form. This approach has been used to understand the relationship between the organization and function of complex systems, leading to targeted therapies. However, this is challenging in the nervous system, since neurons are multifaceted cells with diverse structural, molecular and functional properties that form only partially overlapping groups. Therefore, to understand how the nervous system functions may necessitate an understanding of the assembly, organization and function of its constituent cell types, which can be achieved through studying the development of cell type identities from progenitors. Gene regulatory programs in specific progenitor populations are activated through a series of proliferation and differentiation events generating diverse cell types. Therefore, the central question that my lab focuses on is what cellular and gene regulatory mechanisms drive the differentiation of diverse neuron types from progenitor pools to build a functional nervous system.

Presentation

- ◆ Dhananjay Huilgol "Title: Role of progenitors in cortical circuit assembly" NBRC, Manesar February 2025

Collaborator

- ◆ Dr. Arpan Parichha, CSIR-Institute of Genomics and Integrative Biology (CSIR-IGIB), New Delhi, India

Scientific Report



Ellora Sen
Scientist-VII

Dr. Ellora Sen's research group focuses on understanding how deregulated metabolism and aberrant inflammation influence the epigenetic landscape in glioblastoma, the most aggressive form of brain cancer. Through a combination of epigenetic, biochemical, and cell biological approaches, their work has revealed the presence of distinct metabolic-epigenetic landscapes in gliomas with different molecular profiles, which can serve as valuable prognostic indicators. By analyzing the interactions between these critical factors, the team has identified mechanisms that impact chemosensitivity and has provided new insights into the development of more effective anti-glioma therapies. Their finding suggested how assessment of distinct epigenomic architecture could serve as a predictive biomarker in determining responsiveness to chemotherapeutics.

Research Fellows

- ◆ Kirti Lathoria
- ◆ Archismita Chatterjee
- ◆ Sonia Umdor
- ◆ Prateek Pandey
- ◆ Anushka Srivastava

Technical Assistant

- ◆ Shanker Datt Joshi

Lab Attendant

- ◆ Rajesh Kumar Kumawat

Harnessing Metabolic and Epigenetic Pathways in Gliomas: A New Approach to Chemotherapy

Background and significance

Tumors are characterized by disrupted metabolism, chronic inflammation, and a reprogrammed epigenetic landscape. Numerous studies have mapped out the molecular

networks connecting specific genetic alterations to distinct metabolic phenotypes. The effect is bidirectional as metabolic reprogramming results in modification of the cancer genome through epigenetic, transcriptional and posttranslational modifications. In glioblastoma multiforme (GBM), the most aggressive form of brain cancer, the intersection of metabolic and epigenetic pathways within the tumor microenvironment influences genes linked to resistance to chemotherapeutic agents. Since metabolic reprogramming and epigenetic changes in gliomas with varying driver mutations can differentially affect chemoresistance, investigating how these metabolic vulnerabilities can be targeted therapeutically to enhance chemosensitivity is crucial for developing more effective treatments. In collaboration with AIIMS-Delhi, we investigate the inter-connection between the epigenome and anti-proliferative signatures in gliomas.

1. Mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2) occur in the vast majority of grade II/III gliomas and secondary glioblastomas (grade IV gliomas). IDH1 decarboxylates isocitrate to α -ketoglutarate (α -KG), and IDH1 mutation is associated with a gain of function activity that converts α KG to D-2-hydroxyglutarate (D-2HG). Aberrant accumulation of oncometabolite D-2-HG, is a characteristic feature of gliomas with neomorphic, gain-of-function, hotspot mutations in the IDH genes. IDH1 mutation is known to establish CIMP (CpG island methylator phenotype) by remodeling the methylome and transcriptome; with mutant IDH1 established G-CIMP-positive glioblastomas being predictive of improved survival. IDH mutations are associated with slower growing tumors, better sensitivity to therapy, as well as more favorable disease outcome; and have therefore been established as important prognostic markers in glioma. As dysregulated metabolism is closely linked to inflammation, oncogenic signaling and tumour maintenance, defining how glioma cells coordinate their gene expression in a constantly evolving metabolic-inflammatory milieu will provide new avenues for therapeutic interventions. To identify clinically actionable target genes associated with improved prognosis in IDH1-mutant (IDH1MT) gliomas, we conducted genome-wide methylation profiling using the Infinium Methylation EPIC v2.0 array on patient-derived IDH1-wildtype (IDH1WT) and IDH1MT glioma tissues. The methylation data pointed towards the roles of suppressor of cytokine signaling 3 (SOCS3), lipid metabolism, and actin organization. Currently, our research focuses on investigating clinically relevant targets that regulate: (i) SOCS3-dependent chemoresistance, (ii) the lipid metabolism-cell death axis, and (iii) the inter-regulation between actin filaments and inflammation in the context of the IDH1 mutation.
2. Temozolomide (TMZ) is the frontline chemotherapeutic drug against glioblastoma. As chemoresistance is a severe limitation of TMZ therapy, we synthesized a novel drug by conjugating TMZ with Naphthalimide (known DNA intercalator) via selenourea linkage (redox regulator). In this novel compound, Naph-Se-TMZ, TMZ acts as an alkylating agent, selenium as a ROS generator, and naphthalimide serves as a DNA intercalator. The synthesized Naphthalimide-selenourea-TMZ (Naph-Se-TMZ) elevated ROS levels and exhibited heightened cell death in TMZ-sensitive and TMZ-resistant glioma cells compared to an equivalent dose of TMZ. A ROS-dependent HDAC1 inhibition and decreased total HDAC activity were observed upon Naph-Se-TMZ treatment in glioma cells. Several studies have reported the use of HDACi in combination with chemotherapy as a potential therapeutic strategy. Importantly, the concomitant increase in HDAC1 and antioxidant enzymes expression levels in glioma patients with dismal prognosis (as indicated from TCGA dataset), underscores the importance of HDAC1 in counteracting ROS-induced damage through regulation of antioxidant defenses. The potential of Naph-Se-TMZ to act as an HDAC inhibitor and ROS generator while retaining the functionality of TMZ highlighted its

effectiveness as a potential anti-glioma drug in addressing issues of TMZ chemoresistance. Our findings underscore the potential of Naph-Se-TMZ as a more effective therapeutic alternative to TMZ for glioblastoma treatment.

Publications

- ◆ Sharma S, Roy R, Vartak A, Sen E, Sk UH. Synthesis and characterization of a novel Naphthalimide-Selenium based Temozolomide drug conjugate in glioma cells. Bioorg Chem. 2024 Nov 26;154:107998.

Patent

- ◆ "Naphtalimide-Se-TMZ compound and a method of preparing the same" Indian Patent filed in collaboration with Dr Ugir Hossain Sk CNCI, Kolkata

Presentations

1. "Epigenetic Regulation and Metabolic Reprogramming in Glioma: Therapeutic Perspectives". Presidency University, Kolkata, August 2024
2. Targeting the metabolism- inflammation interface in brain tumors: Therapeutic Implications. 90th Anniversary General Meeting. Indian National Science Academy (INSA) Dec 2024, SRM University
3. Metabolic-Epigenetic Shifts in Gliomas: Role of IDH1 Mutation. Indian 49th Indian Society for Human Genetics, NIMHANS, Bengaluru, January 22nd, 2025
4. Targeting metabolic vulnerabilities in Glioma: The IDH1 story International Conference on Central Nervous System Disorders: From Mechanisms to Medicine 2025 (ICCNS2M-2025) National Institute of Pharmaceutical Education and Research (NIPER) Ahmedabad February 17th 2025
5. "Metabolic Moonlighting": Regulators of Glioma Gene Networks. Transcriptional Assembly Meeting, Bose Institute, Kolkata, March 2025

Others

- ◆ Science and spirituality. "Swami Vivekananda Memorial Lecture", Dept of Philosophy. Ramakrishna Mission Vidyamandira, Belur, Howrah, August 2024

Funding

- ◆ SERB-POWER (Promoting Opportunities for Women in Exploratory Research) Fellowship, 2022
- ◆ Centre for Advanced Research (CAR) by Indian Council of Medical Research (ICMR) sanctioned project "Transforming CNS Tumor Care: Harnessing Histopathological Data, Multi-omics, and Artificial Intelligence for Precision Diagnosis and Effective Management" March 2024 (5 years). Ellora Sen Co-PI in collaboration with Vaishali Suri (PI) AIIMS, Delhi

Collaborators

- ◆ Dr. Vaishali Suri. Professor, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi
- ◆ Dr. Ugir Hossain Sk, Chittaranjan National Cancer Institute, Kolkata

Awards

- ◆ Elected Fellow, Indian National Science Academy INSA

Scientific Report



Khushbu Agarwal
Scientist-III

She holds a Ph.D. in Magnetic Resonance Imaging from the Department of NMR and MRI at the All-India Institute of Medical Sciences (AIIMS), New Delhi, and completed her postdoctoral training at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health (NIH), USA. She is currently a Scientist III and Assistant Professor at the National Brain Research Centre (NBRC), where she is establishing a lab focused on Neuroimaging and Chemosensory Processing in Addiction.

Olfactory-Driven Neural Dynamics in Addiction & Neuropsychiatric Conditions

Our laboratory is driven by the need to identify mechanistically grounded, clinically relevant brain markers that can explain vulnerability to addiction and neuropsychiatric disorders beyond traditional symptom-based classifications. We focus on olfaction because it uniquely interfaces with limbic, reward, and affective circuits that are central to craving, emotional dysregulation, and compulsive behavior. Clinical observations of impaired odor identification and heightened cue reactivity in individuals with substance use disorders and anxiety motivated us to examine olfactory-driven neural dynamics as a transdiagnostic window into brain dysfunction. By integrating behavioral olfactory and physiological measures with functional neuroimaging (task and resting state), MR spectroscopy, DTI and computational modeling, our research asks how individual differences in olfactory processing reflect underlying circuit-level alterations that confer risk for addiction and psychiatric illness. This framework allows us to move from descriptive associations toward predictive, biologically informed models that link sensory processing, emotional state, and maladaptive behavior.

Publications

- ◆ Agarwal K, Chaudhary S, Tomasi D, Volkow ND, Joseph PV. Prediction of alcohol intake patterns with olfactory and gustatory brain connectivity networks. *Neuropsychopharmacology*. 2025 Feb 17. doi: 10.1038/s41386-025-02058-7. Epub ahead of print. PMID: 39962224.

Funding

- ◆ NBRC Core, DBT Ramalingaswami Fellowship

Collaborators

- ◆ Dr. Yatan Pal Singh Balhara, Dr. Siddharth Sarkar, AIIMS, New Delhi; NDDTC, Ghaziabad.
- ◆ Dr. Anindya Ghosh and Dr. Arpan Banerjee, NBRC

Scientific Report



Mayanglambam Dhruba Singh
Scientist-IV

Dr. Dhruba received his Ph.D. from the University of Delhi and pursued his postdoc from Pennsylvania State University and the University of Florida, USA. His lab is interested in neurodegenerative and neurodevelopmental disorders.

PhD Students

◆ Deepti Thapliyal ◆ Athira Sarath ◆ Dipti Chakraborty ◆ Saurabh Bajpayee

MSc Student

◆ Ritu Sarkar

Research Associate

◆ Naorem Tarundas Singh

Project Associate

◆ Bhawna Dahiya

Lab Technicians / Assistants

◆ Mithilesh Kumar-Technician B ◆ Hari Shankar- Technician A

Investigation of the protective role of Pten Knockdown in HD models

Our lab is interested in human neurodegenerative disorders, such as Huntington's disease, Spinocerebellar ataxia 3, and Alzheimer's disease, and in finding novel molecular targets for these disorders. We used the *Drosophila* model to study human neurodegenerative disorders. Large genetic screens are performed to identify molecular targets that could suppress these disorders. The *Drosophila* external eye morphology was used as a read-out of the phenotype. For example, the expression of mutant Huntington protein (Htt.ex1.Q138) or Ataxin-3 (SCA3-Q78) with expanded poly(Q) repeats caused roughness of the eye. A genetic screen was performed in this rough eye background to identify molecular targets of Poly(Q) expressing mutant protein. The knockdown of Pten showed a substantial level of protection in Poly(Q) disorders in the *Drosophila* eye, which showed remarkable improvement in eye pigmentation, roughness, and vision. Pten is a tumour suppressor and negative regulator of Insulin signalling.

Our further analysis revealed the improvement in the eye retinal tissue restoration and improvement in the retinal eye at the pupal stage. The flies expressing Htt.ex1.Q138 do not survive as the control flies. The knockdown of Pten improved the survival of the flies. Furthermore, the mutant Htt caused defects in motor ability and inability to climb the surface of the plastic vial. However, the knockdown of Pten improved this ability to climb the surface of the plastic vial. To check the motor neurons, the thoracic muscle of *Drosophila* was dissected and stained with HRP to analyse the axon projections of the motor neurons in the Doso-longitudinal muscles. The overexpression of Htt.ex1.Q138 caused loss of motor neurons. However, the knockdown of Pten significantly improved the motor neuron structure. One of the hallmarks of HD is the formation of the poly(Q) aggregates in the neuronal tissues, such as the cortex and Basal ganglia of HD patients. Therefore, the expression of mutant Htt protein was investigated. In the *Drosophila* adult eye, large fluorescent puncta were observed in mRFP-Htt.ex1.Q138, which were absent in the control flies. The knockdown of Pten significantly reduced the fluorescence intensities of these puncta. Furthermore, the puncta number was investigated in an age-dependent manner using Or47b-Gal4, which starts expressing in the antennal lobe after eclosion from the pupal stage (Fig. 1A). No fluorescence puncta were observed in the control flies. However, the flies expressing mRFP-Htt.ex1.Q138 showed Htt aggregates even from 2-day-old flies, and the number of these puncta increased significantly in 20-day-old flies (Fig. 1B, D, G). This expression of Htt aggregates was significantly reduced at 2- and 20-days old flies by knockdown of Pten (Fig. 2C, E, G). Moreover, when the total amount of Htt protein was determined by western blot, a significant reduction of Htt was observed (Fig. 2F, H).

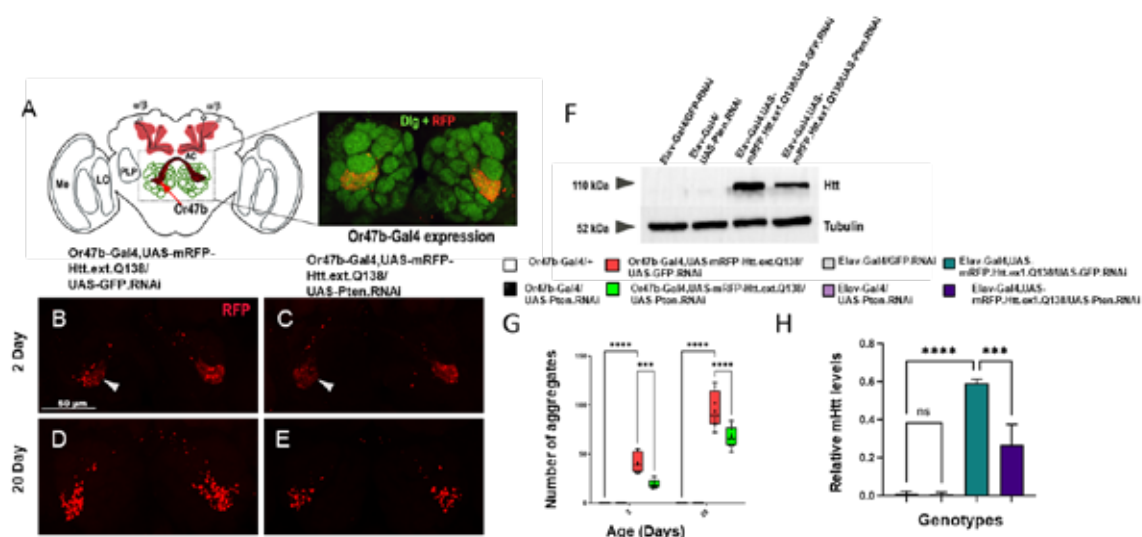


Figure 1. Knockdown of Pten reduces the poly(Q) aggregates. (A) Diagrammatic representation of *Drosophila* olfactory lobe. (B-C) The number of Htt aggregates was reduced in Pten Knockdown flies in 2-day-old flies. (D-E) Similarly, in 20-day-old flies, knockdown of Pten reduced the Htt aggregates in the olfactory lobe. (F) Western Blot also showed a significant reduction of the total amount of Htt aggregates in the brain. (G) Bar Graph representing the number of aggregates in the olfactory lobe. (H) Bar graph representing the total amount of Htt proteins in the brain of adult flies. One-way ANOVA, error bars represent mean $\pm$ SE (ns = non-significant, * P <0.05, ** P <0.01, *** P <0.001, **** P <0.0001). Green: Dlg1, Red: mRFP-Htt.ex1.Q138. Scale Bar: 50 μ m.

The formation of Htt aggregates leads to defects in transcription machinery, axonal transport defects, and neuronal tissue apoptosis. Therefore, cell death markers such as cleaved-Dcp-1 were used to detect cell death by immunohistochemistry and western blot. In the *Drosophila* larval eye disc, a significant increase in Dcp-1 staining was observed in Htt.ex1.Q138 expressing flies compared to the control (Fig. 2A-C, J). Cellular Dcp-1 puncta were significantly reduced when Pten was downregulated in this background (Fig. 2C-D, J). Similarly, in the pupal eye disc, knockdown of Pten reduced the Dcp-1 staining in Htt.ex1.Q93 flies (Fig. 2E-H, K). Furthermore, the level of total Dcp-1 was significantly reduced in Pten knockdown flies compared to Htt.ex1.Q138 expressed alone in western blot (Fig. 2I, L). Our study suggests that knockdown of Pten reduces the Htt aggregates, leading to suppression of cellular death in the *Drosophila* model. Similarly, a significant reduction was observed in the Mouse Neuroblastoma cell line of HD expressing 150 poly(Q) repeats due to feeding a Pten inhibitor. Our study suggests a beneficial effect of Pten knockdown or inhibition in the HD disease models, illustrating potential therapeutic applications of targeting Pten.

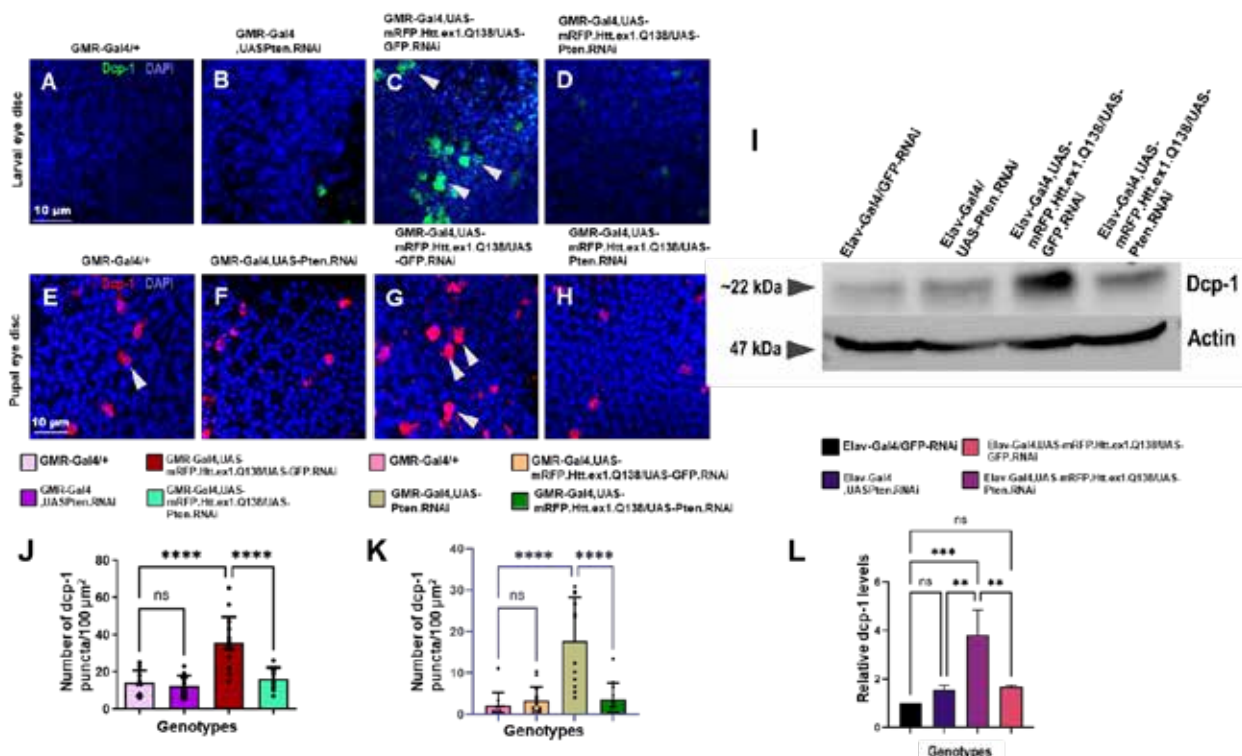


Figure 2. Knockdown of Pten reduces the apoptosis in HD flies. (A-H) Dcp-1 staining of larval and pupal eye disc. (A-B) Basal level of Dcp-1 in the larval eye disc of control and Pten-RNAi flies. (C) The expression of Htt.ex1.Q138 caused a significant increase in the number of Dcp-1 positive puncta. (D) Knockdown of Pten reduced the number of Dcp-1 positive puncta in Htt.ex1.Q138 expressing flies. (E-F) Basal level of Dcp-1 in the pupal eye disc of control and Pten-RNAi flies. (G) Expression of Htt.

ex1.Q93 caused increased cell death in the pupal eye disc. (H) Knockdown of Pten reduced the cell death in Htt.ex1.Q93 flies. (I) The total amount of Dcp-1 was significantly reduced by knockdown of Pten. (J) Bar graph representing Dcp-1 puncta in larval eye disc. (K) Bar graph representing the Dcp-1 puncta in the pupal eye disc. (K) Bar graph showing the quantification of Dcp-1 level in the brain tissue. One-way ANOVA, error bars represent mean $\pm$ SE (ns = non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, ns = non-significant). Green: Dcp-1 (A-D), Red: Dcp-1 (E-H), Blue: DAPI. Scale Bar: 10 μ m.

Publication

- ◆ Nisha, Thapliyal D, Gohil B, Modak AS, Singh NT, Mukherjee C, Ahuja S, Sahu BS, Singh MD (2025). Downregulation of Pten Improves Huntington's Disease Phenotype by Reducing Htt Aggregates and Cell Death. Mol Neurobiol. doi: 10.1007/s12035-025-04816-6.

Presentations

1. M.Dhruba Singh. "Pten knockdown ameliorates Huntington's disease in Drosophila model", Indian Academy of Neuroscience, NIMHANS, Bengaluru, India, November 12-24, 2024.
2. Shreya Borthakur, Mayanglambam Dhruba Singh. "Alleviation of Myc expression suppresses Myotonic Dystrophy 1 in Drosophila model". (Poster) 47th All India Cell Biology Conference, NISER, Bhubaneswar, 16-18 December 2024.

Funding

- ◆ The research in the lab is supported by the NBRC Core fund and SERB- EEQ grant.

Collaborators

- ◆ Bhavani Shanker Sahu, NBRC, India.
- ◆ Sarangthem Indira Devi, IBSD, India

Degrees Awarded (MSc)

- ◆ Shreya Borthakur
- ◆ Ekta Verma

Meetings/Conferences organized:

- ◆ Lead Organizer of Regional Young Investigator meeting (RYIM), Delhi-NCR, March 19-21, 2024-25 at NBRC and Ashoka University.

Scientific Report



Pankaj Seth
Scientist-VII

Research Fellows

- ◆ Bindu Singh
- ◆ Shafaq Aftab
- ◆ Guneet Kaur
- ◆ Maulik Patel
- ◆ Archana Mehta

Masters Dissertation

- ◆ Krishna Rathod
- ◆ Megharanjani Mitra

Project Assistant

- ◆ Ajay Pal

Technical Assistants

- ◆ Durgalal Meena
- ◆ Naushad Alam

Cellular and Molecular Mechanisms of Virus Induced Neuropathogenesis

Our laboratory focuses its efforts to delineate the cellular and molecular basis for virus induced neurodegeneration. Presently, the laboratory is working on the Zika virus (ZIKV) and novel corona virus, SARS-CoV2. This research is warranted as the neurological health of individuals infected by Zika or SARS-CoV2 are deeply impacted. In fact, these viral sequelae are irreversible and debilitating in case of Zika virus as it results into abnormally small head during in utero development or microcephaly in infants born to mothers, infected by the ZIKV during first three months of their pregnancy. Zika virus is an arbovirus and is spread through mosquito bite, particularly by *Aedes aegypti*. In addition to ZIKV research, lab is also studying the cellular and molecular mechanisms of SARS-CoV2 induced neuropathogenesis, particularly to understand complications that lead

to Brain Fog. It is prevalent in around 40-50% Long COVID patients which immensely affects their quality of life.

For addressing our research questions, we use primary cultures of human fetal brain derived neural stem cells (NSCs) developed by this lab at NBRC. We use both the 2D and 3D cultures of human NSCs and a wide variety of cell and molecular biology tools, including high-end time lapse microscopy, live cell intracellular calcium imaging in human brain cells, mRNA and protein expression studies, lncRNA and miRNA sequencing based assays, as well as in silico approaches. Most of the in vitro findings are validated in brain sections from autopsy of patients sourced through collaborations with clinicians.

For the Zika virus project, we employ a dual-cell blood-brain barrier (BBB) model comprising primary human brain microvascular endothelial cells (hBMECs) and astrocytes, to investigate the role of ZIKV envelope (E) protein in virus-induced neuropathogenesis. While the E protein is known for mediating viral entry, we hypothesized that it also disrupts host cellular pathways to favour viral replication. Our findings reveal that E protein expression in hBMECs induces endoplasmic reticulum (ER) stress, as evidenced by upregulation of BiP and activation of the IRE1-XBP1 and ATF6 branches of the unfolded protein response (UPR). This was supported by increased levels of phosphorylated IRE1 α , spliced XBP1 (XBP1s), and downstream pro-apoptotic genes such as CHOP, BAX, GADD34, and CASP3. In addition, we observed heightened oxidative stress marked by elevated ROS and iNOS, along with decreased expression of the antioxidant enzyme SOD1. Disturbed ER homeostasis led to dysregulated intracellular calcium levels. Autophagic disruption was indicated by increased LC3-II levels. Collectively, these findings suggest that ZIKV E protein contributes to endothelial dysfunction at the BBB by inducing ER stress, disruption of redox balance, and impaired autophagy contributing to BBB dysfunction and viral neuropathogenesis.

Further detailed investigation revealed altered microRNA (miRNA) circuitry in hBMECs, which may contribute to BBB dysfunction. miRNAs, small non-coding RNAs that regulate gene expression post-transcriptionally, are known to be modulated during viral infections as a means of immune evasion and cellular manipulation. However, little is known about their regulation in hBMECs in response to ZIKV. Using small RNA sequencing, we identified 39 differentially expressed (DE) miRNAs following ZIKV E protein transfection, with 35 upregulated and 4 downregulated, including 33 novel miRNAs. Five miRNAs relevant to BBB function were validated via qPCR. Gene ontology (GO) analysis revealed enrichment in processes such as transport across the BBB, cell junction assembly, and cell adhesion, while KEGG pathway analysis highlighted Wnt/ β -catenin signaling—a critical pathway for BBB integrity. Notably, miR-1249-5p, one of the upregulated miRNAs, was predicted to target components of the Wnt pathway, suggesting a mechanistic link between miRNA dysregulation and BBB disruption. Wnt2b was found to be a potential target of miR-1249-5p. Ongoing validation of miR-1249-5p targets and exploration of the novel miRNAs will offer further insights into the miRNA-mediated regulation of hBMECs during ZIKV infection. These are represented with a graphical abstract below -

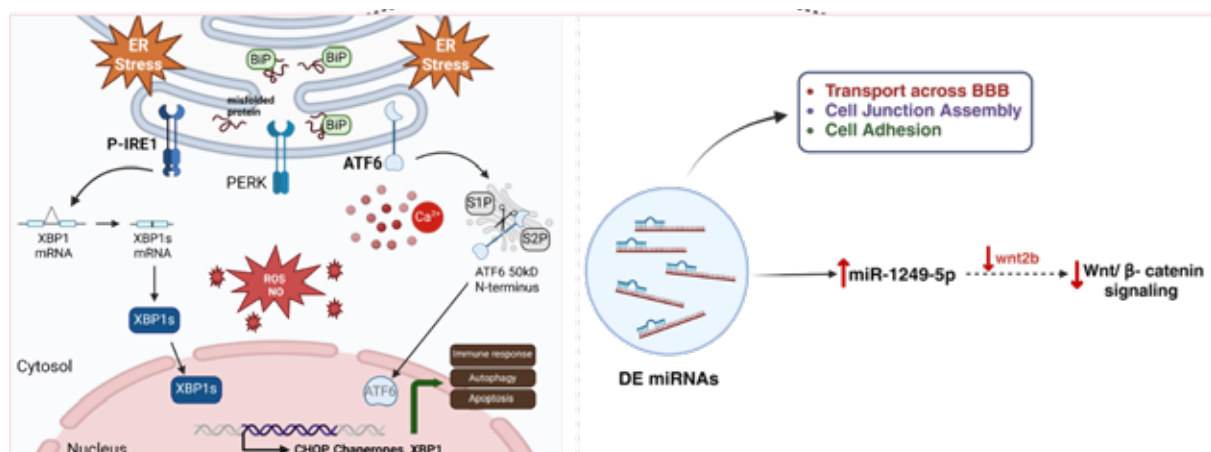


Figure-1: Molecular alterations in human brain microvascular endothelial cells following over expression of ZIKV envelope protein and activation of ER stress cascade and dysregulation of miRNA circuitry.

Under the COVID-19 project, our research provided novel insights into the current understanding of SARS-CoV-2 neuropathology by identifying Orf6 as a primary viral trigger of necroptotic neuronal death and revealing its mitochondria dependent mechanisms. Based on our findings, it is evident that the induction of necroptosis occurs through a non-canonical pathway which happens independently of the death receptor pathway. Herein, Toll like receptor (TLR)3/-4 stimulation by viral dsRNA leads to the recruitment of RIP homotypic interaction motif (RHIM)-mediated association of TLR adaptor molecules TRIF with receptor-interacting protein kinase 3 (RIPK3). Additionally, RIPK3-independent necroptosis is also stimulated by activation of cytosolic dsDNA sensor ZDNA binding protein (ZBP)1/DNA-dependent activator of IFN-regulatory factors (DAI). Upon the binding of viral dsDNA, ZBP/DAI experiences a conformational shift that facilitates its interaction with RIPK3. Subsequently, RIPK3, upon activation by TRIF and ZBP/DAI undergoes autophosphorylation and subsequently phosphorylates mixed lineage kinase domain like protein (MLKL), promoting oligomerization and translocation to membranes, hence eliciting necroptosis characteristics. While prior research suggested the activation of necroptosis gene in ACE-2 expressing murine neurons, our extensive analysis of individual viral proteins reveals Orf6 specific induction of necroptotic markers in human neurons with mitochondrial dysfunction as a critical event. This event is characterized by opening of mitochondrial permeability transition pore (MPTP), loss of mitochondrial membrane potential, increase in mitochondrial ROS and mitochondrial calcium uptake. Mitochondrial dysfunction is increasingly recognized as central to the pathophysiology of Neuro-COVID. Our analysis highlights the link between SARS-CoV-2 Orf6 and the host mitochondrial carrier homolog (MTCH)1, emphasizing the virus's ability to exploit mitochondrial pathways for its pathogenic agenda. MTCH1 may undergo Ca^{2+} -dependent conformational changes, potentially influencing mitochondrial permeability. The SARS-CoV-2-induced mitochondrial stress exacerbates neuroinflammation through ROS production and cytokine release. This inflammatory cascade disrupts the blood-brain barrier (BBB), facilitates immune cell infiltration, and activates resident glial cells, further amplifying neuronal damage. Expression of Orf6 in neurons was correlated with mitochondrial dysfunction, characterized by increased mitochondrial calcium uptake—a phenomenon linked to cellular stress and death. Notably, this mitochondrial dysfunction was mitigated by the application of mitochondrial channel inhibitors, suggesting potential therapeutic avenues. Moreover, the application of necroptotic inhibitor to mitigate necroptotic neuronal cell death in neurons validates the specificity of the system. Finally, the validation of our in vitro findings in the brain sections of COVID-19 patients corroborates the capacity of SARS-CoV-2 virus to elicit necroptosis in the infected individuals.

The neurological symptoms associated with COVID-19 range from mild cognitive impairments to severe encephalopathy and stroke. Our study suggests that necroptosis mediated by Orf6 may underlie these manifestations by driving neuronal loss and inflammation. Identifying Orf6 as a key player provides a molecular basis for these observations and highlights its potential as a therapeutic target. This is graphically depicted below-

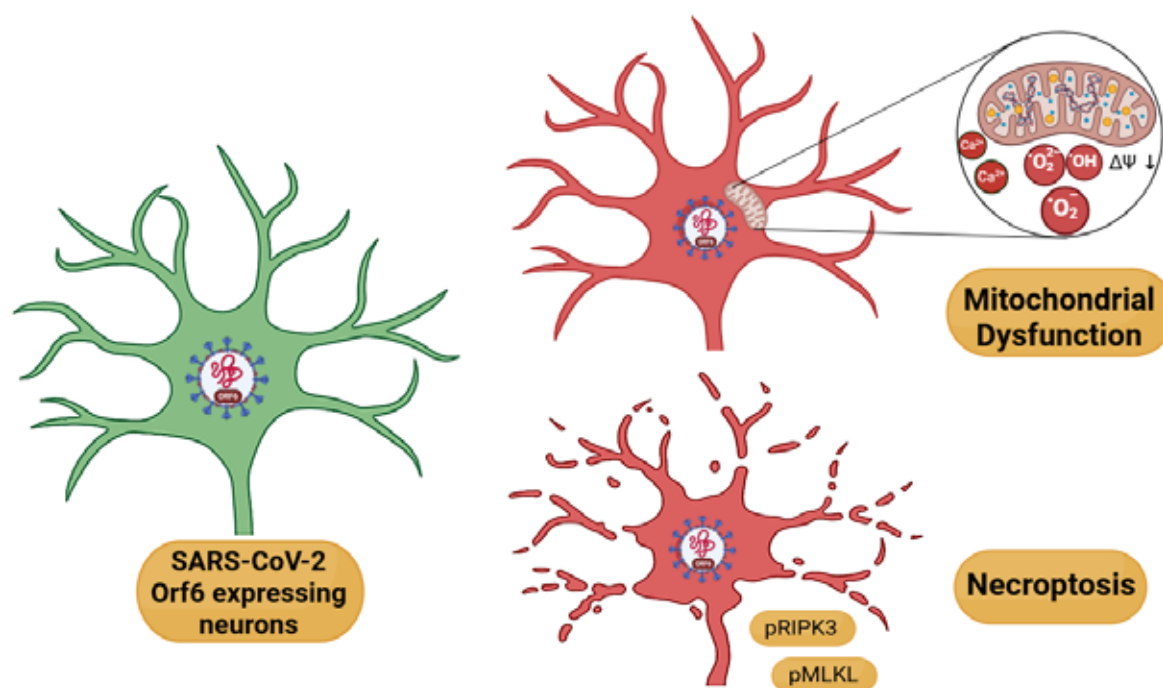


Figure 2: Overexpression of Orf6 in human neurons causes necroptosis and mitochondrial dysfunction.

Maintaining our leadership in our pursuit to understand virus induced neuropathogenesis in physiologically relevant experimental models that represent the disease and offer insights into the cellular and molecular mechanisms of disease pathogenesis in cells of human origin, we have taken our research capabilities to the next level. In addition to use of human astrocytes, neurons and oligodendrocytes derived from human neural stem cells, we have now developed human cerebral brain organoids from iPSCs. We have successfully completed making a batch of human cerebral organoids and currently carrying out detailed characterizations to identify brain layers and other necessary cellular architecture in them.

Our research endeavours are dedicated to addressing the unmet needs of diverse clinical challenges through an in-depth investigation of the molecular mechanisms underlying major neurotropic viruses that impact global populations.

Publications

1. S Dev, S Asthana, P. Singh, P. P. Seth, C. Banerjee C., and CK Mukhopadhyay (2025). Dopamine degrades ferritin by chaperone-mediated autophagy to elevate mitochondrial iron level in astroglial cells. *Free Radic Biol Med.* Jan 14; 229: Pg 39-57.
2. V Shrivastava, S Tyagi, D Dey, A Singh, JK Palanichamy, S Sinha, JB Sharma, P Seth and S Sen (2024). Glial Cholesterol redistribution in hypoxic injury in vitro influences oligodendrocyte maturation and myelination *Biochim Biophys Acta Molecular Basis of Disease* December 1870(8): Pg 167476.

3. S Krishna, B Prajapati, P Seth and S Sinha (2024). LncRNA BASP1-AS1 is a positive regulator of stemness and pluripotency in human SH-SY5Y neuroblastoma cells. **Biochemical and Biophysical Research Communications** Nov 12, 733: Pg 150691.

Presentations

1. Invited Lecture, Exploring Brain Disorders using 2D and 3D models of human brain cells. International Conference on "Challenges and Advancements in the Treatment of Neurological Disorders (ICCATN-25), at Department of Pharmacy, BITS Pilani, India. March 21-22, 2025.
2. Plenary Speaker, Human brain cell model system as an alternative to animal models – a step towards resilient future, National Conference on Bridging Health, Environment and Sustainability: Towards a Resilient Future (NBHES-2025) at MMV, Banaras Hindu University, Varanasi, India, February 20-22, 2025.
3. Invited Speaker, Viruses and the Brain: What We Knew and What is New? Fifth Annual Frontiers of Biology Symposium, at School of Biology, IISER-Trivandrum, India during February 7-9, 2025.
4. Resource Person, Human fetal brain derived neural stem cells as 2D and 3D models to study healthy and diseased brain at the Continued Medical Education on Reverse Pharmacology of Traditional Medicine using Modern Biomedical Techniques, at CSIR-Indian Institute of Chemical Biology, Kolkata, India during February 3-8, 2025.
5. Distinguished Lecture, Novel Insights into pathways of viral neurotoxicity – Implications in cognitive health, Emerging Approaches in Risk Analysis and Translational Aspects of Health and Environment (EARTH- 2024)" being organized by CSIR-Indian Institute of Toxicology Research (CSIR-IITR), Lucknow, India in association with ASTRA (Association of Toxicologists and Risk Assessors) during November 27-30, 2024.
6. Invited Lecture, Insights into SARS-CoV2 mediated neuronal damage-possible mechanism of brain fog in long COVID-19 cases. 42nd Annual meeting of Indian Academy of Neurosciences (IAN), National Institute of Mental Health and Neurosciences, Bangalore, India, November 12-14, 2024.
7. Invited Guest Faculty, 2D and 3D culture for neuroscience research. Workshop on Advanced Techniques in Molecular Neurobiology, during the Annual meeting of Society of Neurochemistry (India) at Panjab University, Chandigarh, India September 23-29, 2024.
8. Invited Lecture, Neuroinflammation, Neuroinfection and its effect on human brain ageing. IBRO-APRC Symposium on Cerebral Organoids Model for Ageing Neurobiology Research, at the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia, August 12-14, 2024.

Funding

- ◆ This work is supported by DST SERB (CRG/2021/002546 February 2022-2025), and DBT (BT/PR44439/MED/29/1582/2021. 2022-2025) extramural funds and NBRC Core funds.

Collaborators

- ◆ A Basu NBRC, Manesar-Gurgaon, India.
- ◆ S. Sharma, and A. Singh, Civil Hospital, Gurgaon, India.
- ◆ Mahadevan, NIMHANS, Bangalore, India.
- ◆ Sachidanandan, IGIB, New Delhi, India.
- ◆ N. Jana, IACS, Kolkata.
- ◆ Awasthi, THSTI, Faridabad, India.
- ◆ S. Vratil, RCB, Faridabad, India.
- ◆ S. Sen, AIIMS, New Delhi, India.
- ◆ S. Sinha, AIIMS New Delhi, India.
- ◆ Mukhopadhyay, Jawaharlal Nehru University, New Delhi, India.
- ◆ Nath, D. Wang, National Institutes of Health, Bethesda, USA.

Awards / Honors

- ◆ Keynote Speaker, Molecular mechanism of SARS-CoV2 mediated neuronal damage in COVID-19, implications in effective management of brain fog patients. International Brain Research Organization (IBRO) sponsored Neuroscience and Pain School organized at Department of Pharmaceutical engineering & Technology, Indian Institute of Technology (IIT-BHU), Varanasi, India, October 10-16, 2024.

Council Member

- ◆ Asia Pacific Society for Neurochemistry (APSN), an international society of countries in Asia Pacific, 2024.

Degrees Awarded (PhD)

- ◆ Bindu Singh
- ◆ Guneet Kaur

Scientific Report



Proloy Das

Scientist-III

Proloy Das received M.Sc. and Ph.D. degrees in Electrical Engineering from University of Maryland, College Park, Maryland, USA. He was a Postdoctoral fellow at the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA (2021-2023) and at the Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University, Stanford, CA, USA (2023-2024). He joined National Brain Research Centre, Gurugram in September, 2024, as a Scientist-III. His research interests include neural signal processing, systems neuroscience, cognitive neuroscience and computational neuroscience.

Research Associate

◆ Aditi Aravind

Noisy neurophysiological signals can turn into gold with a gentle statistics touch

We investigate neuroscience of sensory and cognitive processing through the lens of brain dynamics and build tools to capture brain dynamics from M/EEG. We have two broad themes of research: 1) we develop novel statistical signal processing tools for analyzing high-dimensional time-series data recorded in various electrophysiological modality, namely, EEG/MEG/fMRI. The aim is to gather evidence for hypothesis testing in neuroscience of sensory and cognitive processing. 2) we thrive to demystify whole head brain dynamics in presence of sensory and cognitive task and in also in absence of any. The aim is to identify the normal dynamics, so that the presence of abnormal dynamics can be used as biomarkers of neurodegenerative diseases.

Neurocurrent response function v2.0

This project is aimed to develop a tool for studying how the brain encodes complex and natural stimuli such as speech, music etc. Previously, the PI has developed a unified approach to MEG/EEG source analysis under the naturalistic experiments involving continuous stimuli such as speech [Figure 1]. Characterizing the neural dynamics underlying such sensory processing from

non-invasive recording modality is one of the central areas of investigation in systems and cognitive neuroscience. This previous work introduced Neuro-Current Response Functions (NCRFs), a set of linear filters, spatially distributed throughout the cortex, that can predict the cortical currents giving rise to the observed ongoing MEG/ EEG data in response to continuous speech. Now, we are committed to extend this framework to understand sensory processing of other naturalistic stimuli (like music) and decision making in naturalistic motor control (like eye tracking, object balancing) etc. The goal of this project is being realized as an open-source software (neuro-currentRF): the development of version 2.0 is ongoing with multiple international collaborators.

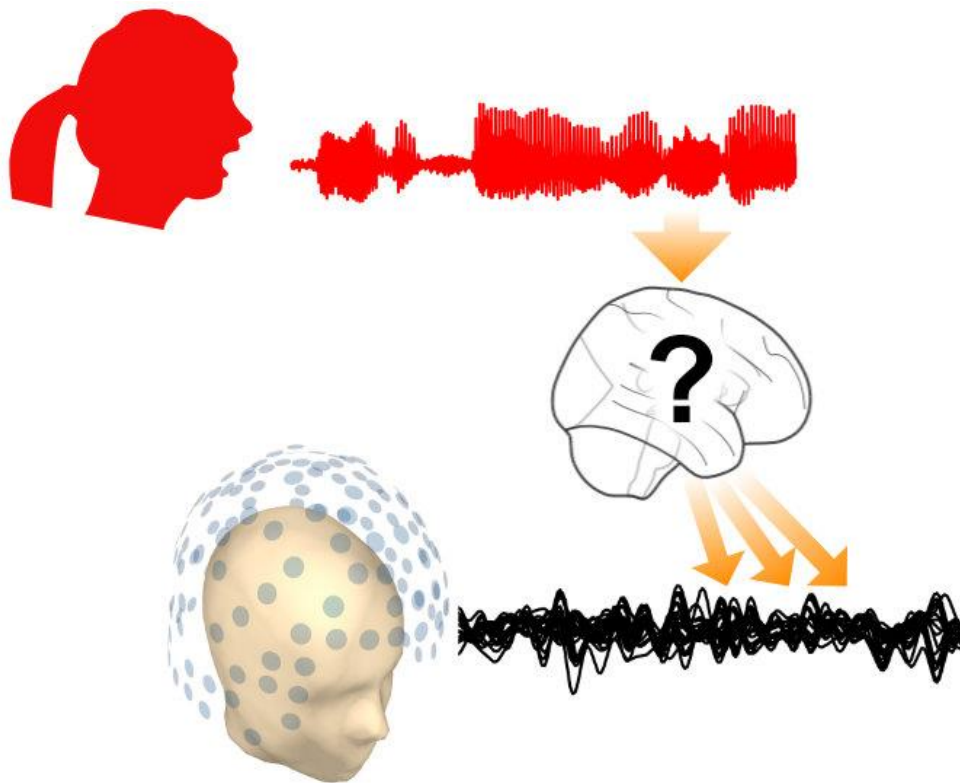


Figure 1: *How the brain encodes complex and natural stimuli such as speech*

A gold-standard for characterizing neural oscillations

Neural oscillations are meso-scale phenomena emerging from synchronous activity of large-scale post-synaptic neuronal populations and are treated as the go-to features of neurophysiological signals for all the studies. However, their characterization is made difficult by the fact these signals never repeat themselves and thus aren't completely predictable from past samples. Conventional methods fall short in taking this stochasticity into account and thus fail to adequately and succinctly characterize these neural oscillations. We try to address this bottleneck by designing filters whose frequency response matches with that of the neural oscillations present in the data, in a completely data-driven way. This is akin to auto-focus feature of microscope with the ability of focusing on multiple scales simultaneously. In turn, 'being able to design a filter' is considered as evidence of presence of an underlying neural oscillation. While we identified the parametric form of such filters, there exists multiple ways to tune these filters against the given data. We are currently exploring several approaches to find out the most efficient, robust and scalable algorithm to do so. In addition, once the oscillations are identified, they can be removed from the neurophysiological signals to study the stereotypical responses evoked by discrete events, event related potentials with significantly higher precision.

Neural substrate of cognitive flexibility

Cognitive flexibility is a crucial component of human cognition that enables an individual to actively realize that the previous response strategy is no longer of relevance, disengage from it, reconfigure a new response strategy, and implement it to the task-in-progress. We operationalize this complex emergent property of efficient executive function via 'task switching' task [FIGURE 2]. The participants are first pre-trained on two tasks, afforded by a single set of stimuli (i.e., do x if the number is odd vs. do y if the number is greater than 5). Then sequences of trials are administered to the participants along with the cues (i.e. the shape, diamond vs square, respectively) for the task that they need to perform. The cue sequence is designed in such a way that participants to either need to maintain (no-switch, NS trials) or change (switch, S trials) task sets. We will recruit young adult (30 yrs or less) volunteers (male and female, 15 each) for neuroimaging recording. As a goal of this study, we aim to understand the neural substrate that supports proactive control processes underlying cognitive flexibility. Specifically, we hope to shed light into how spatially separated but functionally organized nodes in fronto-parietal cortices coordinates information flow to induce the proactive control process necessary for maintaining cognitive flexibility in humans. Having gathered the knowledge about the coordinated functioning of these nodes (i.e., network activity), it would be easier to study how much and in which way these coordination gets affected in healthy aging and/or mild cognitive impairment (MCI) caused by physical trauma or neurodegenerative diseases.

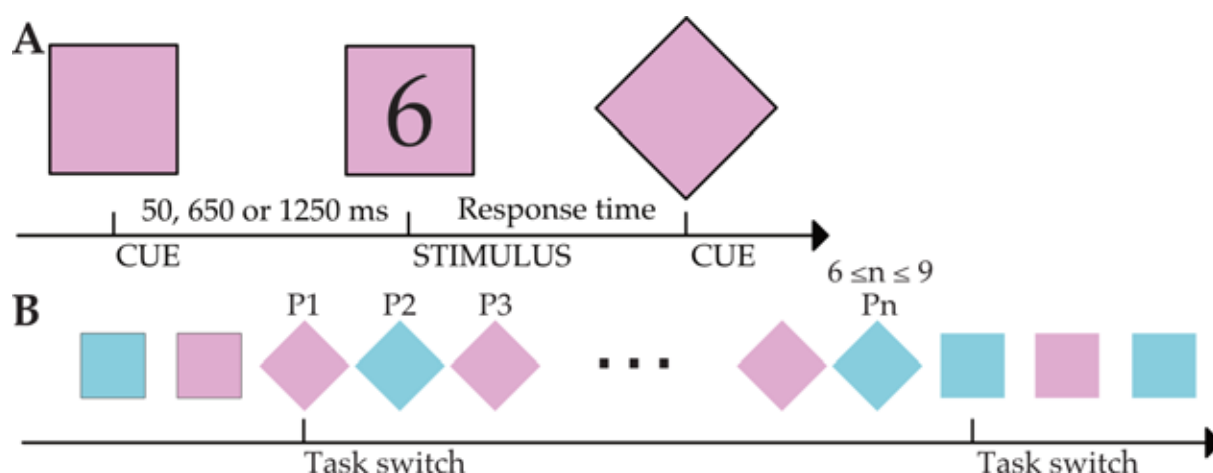


Figure 2: Task Schematic. A. Single trial followed by next cue display. B. Sample sequence of background colored-shapes, either the color or shape changes at every trial.

Presentations

- ◆ Proloy Das. All it needs to quantify neural oscillations is a clever dynamic generative model. Brain Network Dynamics Meeting 2024, Ashoka University, Sonipat, Haryana. December 2024 [INVITED].

Funding

- ◆ These works are supported by NBRC Core funds.

Collaborators

- ◆ Arpan Banerjee, PhD. National Brain Research Centre, India
- ◆ Christian Brodbeck, PhD. McMaster University, Canada
- ◆ Rodrigo Gutierrez, MD, PhD. Universidad de Chile, Chile
- ◆ Patrick L. Purdon, PhD. Stanford University, USA
- ◆ Victor Solo, PhD. University of New South Wales, Australia

Scientific Report



Ranjit Kumar Giri
Scientist-VI

Ph.D. from Institute of Life Science, Bhubaneswar, Odisha & post-doctoral positions from National Institute of Immunology, New Delhi (1997-1999)/University of Southern California, U.S. (1999-2003)/McLaughlin Research Institute, Great Falls, U.S. (2003-2007).

Dr. Giri's research is focused on understanding the mechanisms underlying the neuropathology of Alzheimer's and prion disease using animal and CNS stem/progenitor cell-based models.

Laboratory Attendant

◆ Lalit Bidla

Differential expression of death receptor, Fas as one of the molecular signatures of neuropathology in a mouse model of prion disease

Background and Rationale: Prion diseases are a group of irreversible and transmissible neurodegenerative diseases, which comprises scrapie in sheep and goat, bovine spongiform encephalopathy (BSE) in cattle, and various human disorders like Kuru, Creutzfeldt-Jacob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). Noted by the absence of nucleic acid, these diseases defy conventional pathogen paradigms by inducing the conformational transformation of normal cellular prion protein (PrPC) into a misfolded, infectious isoform (PrPSc). Under physiological condition, this alteration leads to accumulation of PrPSc aggregates in the form of amyloid plaques, driving astrogliosis, microgliosis, spongiform degeneration and massive neuronal loss. This was elegantly proved by grafting neural tissue overexpressing PrPC into the brain of PrPC-deficient mice that are resistant to infection from prion. The results from this experiment clearly pointed towards neuropathology and infectivity related to PrPSc are restricted to PrPC expressing grafted tissue. Therefore, expression PrPC is pivotal for disease progression and underscores the threshold-dependent neurotoxicity of PrPSc. However,

the specific molecular and cellular pathways underlying the neuropathology of prion disease remain partially defined.

Three types of programmed cell deaths are discriminated: 1) apoptosis, 2) autophagy and 3) cytoplasmic cell death. Reports on autophagy is limited and suggest more towards impairment than activation of autophagy in prion disease. A single study suggests the cell death through necroptosis than apoptosis of scrapie-infected SMB-S15 cell line to LPS-activated microglia supernatant and TNF α (tumor necrosis factor- α) stimulations. Stimulation by LPS or TNF α dampened the logical approach of this study towards a true prion disease. Therefore, conflicting data on autophagy and a single study on cytoplasmic cell death leave critical gaps in our understanding regarding the dominant cell death pathway/s mediating the neuropathological conditions of prion diseases.

The misfolding of PrPC is reported to produce neurotoxic stimuli, potentially through oligomerization of PrPC on the cell surface and interacting with unknown transducing partners. Additionally, PrPSc aggresome has been implicated in the activation of caspase-8 and caspase-3, resulting in apoptosis. Collectively, the synthesis of proinflammatory cytokines by activated microglia, oligomerization of PrPC/Sc on cell surface and activation of caspase-8 define the involvement of death receptor pathways in the neuropathology of prion diseases. Six major death receptors (DRs) have been defined in human: TNF receptor 1 (TNFR1/DR1), FS-7-associated surface antigen (Fas/DR2/CD95), DR3, TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 (TRAILR1/DR4), TRAILR2 (DR5), DR6, and the nerve growth factor (NGF) receptor (NGFR/p75NTR). These receptors are single-pass, type-1 transmembrane protein containing a conserved 80-amino acids sequence, referred as death domain (DD). Each DR is specific to its cognate ligand: TNFR1 binds TNF α , Fas associates with FasL, DR3 engages with TL1A, TRAILR1 and TRAILR2 interact with TRAIL, and p75NTR binds either NGF or PrPSc. However, the ligand for DR6 is not fully defined. The availability and specific interaction of death receptor adaptors proteins like TRADD (TNFR1-associated death domain), RIPK1 (receptor interacting protein kinase 1), TRAF2 (TNFR-associated factor 2), and FADD (Fas-associated death domain) with the ligated death receptors determines the ultimate functions of death receptors, ranging from cell survival, inflammation and all kinds of programmed cell death.

The nuanced, pleiotropic functions of DRs, underscored by their redundancy and complex signaling pathways, necessitate an in-depth study at polygenic level to fully elucidate their implications in the neuropathology of prion diseases.

Briefly, the literature on TNF α -TNFR1, FasL-Fas and NGF-p75NTR is remarkably scant in prion disease. Interestingly, research on other death receptors like DR3 and DR5, and their ligands such as TL1A and TRAIL is barren. A similar landscape prevails for DR6, TRADD, TRAF2, FADD, and RIPK1 in prion diseases. To address this unique research gap, I examined the expression of six DRs with death domains (TNFR1, DR3, DR6, DR5, Fas, and p75NTR), scrutinizing their glycosylation, proteolysis status, and their specific ligands (TNF α , TL1A, TRAIL, FasL, proNGF/NGF, and PrPSc) and adaptors (TRADD, TRAF2, FADD, and RIPK1) using a fully penetrant mouse model of prion disease.

A Brief statement on last year's achievement: The study concludes with the analysis of 16 death receptor factors, uncovering critical insights into the neuropathological mechanisms of prion disease. The findings suggest possible inhibition of cell survival pathways (TNFR1, DR3, DR6, p75NTR, partially DR5 and Fas) due to marked reduction in TRADD and TRAF2 expression, the vulnerability of DR3 and DR5 expressing cells indicated by TL1A and TRAIL overexpression, and steady FADD levels coupled with elevated FasL, Fas, TRAIL, and caspase-8 pointing towards apoptotic cell demise. Enhanced RIPK1 proteolysis with caspase-8 cleavage signature confirms

apoptosis, while high levels of RIPK1 and caspase-8 alongside constant FADD may induce apoptosis through Fas, DR5, TNFR1, DR3 and p75NTR ligation. Overexpressed TNFR1, Fas, FasL, and stable TNF α levels combined with reduced DR5 might promote astrocytosis and microgliosis in a TRADD-independent, RIPK1-dependent manner. Novel glycosylated and oligomeric TNFR1 and FAS isoforms imply enhanced ligand binding, and diminished monomeric, oligomeric, and glycosylated soluble TNFR1 and Fas isoforms indicate impaired cell protection, contributing to cell death in prion diseases. Lastly, neurodegeneration in prion diseases appears to be driven not by a single death receptor pathway but by multifactorial, multi-receptor-mediated cell death processes, as evidenced in this mouse model of prion disease. In summation, the present study narrates a complex network of death receptors, their ligand and adaptor proteins elaborately intertwined into the multifarious nature of prion disease neuropathology, thereby laying a robust foundation for future explorations into their functional association with prion-induced neurodegeneration and potential avenues for targeted therapeutic interventions.

Research progress (Since last year): Since last year, a significant time was spent on writing a manuscript, communicating and recommunicating for a publication in a peer-reviewed journal. This year (2024-25) the manuscript was accepted for a publication in the Journal of Translational Medicines.

However, in order to link the data obtained from my earlier study to specific neuropathological condition of prion disease, this year, the regional distribution of Fas expression was studied in mice brains with or without prion disease using immunofluorescence histopathology technique. Furthermore, the expression of Fas was also studied with respect to neuronal loss, astrogliosis and oligodendrocytes using dual-immunofluorescence histopathology. The results from three independent normal mice brains and three prion-diseased mice brains show altered expression pattern of Fas protein both at regional and cell specific level in prion-diseased mice brain than healthy controls (Figure 01). Briefly, Fas expression is increased in most part of the cortex. In addition, Fas is expressed in neurons and oligodendrocytes but not in astrocytes. A similar approach was also used to study altered DR3 expression pattern in prion-diseased mice brains. The data from DR3 study show DR3 expression is reduced in most part of the brain with prominence in hippocampus, M2 region of cortex. DR3 is expressed in neuronal cells but not in astrocytes and oligodendrocytes (data not shown).

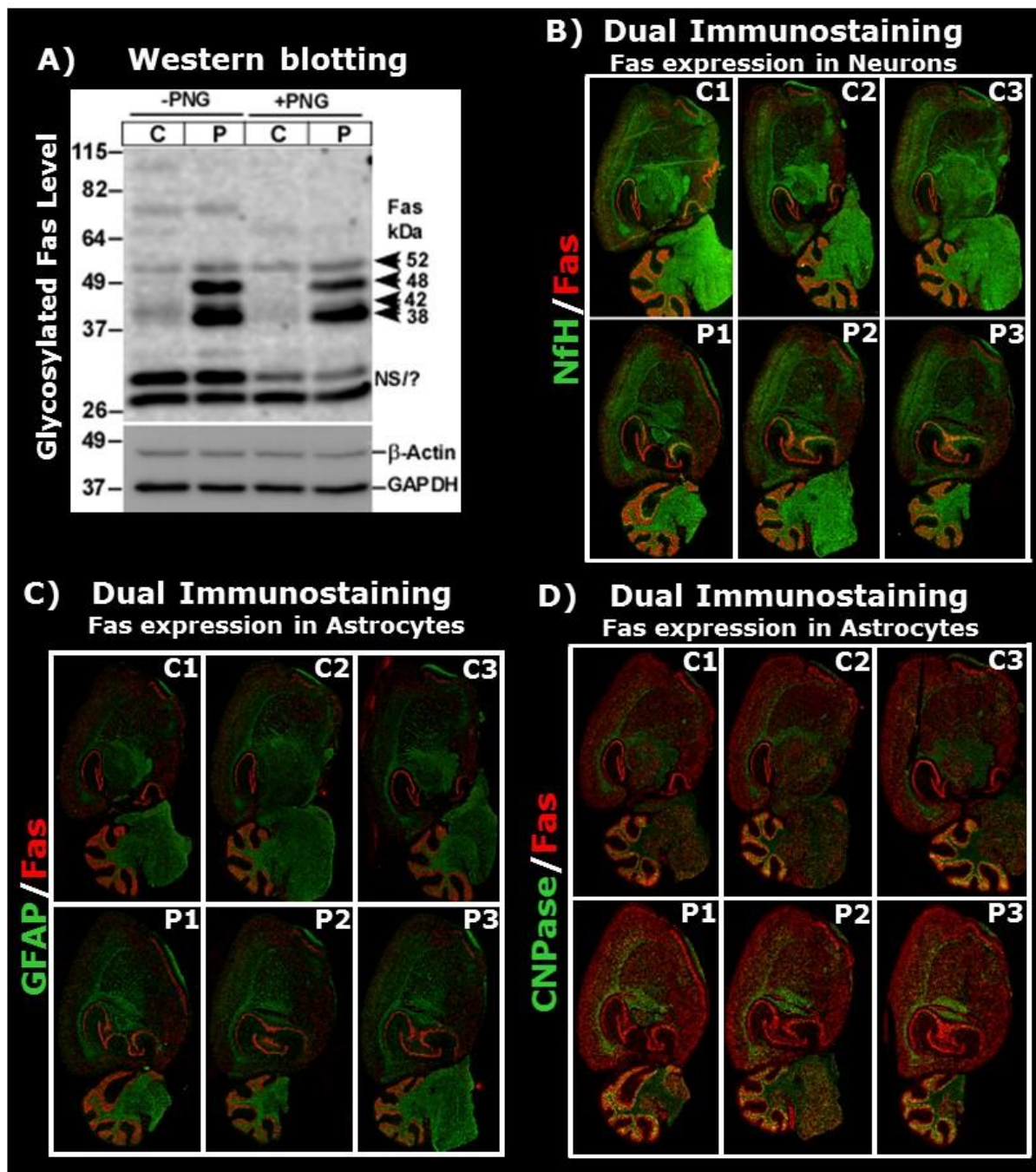


Figure 1: Differential expression of death receptor, Fas in prion-diseased mice brain (P) than healthy control mice brains (C) at regional and cell specific level. A) Western blot analysis of mouse brain homogenates treated with or without PNGase F show increased expression of Fas in prion-diseased mice brains than controls and are glycosylated, a biochemical feature of a mature and functional Fas protein. B) Dual immunostaining of prion-diseased and control mice brain sections by Neurofilament-H (a marker of mature neurons) and Fas. Images show NfH expression is visibly decreased in most parts of cortex, corpus callosum (CC), caudate putamen (CPu), etc. in diseased brains. Fas Expression is increased in these area without any visible changes in cerebellum. Fas expressing neurons in most parts of cortex are prominently reduced in diseased brains. This reduction could be due to increased FasL expression in prion-diseased mice brains. C) Dual immunostaining of prion-infected (P) and control (C) mouse brain sections by GFAP (a marker of astrocytes) and Fas. Images show GFAP+ve astrocytes are increased in prion diseased mice brain sections than controls and they are not positive for Fas. Hence, Fas expression has no effect on astrogliosis. D) Dual immunostaining of prion-infected

(P) and control (C) mouse brain sections by CNPase (a marker of oligodendrocytes) and Fas. Images show CNPase+ve oligodendrocytes are increased in prion-diseased mice brains than controls. Fas+ve oligodendrocytes are less in control mice brains but are prominently higher in prion-diseased mice brains.

Publication

- ◆ Giri RK. Molecular Signatures in Prion Disease: Altered Death Receptor Pathways in a Mouse Model, *Journal of Translational Medicines*, 2024 May 27; 22(1):503. doi: 10.1186/s12967-024-05121-x.

Funding

- ◆ This work is supported by NBRC Core fund.

Collaborator

- ◆ Prof. George A Carlson for providing RML scrapie prion

Scientific Report



Sourav Banerjee
Scientist-VI

Dr Banerjee's laboratory is focused on long non-coding RNAs (lncRNAs) -mediated regulatory mechanisms of synapse formation, synaptic plasticity and memory. His laboratory has identified synaptic lncRNAs that plays a pivotal role in excitatory and inhibitory synapse development. The laboratory has elucidated how synapse-specific, transcript-specific and neuronal state -dependent translation is regulated by lncRNA and how this regulatory process contributes to memory. The laboratory investigated how pathological conditions of developing and aging brain cause memory deficit and how such deficits can be rescued by lncRNA activity. The laboratory has currently expanded his focus to investigate how alteration of synapse development and its activity involving lncRNAs contribute to behavioural deficits observed in autism.

PhD Students

- | | | |
|----------------------|-------------------------|-----------------|
| ◆ Dipanjana Banerjee | ◆ Karthick Ravichandran | ◆ Kamakshi Garg |
| ◆ Sania Sultana | ◆ Pallabi Kisku | ◆ Reena Kaneria |
| ◆ Abhinav Ravindran | | |

MSc Students

- | | |
|-----------------|-----------------|
| ◆ Shreyas Miraj | ◆ Gauri Shintre |
|-----------------|-----------------|

Research Associates

- | | |
|--------------------|------------------------|
| ◆ Sarbani Samaddar | ◆ Balakumar Srinivasan |
|--------------------|------------------------|

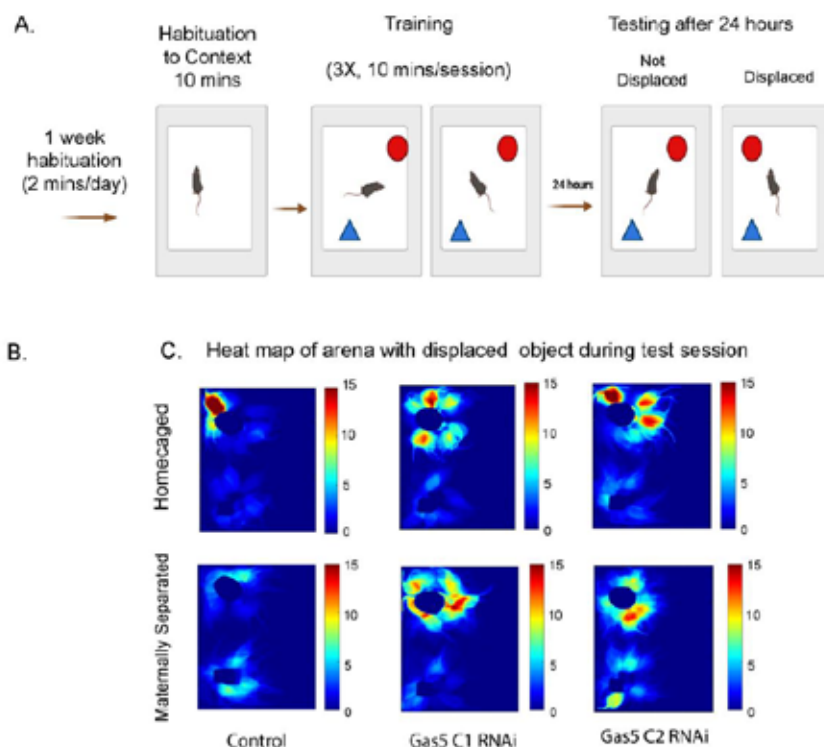
Lab Technicians/Assistants

- | | |
|------------|-----------------|
| ◆ Narendar | ◆ Kamlesh Bisht |
|------------|-----------------|

Long non-coding RNA: A reversal switch for memory deficit induced by early life stress and sleep loss.

Early life is a critical period for neuronal growth and development. During this pivotal stage, the brain is especially susceptible to environmental stimuli and stress. Recent transcriptomic studies indicate that stress during critical periods of development alters gene expression and subsequently affects cognitive function in the adult brain. Although much research has focused on how early-life stress (ELS) impacts the expression of protein-coding genes and influences the development and function of the adult brain, our understanding of non-coding RNA activity following ELS remains limited. Among the diverse classes of non-coding RNAs, we have focused on long non-coding RNAs (lncRNAs) (>200 nucleotides and without conserved coding potential) to define ELS-induced deficits in memory and anxiety.

This study concentrated on a subset of synapse-localized lncRNAs identified in the hippocampus through a transcriptomic screen. A candidate-based approach to identify differentially expressed lncRNAs following ELS was implemented using quantitative PCR. The study focused on Gas5, among other differentially expressed lncRNAs, as it showed a male-specific enhancement upon exposure to ELS. Furthermore, Gas5 lncRNA is abundant in both the dorsal and ventral hippocampus, areas known to influence memory and anxiety, respectively. Extensive literature has demonstrated that memory and anxiety are the predominant cognitive deficits impacted by ELS. Gas5 knockdown in the mouse hippocampus resulted in improved spatial memory and reduced anxiety, both of which were previously impaired by ELS. This demonstrates that regulating lncRNAs like Gas5 during ELS can positively influence memory formation and anxiety later in life. The Gene Ontology analysis further identified that Gas5 targets are predominantly involved in RNA metabolism.



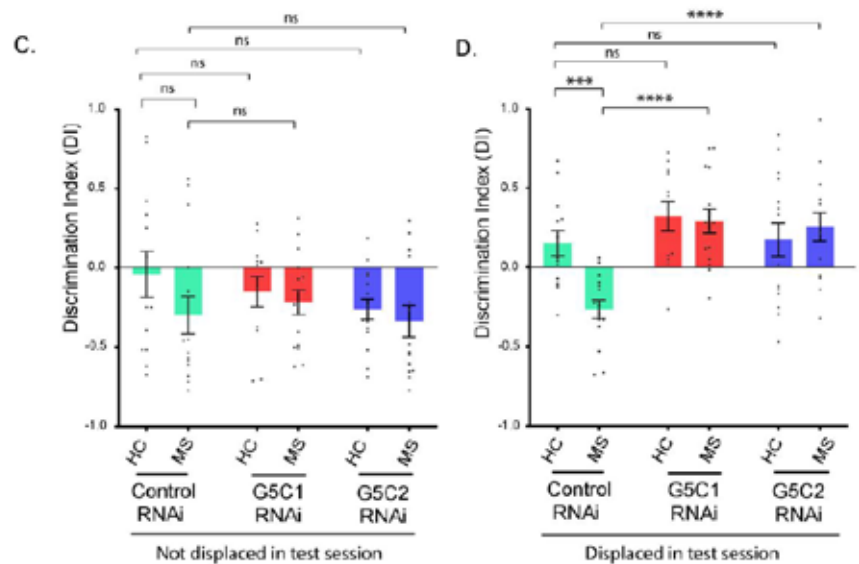


Figure 1: Gas5 reverses the effect of MS-induced deficits in memory. A. Schematic showing paradigm for SOR. B. Representative heat maps in the arena with the displaced object during the test session, circular (glass) object represents the displaced object. C. HC=Homecaged, MS=Maternally Separated, G5C1= shRNA # 1, G5C2= shRNA # 2. Discrimination Index (DI) in the arena with no displaced object during the test session. D. DI in the arena with a displaced object during the test session.

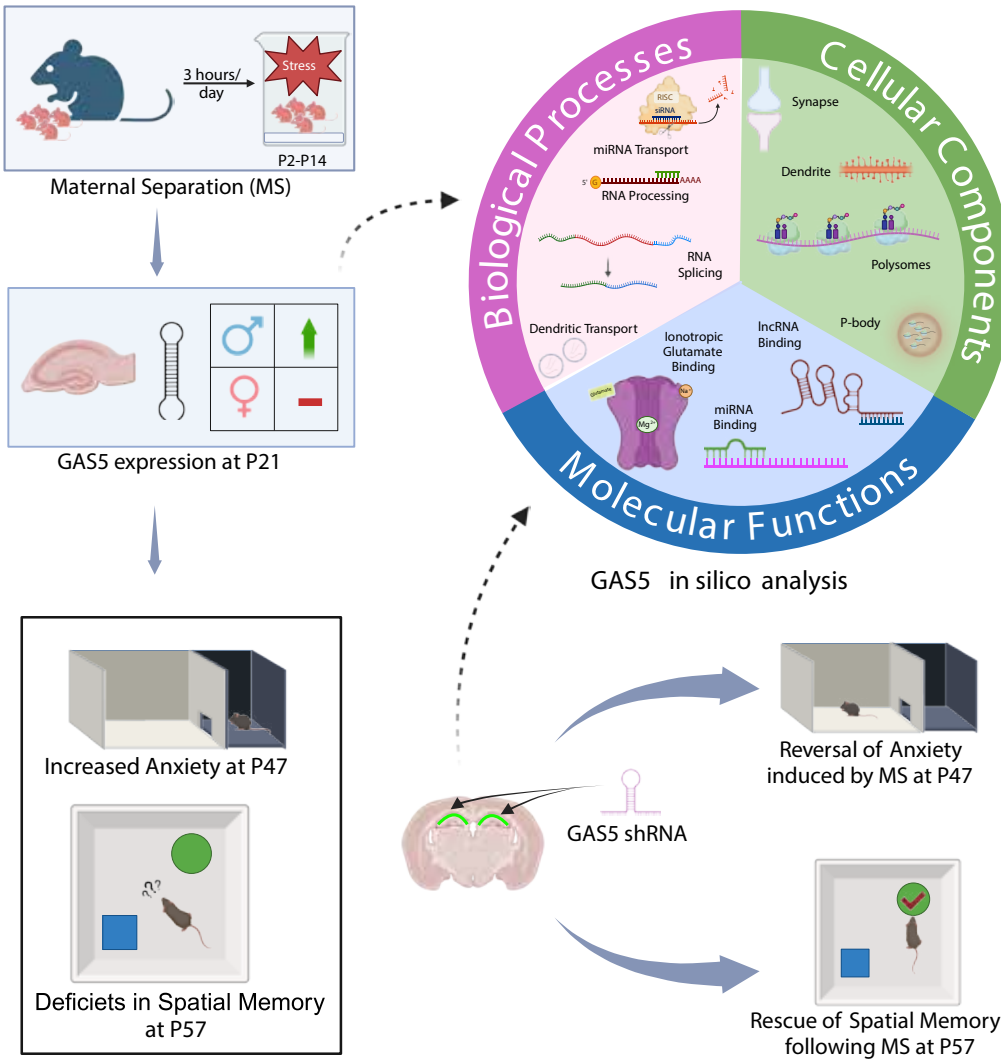


Figure 2: Early life stress -induced behavioural deficit ameliorated by Gas5 lncRNA knockdown. *Gas5* expression is induced by early life stress. Knockdown of *Gas5* in developing brain could reverse anxiety and memory deficit. Gene Ontology analysis showed *Gas5* regulates RNA metabolism.

To elucidate the mechanistic insights of ELS-induced gene expression, the study focused on epigenetic modifications of both coding and non-coding transcripts. The most abundant epigenetic regulation of RNAs involves N6-methyladenosine (m6A) methylation. The m6A modifications are reversible and can significantly alter the entropy and secondary structure of RNAs. Thus, they can act as a regulatory switch affecting interactions of the RNAs with other molecular components. Aberrant m6A methylation may result in lncRNA dysregulation, leading to impaired synaptic signalling and development.

Guided by this understanding, we conducted a transcriptomic screen following m6A-RNA immunoprecipitation from hippocampal tissue. The screen identified significantly hypermethylated and hypomethylated RNAs following ELS. We observed that ELS predominantly induced m6A hypermethylation of transcripts. This hypermethylation resulted from reduced levels of the brain-enriched demethylase FTO (Fat mass and obesity-associated protein). Overexpression of FTO in hippocampal neurons in vivo rescued memory deficits but did not affect anxiety.

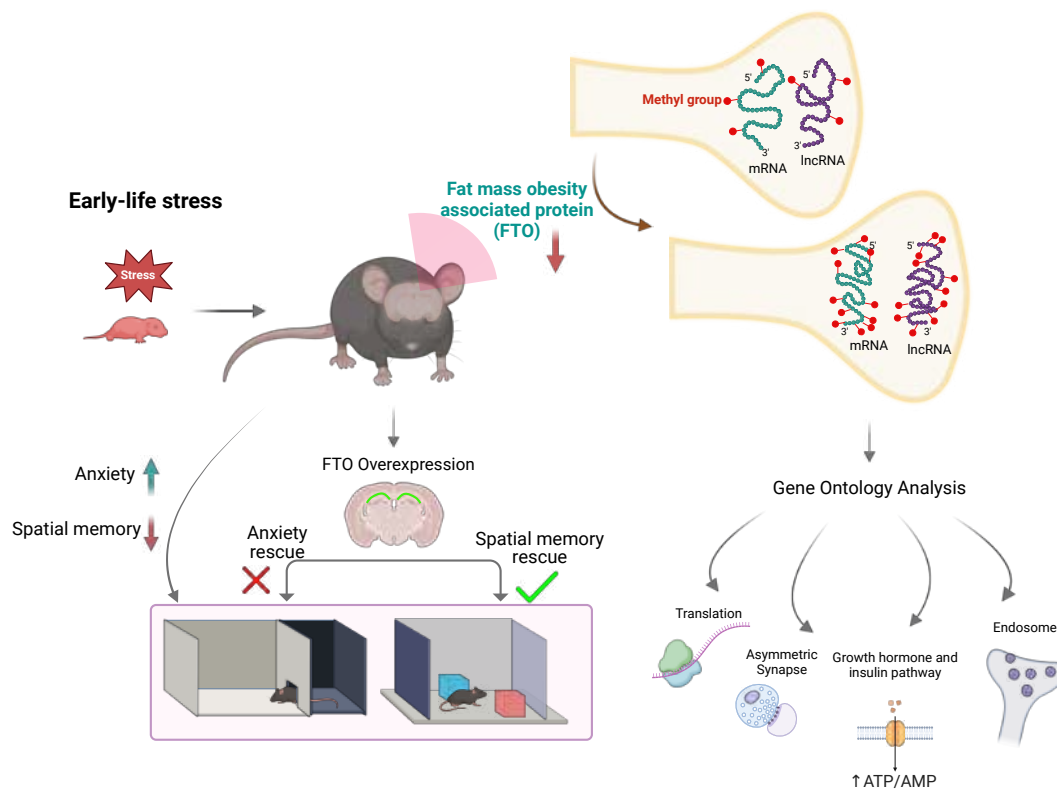


Figure 3: Early life stress induces memory deficit due to RNA modification in hippocampus. RNA-IP Seq profiled hypermethylated (m6A) transcripts following maternal separation paradigm in mouse. The hypermethylation is caused by reduction in FTO, a demethylase. AAV-mediated overexpression of FTO rescue memory deficit, but not anxiety, upon early life stress.

Our study provides a comprehensive view of how ELS impacts long non-coding RNA activity and influences gene expression during critical neuronal development and function. The observations demonstrated that ELS-induced alterations in lncRNA activity during development affect memory and anxiety in adult mice. Additionally, the study highlighted that reversing lncRNA activity in the developing brain could partially reverse memory deficits. Taken together, the thesis

enumerates a non-coding RNA-based mechanism of gene regulation following ELS and provides insights into mitigating the debilitating impacts of ELS on cognitive function.

Sleep is essential for numerous brain functions, particularly memory. By lowering metabolic demand and reactive oxygen species (ROS) accumulation, sleep supports cellular recovery and energy balance. Sleep deprivation has been associated with cognitive decline and neurodegenerative diseases. Prolonged wakefulness alters gene expression, impacting memory storage. In rodents, lack of sleep disrupts processes like PKA-CREB signaling in the hippocampus, impairing long-term memory formation and reducing translation of synaptic plasticity-related proteins.

Sleep also conserves neuronal energy, as maintaining synapses is highly energy intensive. Mitochondria are central to this process, with studies showing that sleep loss leads to mitochondrial changes in hippocampal neurons, including altered cristae structure and impaired enzyme complexes (Complexes I-III), which relate to learning deficits.

Despite known impacts, the mechanisms behind sleep loss-induced changes in translational control and energy use remain unclear. Some studies have explored non-coding RNAs, particularly lncRNAs, which show brain-specific, activity-regulated expression and play roles in synaptic plasticity and behavior. lncRNAs are tightly regulated in neurons, localize to distal processes, and influence translation in an activity-dependent manner. Some are even linked to ATP production in non-neuronal cells.

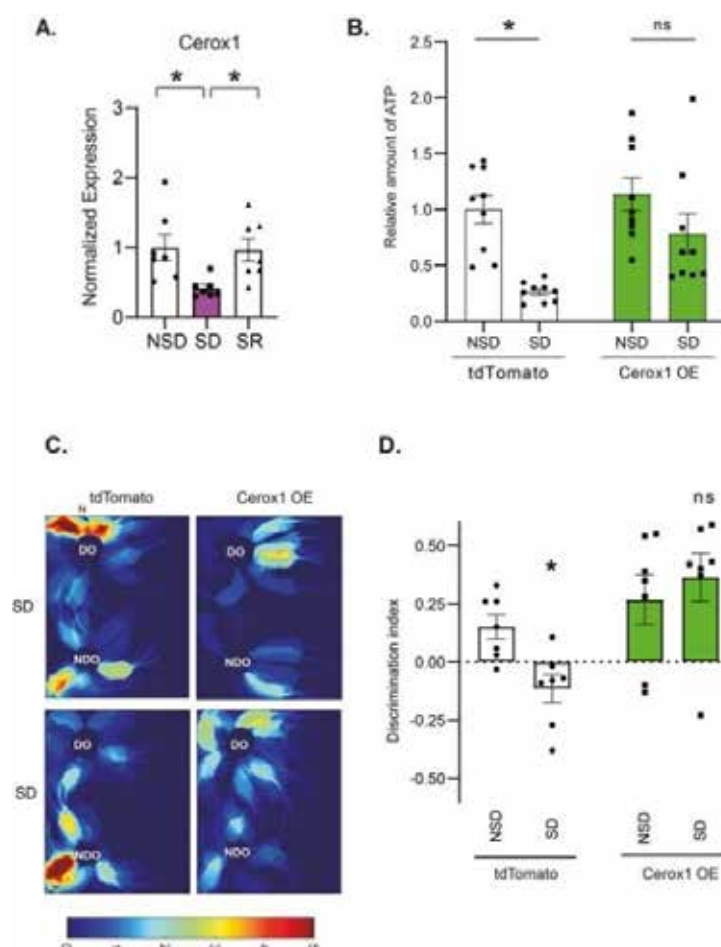


Figure 4: Sleep-regulated lncRNA Cerox1 regulates memory involving enzymatic activity producing ATP. (A) Cerox1 expression upon sleep deprivation or rescue sleep after sleep deprivation. (B) Overexpression of Cerox1 in hippocampus reverses reduction in ATP that is caused by sleep deprivation.

(C) Heat map showing sleep deprivation impairs exploration of displaced object within an arena and this deficit is reversed by overexpression of Cerox1 in hippocampus.

Building on this, we hypothesize that a specific set of synaptic lncRNAs may help regulate energy production during sleep, thus influencing memory processes. The maintenance of potentiated synapse requires a constant source of energy to sustain synaptic efficacy. Both the presynapse and postsynapse function rely on mitochondria to meet their energy demands.

To identify sleep-regulated synaptic lncRNA, the study compared synapse-enriched lncRNAs identified by RNA-Seq from synaptoneurosomes with differentially expressed transcriptome following 5 hours of sleep deprivation. The study focused on four lncRNA candidates, such as GM42770, AI504432, Gas5, and Cerox1, that are differentially expressed upon sleep deprivation. We further tested their expression from dorsal hippocampus, a key brain area involved in spatial memory. Quantitative measurement of expression of these lncRNAs demonstrated that Cerox1 lncRNA is downregulated by 5 hours of sleep deprivation and a rescue sleep for 2.5 hours after sleep deprivation reversed the expression. However, other three lncRNAs expression has no effect either after sleep deprivation or after rescue sleep. The study selected Cerox1 for further characterization of its role in memory deficit upon sleep loss. Cerox1 has been shown to regulate energy metabolism in Neuro2A cell line with a profound effect on

The study analyzed the activities of complex I and complex II of mitochondrial electron transport chain following knockdown or overexpression of Cerox1. We observed that the knockdown of Cerox1 reduced the complex I activity, whereas its overexpression enhanced it. However, complex II activity remained unaltered. The study examined the expression of 12 subunits of complex I using qPCR. The expression analysis showed a consistent downregulation of Ndufa3, Ndufs1, Ndufs3 and Ndufs6 subunits upon knockdown of Cerox1 and overexpression of the transcript reversed it. Further, western blot analysis of Ndufs1 and Ndufs3 recapitulated the data at the protein level. The study examined whether the overexpression of Cerox1, which is downregulated upon sleep loss, could alter the ATP level. The data showed that the sleep deprivation reduced the ATP level, and this was rescued following overexpression of Cerox1. Consistent with these observations, overexpression of Cerox1 could rescue deficit in spatial memory consolidation that is caused by sleep deprivation.

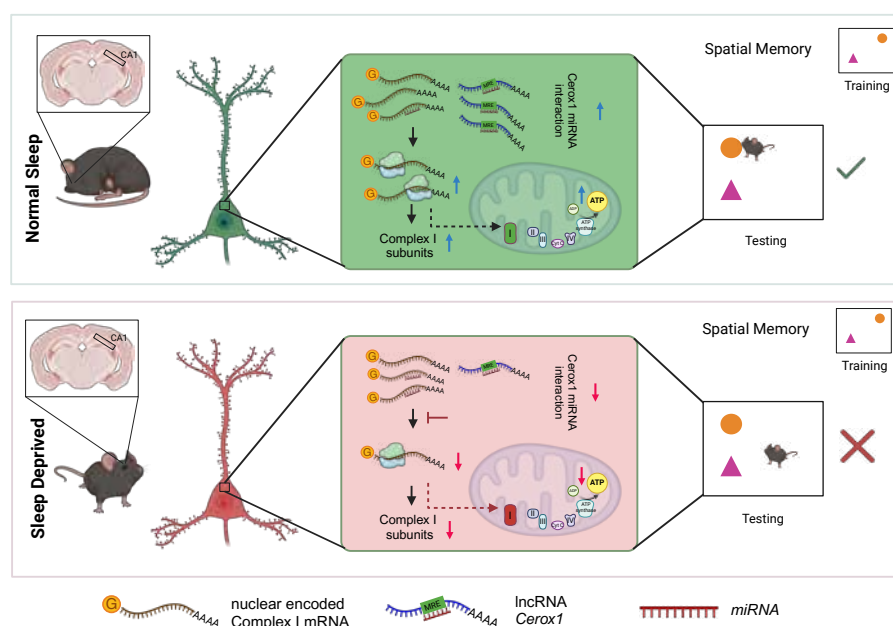


Figure 5: Cerox1 rescues sleep-deprivation -induced memory deficit. Sleep deprivation reduces the expression of Cerox1 that function as a decoy for miRNA. Cerox1 has been shown to regulate the activity of mitochondrial electron transport chain activity leading to ATP production. AAV -mediated overexpression of Cerox1 in hippocampus prevents memory deficit caused by sleep deprivation.

Taken together, our findings provided a comprehensive understanding of how alteration of lncRNAs activities could be used to design RNA-based therapy for brain disorders of developing or aging brain.

Publications

1. Banerjee, D., Sultana, S., and Banerjee, S., (2024). Gas5 regulates early-life-stress-induced anxiety and spatial memory. *Journal Of Neurochemistry*, July 3. doi: 10.1111/jnc.16167
2. Singh AK, Joshi I, Reddy NMN, Purushotham SS, Eswaramoorthy M, Vasudevan M, Banerjee S, Clement JP, Kundu TK. (2025). Epigenetic modulation rescues neurodevelopmental deficits in Syngap1^{+/-} mice. *Aging Cell*. 2025 Mar;24(3): e14408. doi: 10.1111/accel.14408. Epub 2025 Jan 29.
3. Garg K, Sharma G, Samaddar S, Banerjee S. The E3 ligase MEX3B forms a tripartite complex with Rest and Hotair to determine the proliferative capacity of neural progenitor cells. *Open Biol*. 2025 Sep;15(9):250164. doi: 10.1098/rsob.250164. Epub 2025 Sep 10. PMID: 40925537; PMCID: PMC12419896.

Presentations

1. Sourav Banerjee. Synapse-enriched long non-coding RNA SynLAMP regulates local protein synthesis and memory. Short talk at Cold Spring Harbor Symposium on "Mechanisms of Neuronal Connectivity". September 2024.
2. Sourav Banerjee. Local lncRNome at the synapse: Long non-coding RNAs in synapse development and memory. Invited talk at Neuroscience Research Institute Seminar Series. University of California, Santa Barbara. September 2024
3. Sourav Banerjee. Invited talk "Long non-coding RNAs in regulation of memory" at Iowa Neuroscience Institute Seminar Series. University of Iowa, Iowa City. September 2024.
4. Sourav Banerjee. "Synapse-enriched long non-coding RNAs regulates fear memory formation involving dendritic protein synthesis." Invited talk at Korean Society of Brain and Neural Sciences Annual Meeting. Gyeongju. October 2024.
5. Sourav Banerjee. Invited talk "Synapse-enriched long non-coding RNAs in dendritic protein synthesis and memory" at non-coding RNA in brain development, function and evolution symposium organized by ETH, Zurich. Ascona. October 2024.
6. Sourav Banerjee. Invited talk "Long non-coding RNAs at the synapse: Localized partnership with RNA binding proteins to regulate memory" at Institute of Molecular and Cellular Pharmacology, CNRS, Nice. October 2024.
7. Sourav Banerjee. Invited talk "RNA-based mechanism of inhibitory synapse development: Implications in autism" at XLII Annual Meeting of Indian Academy of Neurosciences 2024. Bengaluru, November/2024.

8. Sourav Banerjee. Invited talk "RNA-based mechanisms of memory: Implications in early life stress" at Institute for Stem Cell Science and Regenerative Medicine, Bengaluru. January 2025.
9. Sourav Banerjee. Invited talk "Synapse-enriched long non-coding RNAs in regulation of memory". Molecular Cellular Cognition Society (Asia) meeting at New York University, Abu Dhabi campus. Abu Dhabi. February 2025.
10. Sourav Banerjee. Invited talk "Long non-coding RNAs in the regulation of memory" at SCAN Centre at Indian Institute of Technology, Mumbai. "Neurons and Epigenetics" symposium jointly organized by TIFR Mumbai and IIT Mumbai. March 2025.

Funding

This work is supported by

1. Regulation of homeostatic plasticity by long non-coding RNAs. ANRF (SERB) grant number CRG/2022/003117. Start Year 2023
2. Investigating the impact of sleep deprivation on memory deficits involving long non-coding RNAs and its implications in Alzheimer's Disease. DBT grant number BT/PR45525/MED/122/311/2022. Start Year 2023.
3. Core fund from National Brain Research Centre.

Collaborators

- ◆ Dasaradhi Palakodeti, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru, India
- ◆ Sheffali Gulati, All India Institute of Medical Sciences, New Delhi, India
- ◆ Swadhin Chandra Jana, National Centre for Biological Sciences, Bengaluru, India.
- ◆ Sharba Bandyopadhyay, Indian Institute of Technology, Kharagpur, India
- ◆ Dhananjay Huilgol, National Brain Research Centre, Manesar, India
- ◆ Soumya Iyengar, National Brain Research Centre, Manesar, India
- ◆ Barabara Bardoni and Carole Gwizdek, Institute of Molecular and Cellular Pharmacology, Nice, France
- ◆ Timothy Bredy, Queensland Brain Institute, St. Lucia, Australia
- ◆ Ted Abel, Iowa Neuroscience Institute, Iowa City, USA

Degrees Awarded

- ◆ Dipanjana Banerjee, PhD
- ◆ Karthick ravichandran, PhD
- ◆ Shreyas Miraj, MSc

Meetings/Conferences organized

- ◆ India | EMBO Lecture course on RNA-protein complexes: from molecular assembly to physiological functions and disease. February 2025.
- ◆ 21st NBRC Foundation Day symposium on "Brain and Society: Clinical and physiological perspective of brain disorders." December 2024.

Scientific Report



Soumya Lyengar

Scientist-VII

Research in my laboratory focuses on understanding changes in the brain involved with cognition in corvids. We also study the effects of the endogenous opioid system on modulation vocalization and vocal learning. A third project focuses on studying structural changes in the developing human auditory cortex.

Senior Research Fellow

◆ Mukta Kumari

Technical Officer

◆ Arvind Singh Pundir

Role of μ -opioid receptor neuromodulation in song learning

The endogenous opioid system is an important neuromodulatory system in the brain, consisting of three main opioid receptor subtypes, μ -, δ - and κ -, respectively) and the opioid ligands, endorphin, enkephalin and dynorphin. The endogenous opioid system has been implicated in a host of neural functions from modulating pain, neuroendocrine functions, food and water intake to complex behaviors such as socialization, motivation and reward. We wanted to study if they were also involved in naturally-occurring reinforcement learning behaviors such as vocal learning, using the zebra finch model system. In this species, only male zebra finches sing in adulthood, having learnt their songs during a sensitive period early in development from a tutor, typically their fathers. The song itself is used for courtship (female-directed or FD song) or for song maintenance (undirected or UD song). Song learning in males is affected by factors such as the social environment and internal reward, both of which are modulated by endogenous opioids.

Earlier studies from our lab had demonstrated that blocking opioid receptors with the general opioid antagonist naloxone led to significant decreases in the number of FD and UD

songs sung by adult male zebra finches. Administration of naloxone also led to changes in the acoustic features of song (significant decreases in goodness of pitch and frequency modulation and a significant increase in inter-syllable intervals). We then decided to study if altering μ -OR modulation was also involved in naturally-occurring reinforcement learning behaviors such as vocal learning, using the zebra finch model system. For our experiments, pairs of juvenile male siblings (35-day-old) were systemically administered the μ -OR-selective antagonist CTAP or vehicle (saline) for a period of 10 days, during the sensitive period. This period corresponds to the beginning of the sensorimotor period when young male zebra finches are listening to their fathers' songs and have begun practicing these songs to perfect them. An analysis of female-directed (FD) songs (recorded when experimental birds attained adulthood) demonstrated that CTAP-treated birds sang significantly more motifs (Figure 1a) and introductory notes versus controls. Furthermore, spectral features of the FD songs including pitch, mean frequency and frequency modulation of CTAP-treated birds were significantly lower than those of their control siblings (Figure 1b-1d). However, there were no significant differences between UD songs with regard to acoustic features across control and treated siblings.

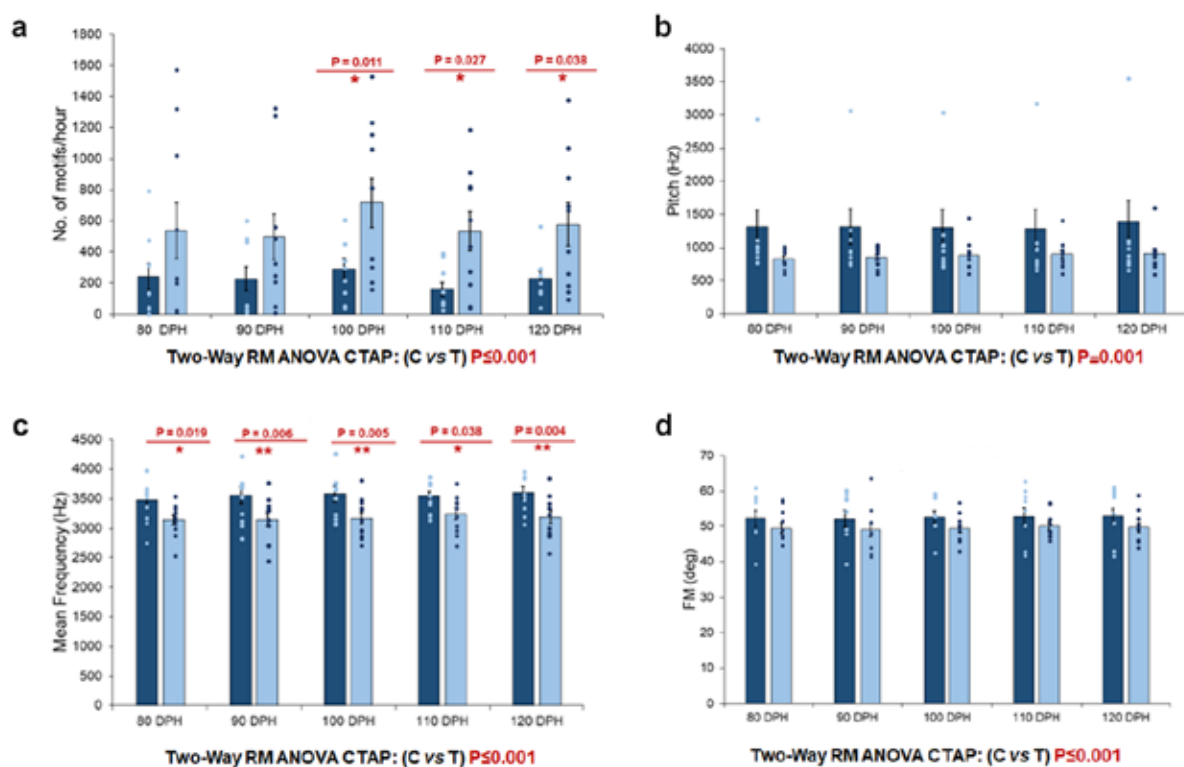


Figure 1: (a) Birds which had been treated with CTAP during the sensitive period sang significantly more motifs per hour compared to their control siblings. There was a significant decrease in (b) pitch, (c) mean frequency and (d) frequency modulation in the songs of treated birds versus those of their control siblings. Bars represent means (dark blue = control and light blue = treated), whiskers represent SEM and scatter plots represent individual data points (Two-Way RM ANOVA followed by Holm-Sidak tests).

Interestingly, we also found that blocking μ -ORs during the sensitive period led to changes in vocal learning. When syllables in the songs of the control and CTAP-treated siblings were compared to those of their fathers, we found that whereas treated birds were able to learn all kinds of syllables that their fathers and controls produced, they copied a significantly greater number of non-paternal syllables versus those sung by controls (Figure 2). Since μ -ORs are known

to be involved in socialization, it is possible that young birds which had been treated with CTAP during the sensitive period also interacted less with their fathers compared to their control siblings, and therefore learned a smaller number of their fathers' syllables.

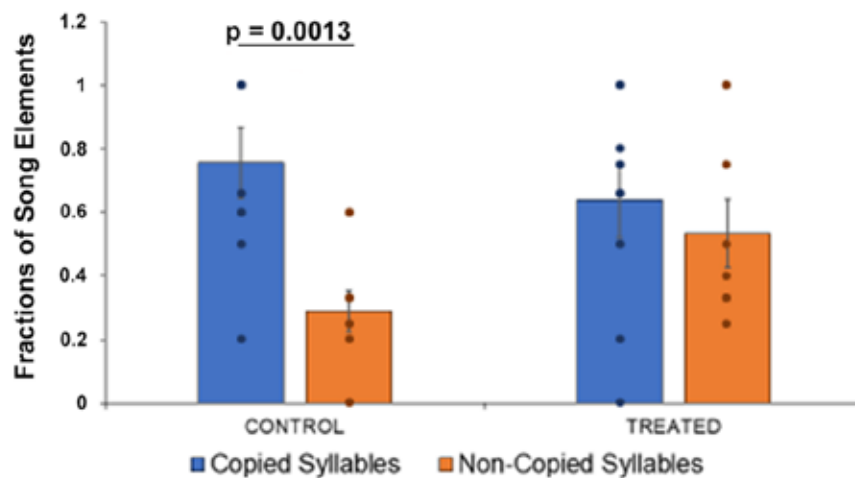


Figure 2: A comparison of copied syllables (blue) versus non-copied syllables (orange) demonstrated that control birds copied more of their father's song and incorporated fewer syllables which were non-copied. In contrast, treated birds learned the same number of copied and non-copied syllables, which were incorporated into their adult songs. Bars represent means, whiskers represent SEM and dots represent data from individual birds (Student T-tests)

Publications

1. Singh UA and Iyengar S (2025). Delta Opioid Receptors affect Acoustic Features of Song during Vocal Learning in Zebra Finches. *BMC Neuroscience*; 26:4; <https://doi.org/10.1186/s12868-025-00927-x> (In the Collection: 'Behavioral neuroscience of vocal learning in avian and mammalian species').
2. Bhatt, S, Verma, AK, Dastidar PG, Kumar, P, Thapa, P, Jacob TJ, Roy, TS, Iyengar, S, Kumaran, S, Ahluwalia BS and Mehta DS (2025). Investigation on morphological and molecular fingerprints of penguin brain using label-free optical imaging and spectroscopic techniques. *Sci. Reports*, 15:4923 1; <https://doi.org/10.1038/s41598-024-76127-0>
3. Parishar P, Rajagopalan M and Iyengar S (2024). Changes in the Dopaminergic circuitry and Adult Neurogenesis linked to Reinforcement Learning in Corvids. *Front Neurosci*. 2024 May 14; 18:1359874. doi: 10.3389/fnins.2024.1359874. PMID: 38808028; PMCID: PMC11130420.

Presentations

1. Soumya Iyengar: Introduction to Neuroanatomy. NeuroTechLab: Applied Techniques in Neuroscience Research; NBRC, Manesar; Aug 6th, 2024.
2. Soumya Iyengar: Using Zebra finches as a model system to study Vocal Deficits in Neurodevelopmental Disorders. Mini Symposium: Autism Spectrum Disorder: Genetic and neural circuit dysfunction of developing brain. Annual Meeting of the Indian Academy of Neuroscience, NIMHANS, Bengaluru; Nov 12-14th, 2024.

3. Soumya Iyengar: The Role of the Opioid System in Singing and Song learning in Zebra Finches. EMBO Workshop on Neuropeptides and Behavioral flexibility. NISER, Bhubaneswar; Dec 5th-8th, 2024.
4. Soumya Iyengar: A Songbird Model System to study Vocal Deficits in Neurodevelopmental Disorders. 21st NBRC Foundation Day Symposium Schedule, NBRC, Manesar ; Dec 13th-15th, 2024.
5. Soumya Iyengar: Wiring the Human Auditory Cortex: Structural Changes during the Sensitive Period; Dr Shankar Oration, BBIF International Biobanking Conference; JNU, New Delhi; Feb 24th -25th, 2025.
6. Soumya Iyengar: Neural Correlates of Learning in House Crows; Brain Ecology and Behavior, National Symposium on Avian Biology, IISER Mohali; March 10th -12th; 2025.

Funding

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Collaborators

- ◆ Prof PC Dikshit, formerly at the Guru Tegh Bahadur Hospital, Delhi
- ◆ Prof B Radotra, formerly at the Dept. of Histopathology, PGIMER, Chandigarh
- ◆ Prof A Mahadevan, Dept. of Neuropathology, NIMHANS, Bangalore
- ◆ Prof TS Roy, AIIMS, New Delhi, Dept. of Anatomy, North Delhi Municipal Medical College and Hindu Rao Hospital.
- ◆ Prof S Gupta, Dept. of Forensic Medicine, AIIMS, New Delhi
- ◆ Prof S. Senthil Kumaran, Dept. of NMR, All India Institute of Medical Sciences, New Delhi.

Degrees Awarded

- ◆ Mukta Kumari, PhD
(Awarded the degree of PhD for her dissertation research entitled 'Role of Mu-Opioid receptors in song learning in male zebra finches (*Taenopygia guttata*)', Sept 2024.)

Meetings/Conferences Organized

1. Training session for teachers of local schools on Neurodiversity in collaboration with Action for Autism (an Indian non-profit, education, training and advocacy organization) at NBRC, Manesar; Sept 9th; 2024.
2. Co-organized an Expert Committee Meeting at NBRC to discuss the proposal 'A Nationwide Consortium for Autism' with Prof Sourav Banerjee at NBRC, Manesar; Sept 20th 2024.
3. Training session for teachers of local schools on Neurodiversity in collaboration with Action for Autism (an Indian non-profit, education, training and advocacy organization) at NBRC, Manesar; Dec 13th; 2024; in conjunction with NBRC's Foundation Day celebrations.

Scientific Report



Vidhya Munnamalai

Scientist-IV

Vidhya Munnamalai, Ph.D. has trained at Rutgers University, Purdue University, the University of Washington and worked as an Assistant Professor in The Jackson Laboratory for 6 years before joining NBRC in late September 2024.

MSc Students

- ◆ Vartika Guleria

Inner ear development and Regeneration

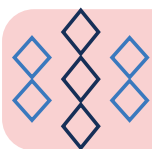
The sensory cells of the inner ear are highly susceptible to damage, and this leads to balance disorders and hearing loss. Like the central nervous system, the sensory cells of the inner ear do not regenerate. We study how progenitors developmentally transition from a proliferative state to organized sensory epithelia. This work is then applied at a translational level to determine we can regenerate damaged/lost sensory cells to curing inner ear deficits.

Presentations

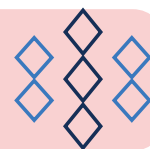
1. **Munnamalai V** (February 2025). EMBO Satellite Meeting, NBRC, Breaking down the barriers to Regeneration in the cochlea.
2. **Munnamalai V** (March 2025). Regional Young Investigator's Meeting, Evolutionary conservation of the auditory system.

Funding

- NBRC Core funds



Publications

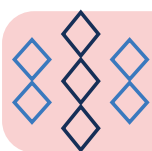


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2. Majumdar A, Siva Venkatesh IP, Swarup V, **Basu A**. Short-chain fatty acids abrogate Japanese encephalitis virus-induced inflammation in microglial cells via miR-200a-3p/ZBTB20/IK β a axis. *mBio*. 2024 Jul 17;15(7):e0132124. doi: 10.1128/mbio.01321-24. Epub 2024 Jun 13. PMID: 38869276; PMCID: PMC11253640.
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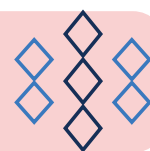
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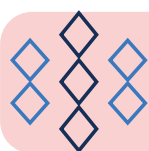
Presentations



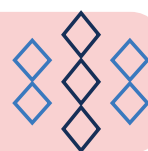
1. **Khan AR.** "MRS principle and applications." NMR based Metabolomics and in vitro Diagnostic Research Workshop, CBMR, SGPGIMS campus, Lucknow, 25 Feb 2025.
2. **Khan AR.** "Diffusion MRI principle and applications." NMR based Metabolomics and in vitro Diagnostic Research Workshop, CBMR, SGPGIMS campus, Lucknow, 26 Feb 2025.
3. **Khan AR et al.** "Microstructural Alterations in Mild & Repetitive Mild Close Head Injuries." SMRM Workshop on 40 Years of Diffusion: Past, Present & Future Perspectives, Kyoto, Japan, 15–20 (17th) February 2025.
4. **Ghosh-Roy A.** "Functional rewiring of neural circuits." Invited seminar, Department of Genetics, Delhi University South Campus, 26 Apr 2024.
5. **Ghosh-Roy A.** "Neural Circuit Repair." Invited seminar, Asia Pacific Worm meeting-24 (APWM24), Indian Institute of Science, Bangalore, 13–16 June 2024.
6. **Ghosh-Roy A.** "Functional rewiring of neural circuits." Invited seminar, National Centre for Biological Science (NCBS), Bangalore, 17 June 2024.
7. **Ghosh-Roy A.** "Regenerating and Reconnecting Neural Circuits." Invited seminar, Centre for DNA Footprinting (CDFD), Hyderabad, 14 Aug 2024.
8. **Ghosh-Roy A.** "Functional rewiring of injured neural circuits." Conference: Intracellular Quality and Metabolic Control from E. Coli to Homo Sapiens, MAHE-MIRM, Bangalore, 27 Aug 2024.
9. **Ghosh-Roy A.** 'RNAi screening using a new neurite injury protocol reveals FGFR receptor tyrosine kinase signalling underlying dendrite regeneration.' Presentation at Cold Spring Harbor meeting: Molecular Mechanisms of Neuronal Connectivity, New York, USA, 10–14 Sept 2024.
10. **Ghosh-Roy A.** "Regenerating and Reconnecting Neural Circuits." Invited talk, 49th Annual Meeting of ISHG and International Conclave on Neurogenetics, NIMHANS, Bengaluru, 20–22 Jan 2025.
11. **Ghosh-Roy A.** "The conserved Fibroblast Growth Factor Receptor based signaling is required for dendrite regeneration." Invited speaker, Molecular Motors Transport & Tracks (M2T2-2025), IIT Jodhpur, 14–17 (17–19) Feb 2025.
12. **Basu A.** "Emerging and Re-emerging Viral Diseases: Host Immunity and Therapeutic Interventions." Durgapur Govt College, DBT Star College event, 21 Aug 2024.
13. **Basu A.** "The Gut-Brain Axis in Viral Infections: How the Microbiome Affects Brain Inflammation." SIRCON-2024, MGM Institute of Health Sciences, Navi Mumbai, 7 Dec 2024. (Oration lecture of Society of Inflammation Research-India)
14. **Basu A.** "The Gut-Brain Connection: Unlocking Potential to Revolutionize CNS Disorder Treatment." ICCNS-2M-2025, NIPER, Ahmedabad, 17–19 Feb 2025. (Plenary lecture)
15. **Basu A.** "Reimagining Therapeutics: Repurposed Drugs for Emerging Viral Diseases." INSA science academies lecture workshop, Department of Biotechnology, Dhanalakshmi Srinivasan University, Trichy, 24–25 Feb 2025.
16. **Basu A.** "Gut Feelings: How the Gut-Brain Axis Influences Brain Health." INSA science academies lecture workshop, Dhanalakshmi Srinivasan University, Trichy, 24–25 Feb 2025.
17. **Basu A.** "The Gut-Brain Axis Explained: Why What You Eat Matters." Microbes: Miracle or Menace, Dept. of Microbiology, Ram Krishna Mission Vivekananda Centenary College, Rahara, 18–19 Mar 2025. (Keynote speaker)

18. **Basu A.** "The Microbiome-Gut-Brain Axis: Mechanisms, Nutrition, and Disease Implications." Institute of Health Science, Presidency University, Kolkata, 21 Mar 2025. (Colloquium speaker)
19. **Banerjee A.** "AI based connectomics for ageing disorders." Invited talk, AAIC 2025, Feb 2025.
20. **Banerjee A.** "Whole brain connectomics platform to gain insights to health and disease." Invited talk, CMC Vellore, Feb 2025.
21. **Banerjee A.** "Whole brain connectomics platform to track health and disease." Invited talk, IISER Berhampore, Aug 2024.
22. **Huilgol D.** "Role of progenitors in cortical circuit assembly." NBRC, Manesar, Feb 2025.
23. **Sen E.** "Epigenetic Regulation and Metabolic Reprogramming in Glioma: Therapeutic Perspectives." Presidency University, Kolkata, Aug 2024.
24. **Sen E.** "Targeting the metabolism-inflammation interface in brain tumors: Therapeutic Implications." 90th Anniversary General Meeting, INSA, SRM University, Dec 2024.
25. **Sen E.** "Metabolic-Epigenetic Shifts in Gliomas: Role of IDH1 Mutation." 49th Indian Society for Human Genetics, NIMHANS, Bengaluru, 22 Jan 2025.
26. **Sen E.** "Targeting metabolic vulnerabilities in Glioma: The IDH1 story." International Conference on CNS Disorders (ICCN2M-2025), NIPER Ahmedabad, 17 Feb 2025.
27. **Sen E.** "Metabolic Moonlighting": Regulators of Glioma Gene Networks." Transcriptional Assembly Meeting, Bose Institute, Kolkata, Mar 2025.
28. **Singh MD.** "Pten knockdown ameliorates Huntington's disease in Drosophila model." Indian Academy of Neuroscience, NIMHANS, Bengaluru, 12–24 Nov 2024.
29. **Borthakur S, Singh MD.** "Alleviation of Myc expression suppresses Myotonic Dystrophy 1 in Drosophila model." Poster, 47th All India Cell Biology Conference, NISER, Bhubaneswar, 16–18 Dec 2024.
30. **Seth P.** "Exploring Brain Disorders using 2D and 3D models of human brain cells." Invited Lecture, ICCATN-25, Department of Pharmacy, BITS Pilani, 21–22 Mar 2025.
31. **Seth P.** "Human brain cell model system as an alternative to animal models – a step towards resilient future." Plenary Speaker, NBHES-2025, MMV, BHU, Varanasi, 20–22 Feb 2025.
32. **Seth P.** "Viruses and the Brain: What We Knew and What is New?" Invited Speaker, Fifth Annual Frontiers of Biology Symposium, IISER-Trivandrum, 7–9 Feb 2025.
33. **Seth P.** "Human fetal brain derived neural stem cells as 2D and 3D models to study healthy and diseased brain." Resource Person, Continued Medical Education on Reverse Pharmacology, CSIR-IICB, Kolkata, 3–8 Feb 2025.
34. **Seth P.** "Novel Insights into pathways of viral neurotoxicity – Implications in cognitive health." Distinguished Lecture, EARTH-2024, CSIR-IITR, Lucknow, 27–30 Nov 2024.
35. **Seth P.** "Insights into SARS-CoV2 mediated neuronal damage–possible mechanism of brain fog in long COVID-19 cases." Invited Lecture, 42nd Annual meeting of IAN, NIMHANS, Bangalore, 12–14 Nov 2024.
36. **Seth P.** "2D and 3D culture for neuroscience research." Invited Guest Faculty, Workshop on Advanced Techniques in Molecular Neurobiology, SNCI Meeting, Panjab University, Chandigarh, 23–29 Sept 2024.
37. **Seth P.** "Neuroinflammation, Neuroinfection and its effect on human brain ageing." IBRO-APRC Symposium, Universiti Putra Malaysia, 12–14 Aug 2024.
38. **Seth P.** Molecular mechanism of SARS-CoV2 mediated neuronal damage in COVID-19, implications in effective management of brain fog patients. International Brain Research Organization (IBRO) sponsored Neuroscience and Pain School, Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (IIT-BHU), Varanasi, India, October 10–16, 2024. (Keynote speaker)

39. **Das P.** "All it needs to quantify neural oscillations is a clever dynamic generative model." Brain Network Dynamics Meeting 2024, Ashoka University, Sonapat, Dec 2024. [Invited]
40. **Banerjee S.** "Synapse-enriched long non-coding RNA SynLAMP regulates local protein synthesis and memory." Short talk, Cold Spring Harbor Symposium on Mechanisms of Neuronal Connectivity, Sept 2024.
41. **Banerjee S.** "Local lncRNome at the synapse: Long non-coding RNAs in synapse development and memory." Invited talk, Neuroscience Research Institute Seminar Series, University of California, Santa Barbara, Sept 2024.
42. **Banerjee S.** "Long non-coding RNAs in regulation of memory." Invited talk, Iowa Neuroscience Institute Seminar Series, University of Iowa, Sept 2024.
43. **Banerjee S.** "Synapse-enriched long non-coding RNAs regulates fear memory formation involving dendritic protein synthesis." Invited talk, Korean Society of Brain and Neural Sciences Annual Meeting, Gyeongju, Oct 2024.
44. **Banerjee S.** "Synapse-enriched long non-coding RNAs in dendritic protein synthesis and memory." Invited talk, non-coding RNA symposium, ETH Zurich, Ascona, Oct 2024.
45. **Banerjee S.** "Long non-coding RNAs at the synapse: Localized partnership with RNA binding proteins to regulate memory." Invited talk, Institute of Molecular and Cellular Pharmacology, CNRS, Nice, Oct 2024.
46. **Banerjee S.** "RNA-based mechanism of inhibitory synapse development: Implications in autism." XLII Annual Meeting of IAN 2024, Bengaluru, Nov 2024.
47. **Banerjee S.** "RNA-based mechanisms of memory: Implications in early life stress." Invited talk, inStem, Bengaluru, Jan 2025.
48. **Banerjee S.** "Synapse-enriched long non-coding RNAs in regulation of memory." Invited talk, Molecular Cellular Cognition Society (Asia) meeting, NYU Abu Dhabi, Feb 2025.
49. **Banerjee S.** "Long non-coding RNAs in the regulation of memory." Invited talk, SCAN Centre, IIT Mumbai, "Neurons and Epigenetics" symposium, Mar 2025.
50. **Iyengar S.** "Introduction to Neuroanatomy." NeuroTechLab: Applied Techniques in Neuroscience Research, NBRC, Manesar, 6 Aug 2024.
51. **Iyengar S.** "Using Zebra finches as a model system to study Vocal Deficits in Neurodevelopmental Disorders." Mini Symposium: Autism Spectrum Disorder, IAN Meeting, NIMHANS, Bengaluru, 12–14 Nov 2024.
52. **Iyengar S.** "The Role of the Opioid System in Singing and Song learning in Zebra Finches." EMBO Workshop on Neuropeptides and Behavioral Flexibility, NISER, Bhubaneswar, 5–8 Dec 2024.
53. **Iyengar S.** "A Songbird Model System to study Vocal Deficits in Neurodevelopmental Disorders." 21st NBRC Foundation Day Symposium, NBRC, Manesar, 13–15 Dec 2024.
54. **Iyengar S.** "Wiring the Human Auditory Cortex: Structural Changes during the Sensitive Period." Dr Shankar Oration, BBIF International Biobanking Conference, JNU, New Delhi, 24–25 Feb 2025.
55. **Iyengar S.** "Neural Correlates of Learning in House Crows." Brain Ecology and Behavior, National Symposium on Avian Biology, IISER Mohali, 10–12 Mar 2025.
56. **Munnamalai V.** "Breaking down the barriers to Regeneration in the cochlea." EMBO Satellite Meeting, NBRC, Feb 2025.
57. **Munnamalai V.** "Evolutionary conservation of the auditory system." Regional Young Investigator's Meeting, Mar 2025.



Awards & Honours – Scientists



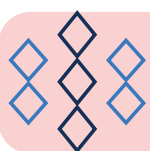
- ◆ **Dr Pankaj Seth, Scientist-VII** - Council Member, Asia Pacific Society for Neurochemistry (APSN), an international society of countries in Asia Pacific, 2024.
- ◆ **Dr Ellora Sen, Scientist-VII** - Elected Fellow of Indian National Science Academy (INSA)-2025
- ◆ **Dr Arpan Banerjee, Scientist-VI** - Elected as Fellows, the National Academy of Sciences, India 2025
- ◆ **Dr Anindya Ghosh Roy, Scientist-VI** - Elected as Fellows, the National Academy of Sciences, India, 2025



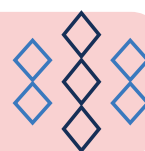
Awards & Honours – Researchers

Researcher	PI	Award
Mr Shashank Saxena	Dr B S Sahu	Won the P.R. Sudhakaran Best Poster Award at the Annual Meeting of the Society of Biological Chemists held at MSU, Baroda, from 27-29 December 2024.
Mr Shashank Saxena	Dr B S Sahu	Won the Best Poster Award at the Workshop on Molecules, Membranes & Organelles, held at TIFR Science, Mumbai. This workshop is part of the renowned Mahabaleshwar Seminar Series.
Dr Sushma Dagar	Dr B S Sahu	Won the Best Poster Award at the Organellar Biology and Membrane Trafficking Meeting (OBMT2024) held at IISER Pune.
Dr Puyam Milan Meitei	Dr B S Sahu	Awarded the DBT-RA Fellowship for the year 2024-2025.





Prestigious National/International Grants & Fellowships



- ◆ **Ignite Life Sciences Foundation** – Dr B S Sahu
- ◆ **ICGEB, Trieste, Italy** – Dr B S Sahu
- ◆ **IBRO, Paris** – Dr B S Sahu
- ◆ **Gate Foundation** – Dr Arpan Banerjee
- ◆ **Wellcome Trust-DBT Senior Fellowship** – Dr Anindya Ghosh Roy
- ◆ **J C Bose Fellowship** – Dr Anirban Basu
- ◆ **SERB-POWER (Promoting Opportunities for Women in Exploratory Research) Fellowship** – Dr Ellora Sen

Patent



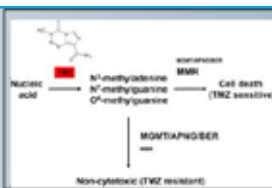
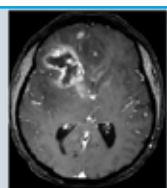
Dr Ellora Sen

Naphthalimide-Se-temozolomide compound and method of preparing the same.

Patent application number: 202431048630

Dated: 25.06.2024 (Filed)

Synthesis and Characterization of a Novel Naphthalimide-Selenium Based Temozolomide Drug Conjugate in Glioma Cells



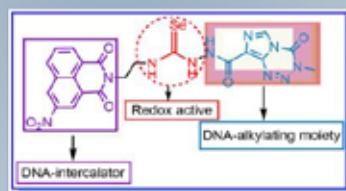
- Gliomas - highly malignant brain tumours
- Standard treatment - alkylating chemotherapeutic agent Temozolomide (TMZ)
- Poor prognosis in patients due to temozolomide resistance
- TMZ resistance associated to diminished oxidative stress and reactive oxygen species (ROS) levels

There is a need for novel drugs to improve the efficacy of TMZ



Synthesis of Naph-Se-TMZ conjugate

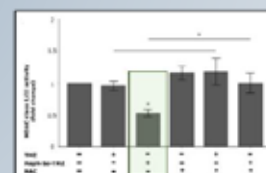
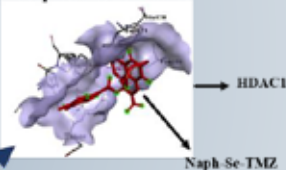
- TMZ: alkylating agent
- Naphthalimide: DNA intercalator
- Selenium: ROS generation



Naph-Se-TMZ

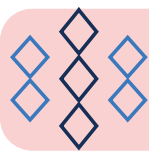
- Significant decrease in cell viability in TMZ-sensitive and TMZ-resistant glioma cells compared to only TMZ treatment
- Higher levels of ROS generation as compared to TMZ

Naph-Se-TMZ inhibits HDAC

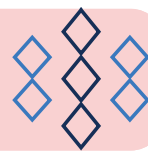


ROS dependent HDAC inhibition

Patent: Naphthalimide-Se-temozolomide compound and method of preparing the same
Patent application number: 202431048630
Dated: 25/06/2024



Events & Outreach



Symposiums & Workshops

The **Regional Young Investigators Meeting (RYIM)** "Building Networks and Collaborations in Interdisciplinary Science," the event brought Delhi-NCR was successfully held from 19 - 21 March 2025, jointly organized by the National Brain Research Centre (BRIC-NBRC), Manesar and Ashoka University (AU), Sonipat. Centered around the theme brought together over 100 participants from across the Delhi-NCR region and neighboring cities.



Crafting Career Workshop at BRIC-NBRC as part of regional young investigator meeting being organized by India bio science /Ashoka university and NBRC.



The BRIC - National Brain Research Centre hosted an **EMBO satellite meeting** on "RNA-based Mechanisms of Neural Development and Physiology" on 21 February 2025, highlighting cutting-edge research on RNA-mediated regulation of neural development, cognition, and autism.

The meeting brought together leading experts in RNA biology, behavioural neuroscience, and developmental neurobiology. Keynote speakers Prof. Ted Abel (Iowa Neuroscience Institute) and Prof. Eric Klann (New York University) presented pioneering work on protein synthesis-dependent control of locomotion and translational regulation of repetitive behaviours in autism models.

Highlights included Dr. Oraine Mauger (Max Planck Institute) on RNA splicing in memory, Dr. Sourav Banerjee (NBRC) on non-coding RNA at synapses, and Dr. Ravi Muddashetty (Centre for Brain Research, Bangalore) on RNA-driven neuronal development in autism organoids. Additional talks covered nerve regeneration, neuronal polarity, cortical cell-type specification, and cochlear development. The event also provided a platform for young researchers to share their work and network with global leaders.



The meeting preceded the main EMBO conference, “RNA–Protein Complexes: From Molecular Assembly to Physiological Functions” (24–28 February, Pune), organized by Dr. Sourav Banerjee, Dr. Amitava Majumder, and Dr. Florence Besse.

The National Brain Research Centre celebrated its **21st Foundation Day** during 15th – 16th December 2024 with a symposium titled “**Brain and Society: Clinical and Physiological Perspectives of Brain Disorders.**” The event spotlighted recent advances in neurodevelopmental research, with a special emphasis on autism spectrum disorders.

This hybrid meeting organized by Prof. Sourav Banerjee, Prof. Anindya Ghosh Roy and Prof. Sheffali Gulati brought together leading national and international scientists who have made pioneering contributions to both clinical and fundamental autism research.

Keynote highlights included:

- ◆ **Prof. Peter Scheiffele (Biozentrum, Switzerland)** – neuromodulation of neural circuits in autism and European initiatives in autism research.
- ◆ **Prof. Vikaas Sohal (UCSF, USA)** – how rhythmic brain activity shapes emotional states and its alterations in autism and schizophrenia.
- ◆ **Prof. Sheffali Gulati (AIIMS, New Delhi)** – changes in the genetic landscape of autistic patients and their link to phenotypic variation.
- ◆ **Dr Soumya Sundaram (Sree Chitra Institute, Thiruvananthapuram)** – Developmental changes in autism using medical imaging.
- ◆ **Dr. Moinak Banerjee (RGCB, Thiruvananthapuram)** – epigenetic studies in autistic patients from southern India.

- ◆ **Dr. Manojit Debnath (NIMHANS, Bangalore)** – immune profiling of autism patients.
- ◆ **Dr. Vinod Scaria (Karkinos Healthcare, Bangalore)** – efforts to identify autism risk genes in Indian patients.
- ◆ **Dr. Soumya Iyengar (NBRC, Manesar)** – insights into social communication from vocalization deficits in songbird models.
- ◆ **Dr. Sharba Bandyopadhyay (IIT Kharagpur)** – neural circuit mechanisms of communication and vocalization deficits.
- ◆ **Dr. Arkarup Banerjee (CSHL, USA)** – neural basis of social communication.
- ◆ **Dr Dhanjay Huilgol (Duke University, USA)** – developmental basis of cell type specificity
- ◆ **Dr. Vidhya Munnamalai (NBRC, Manesar)** – auditory circuit development and its disruption in autism.
- ◆ **Dr. Sourav Banerjee (NBRC, Manesar)** – developmental neural circuit defects mediated by non-coding RNAs.

The symposium also explored fundamental aspects of neural communication and synaptic physiology, with Prof. Krishanu Ray presenting on neural transport and Dr. Anindya Ghosh Roy on the molecular framework of touch sensation. Dr Proloy Das highlighted newly developed machine learning tools for sensory and cognitive processing.

The symposium provided a platform for graduate students and postdoctoral researchers to present their work and engage with peers group worldwide. The event concluded with a cultural evening featuring Santoor maestro Chiradeep Sarkar, accompanied on tabla by Rupak Bhattacharjee.



One day symposium in collaboration with Ashoka to discuss scientific research & future collaboration (28th September, 2024).



Outreach Activities for Societal Benefit

Under the **World Health Day** week, the Health Department organized a district-level awareness program and seminar in Jhajjar, Haryana. Prof. Krishanu Ray attended as the Chief Guest, & Dr Pankaj Seth participated as the keynote speaker.



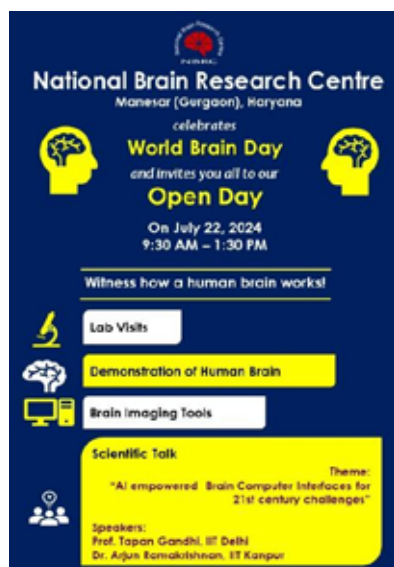
Government School Teacher Sensitization Programs on ASD

(9th September & 13th December, 2024)



Visits by School and College Students – Open Days

World Brain Day (22nd July, 2024)



National Science Day (28th February, 2025)



National Space Day (23rd August, 2024)

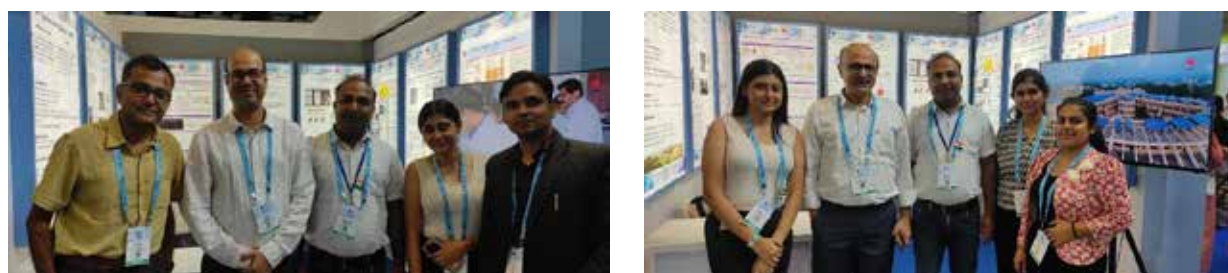


National Exhibitions

IISF 2024 (November 30 to December 3, 2024)



Global Bio India 2024 (12-14 September, 2024)



Training Activity

The **NeuroTechLab** (5-9 August, 2024) aims to train & empower individuals in cutting-edge neuroscience research.



NBRC Student and faculty community attended virtually the inaugural event of the spectacular **student placement conclave**.



Seminars & Talks



Dr. Anna Sircova
Creative Time Studio



Dr. Praveen Kulkarni
North Eastern University



Prof Mriganka Sur
MIT



Dr. Tapan Gandhi
IIT Delhi



Dr. Anand Deshpande
Persistent Systems



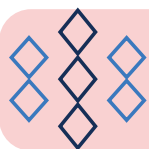
Dr. Kavita Babu
IISc, Bangalore



Dr. Monsheel Sodhi
Loyola University, Chicago, USA



Dr. Uma Sharma
AIIMS, New Delhi



Acknowledgment



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