APSN–FAONS–HKSN 2026

CONFERENCE ABSTRACT BOOK

Symposia, Lectures, Oral Sessions and Posters

23–26 August 2026

Cheung Kung Hai Conference Centre, University of Hong Kong

147 scheduled talks • 170 poster abstracts

Booklet contents

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PART I

Symposia, Lectures and Oral Sessions

Session introductions, chairs, speakers, individual talk abstracts and supplied biographies

Sunday, 23 August 2026

SS1 ALBA-IBRO Session on Scientific Mobility and Identity in Neuroscience Careers

14:30–16:00 | LT 1

Session overview

This forum explores how scientific mobility, cultural identity, and international collaboration shape careers in neuroscience. Through structured reflection and discussion, it considers the opportunities and barriers that accompany cross-border training, institutional mobility, and participation in global research networks. The session aims to strengthen inclusive professional communities, mentorship, and regional collaboration across the neuroscience ecosystem.

Participants

Dorothy Tse • *Jee Hyun Kim* • *Mohamed Shaker* • *Jacque Ip* • *Tasia Asakawa* • *Sung-Jin Jeong*

SS2 Advanced Neuroimaging for Circuit & Brain-wide Analysis

14:30–16:30 | LT 3–4

Chair: *Wing Ho Yung*

Session overview

This session examines how advanced neuroimaging is expanding the scale and precision of circuit neuroscience. It brings together approaches for recording cellular activity in behaving animals, mapping molecular and circuit features across intact tissue, and visualizing fast intracellular signalling in living brain networks. Together, these methods illustrate how multimodal imaging can connect dynamic neural activity with molecular organization and brain-wide architecture.

Bernd Kuhn

Okinawa Institute of Science and Technology, Japan

14:35–15:10 Imaging neuronal activity in the cerebellar cortex of behaving mice

The cerebellum is one of the key structures for motor coordination and adaptation. In my talk, I will give examples of how we combine behavioral tasks with 1P and 2P imaging of neuronal activity of the cerebellar cortex.

At first, I will present a tongue-interception task in which naïve mice use a reactive strategy to catch a food pellet, while expert mice use an anticipatory strategy. The anticipatory strategy relies on visual cues and requires ipsilateral neuronal activity in Crus I of the cerebellum. Specifically, molecular layer interneurons in Crus I, but not in Crus II, show a plateau of Ca2+ activity seconds before the pallet passes in front of anticipatory mice, but not reactive mice. This indicates that anticipatory control via the cerebellum is built upon sensory representations encoded by interneurons.

In the second part of my talk, I will focus on Purkinje neurons, the sole output neurons of the cerebellar cortex. Purkinje neurons receive and integrate excitatory input from one or two climbing fibers and about 70000 parallel fibers, the axons of granule cells, and inhibitory input from molecular layer interneurons. I will present two-photon voltage-imaging experiments using synthetic and genetically encoded voltage sensors in Purkinje neurons and molecular layer interneurons. With this method, not only can dendritic complex spikes be detected and resolved, but also local dendritic spikes and excitatory postsynaptic potentials in awake mice. We can show that the Purkinje dendrite acts as a coincidence detector of the climbing fiber and the parallel fiber inputs.

In the last part, I will present a more general topic: In vivo imaging experiments are often hampered by motion artifacts. Therefore, we developed a new motion correction toolbox, Flow-Registration. Flow-Registration is based on a variational optical flow framework and is optimized for confocal and two-photon imaging data. The toolbox can handle 1D, 2D, and 3D data for motion analysis, compensation, and amplification. The toolbox can be downloaded here: https://github.com/FlowRegSuite.

Hei Ming Lai

The Chinese University of Hong Kong

15:10–15:45 Routine 3D multi-omics for system-wide circuit- and molecular-level imaging

We review and present the novel techniques that can achieve routine 3D whole mouse organ imaging with referenced multi-omics in standard biology labs with reasonable core facility equipment. Historically, whole mouse organ 3D imaging requires meticulous planning and sophisticated techniques with questionable reproducibility. The core of the problem lies in sample processing, where probe penetration can be suboptimal, uneven, fluctuates in performance, or consumes the tissue due to degradations. We developed the chemistry for whole mouse brain multiplexed immunostaining and tracer imaging, which achieves robust, fast and uniform probe penetration without any specialized equipment. Combined with light-sheet microscopy, one can obtain whole brain 4-plex immmunostaining in 1 week, with a cyclical 3D staining adaptation achieving 28-plex imaging in 1000μm-thick mouse brain sample. Since 2025, this techniques has been used in >100 labs in 15 countries via a commercialized kit. Importantly, the tissue remains intact for downstream sequencing and spatial transcriptomics studies, which we demonstrate by mapping >0.5 billion transcripts of 6518 genes to a 3D-imaged human cancer block with subcellular registration precision. We will conclude the talk by providing a practical guidance on how every laboratory can gain access to these powerful methodological platforms.

Hideji Murakoshi
National Institute for Physiological Sciences, Japan

15:45–16:20 **Imaging RhoGEF-RhoGTPase signaling by 2-photon fluorescence lifetime imaging microscopy**

Intracellular signal transduction involves numerous biochemical reactions, primarily comprising protein-protein interactions and protein conformational changes. Monitoring Förster resonance energy transfer via two-photon fluorescence lifetime imaging microscopy (2pFLIM-FRET) is a powerful approach for visualizing such biochemical reactions in living cells within tissue. In neurons, structural long-term potentiation (sLTP)—the long-lasting enlargement of dendritic spines—requires mechanisms that convert transient calcium influx into sustained biochemical signaling. Although Rho GTPases exhibit long-lasting activation essential for sLTP, their upstream regulators remain elusive.

To systematically address how Rho guanine nucleotide exchange factors (RhoGEFs) regulate Rho GTPases, we used 2pFLIM-FRET to profile the substrate specificity of all ~80 human Dbl/Pleckstrin homology (DH/PH) domains at the single-cell level. Based on this screen, we focused on the spatiotemporal dynamics of FGD1, a Cdc42-specific GEF, during sLTP in mouse hippocampal slice cultures using glutamate uncaging and FLIM-based probes. FGD1 accumulated in dendritic spines in an input-specific manner following glutamate uncaging, remaining enriched for over 30 minutes. FGD1 knockdown significantly impaired the maintenance of spine enlargement and reduced Cdc42 activity. Domain analysis indicated that the N-terminal region targets actin-rich regions, while the PH1-FYVE domain drives membrane binding, together underlying its spine-specific retention.

By leveraging advanced 2pFLIM, we established a foundational framework for RhoGEF specificity and identified FGD1 as a key molecular node sustaining Cdc42 activation during synaptic plasticity. This study demonstrates how systematic molecular imaging bridges the gap between biochemical networks and circuit-level structural plasticity.

GL1 Large Scale Cortical Population Codes

14:30–15:20 | LT 2

Chair: *Michael Hausser*

Kenneth Harris
UCL Queen Square Institute of Neurology, United Kingdom

14:30–15:20 Large Scale Cortical Population Codes

The cortex processes information through the parallel activity of millions of neurons, and understanding the "population code" these cells use to express information is key to understanding cortical function. Theories for cortical population coding have a long history, but only in the last decade has it become possible to monitor enough neurons simultaneously to address the question experimentally. This talk will describe how large neuronal populations in visual cortex encode sensory and non-sensory information, based on large-scale two-photon calcium imaging, Neuropixels electrodes, and transcriptomic cell type identification.

The results indicate that primary visual cortex encodes visual stimuli and non-visual information in orthogonal dimensions, with activity in different non-visual dimensions related to the activity of different inhibitory transcriptomic subtypes. Cortical responses to even simple visual stimuli such as oriented gratings use a high-dimensional population code, which is theoretically advantageous but contradicts classical models based on smooth tuning curves. We resolved this contradiction using an AI-science system, which found an equation accurately matching both non-smooth single-cell tuning and high-dimensional population coding. High-dimensional population codes allow downstream neurons to perform complex computations using simple linear synaptic integration, and we suggest that encoding information into high-dimensional form is the cortex's primary function.

Biography

Professor Kenneth Harris studied mathematics at Cambridge University, obtaining a B.A. and Part III in mathematics in 1993. He received his PhD in computational neuroscience at UCL in 1998, and then moved to Rutgers University for postdoctoral work with Gyuri Buzsaki. He started his independent laboratory at Rutgers University in 2003, studying neuronal population activity in the neocortex. In 2009 he moved to Imperial College London as Professor of Neurotechnology. In 2012 he moved to UCL where he is Professor of Quantitative Neuroscience and co-leads the Cortex Lab together with Matteo Carandini.

FLASH Flash Talks: Selected Posters

15:30–16:30 | LT 2

Chair: *Kwok On Lai*

15:30–15:35 **Introduction**

Hanane Tahiri

15:35–15:40 **24-EP3 — Inhibiting Connexin 43 Hemichannel Opening Tempers Irradiation-induced p65 NF-κB And YAP Modulation In Astrocytes And Limits Astrogliosis**

Haoyu Xu

15:40–15:45 **26-P003 — Posterior perirhinal cortex directs dorsal CA1 cognitive map formation**

Xuejun Li

15:45–15:50 **25-P033 — C1qtfn4 is a locally translated mRNA that encodes the secretory factor CTRP4 for synapse formation of hippocampal neurons**

Yoon Ji Kwon

15:50–15:55 **25-P046 — Low-frequency electrotherapy for neocortical epilepsy depends on sensory deficits**

Priya Dev

15:55–16:00 **25-P017 — Transcriptomic Analysis Reveals Neuroinflammatory, Viral-Response, and Synaptic Pathway Dysregulation in Vascular Dementia**

Xinyu Chen

16:00–16:05 **25-P030 — Young Fecal Microbiota Transplantation Rejuvenates Neural Regenerative Capacity in Aged Mice via Remodelling of the Gut Microbiota-Metabolite Axis**

Siya Peng

16:05–16:10 **25-P036 — The association of associative striatum glutamatergic levels and whole-brain resting-state functional connectivity in clinical high risk for psychosis**

Haruka Takano

16:10–16:15 **25-EP2 — Fixation with the two-carbon dialdehyde glyoxal facilitates multiscale label-free 3D brain imaging in mice**

Hong-Yan Geng

16:15–16:20 **26-P043 — Regulation of Motor Learning by Apical and Basal Dendritic Inputs to M1 L5 Pyramidal Neurons**

Jing-Da Qiao

16:20–16:25 **26-P018 — Mechanism-Based Drugs and Oligogenic Refractory Epilepsy**

Quanxiang Xian

16:25–16:30 **26-P029 — Rapid rescue of despair behaviors by sonogenetic neuromodulation of the mPFC-DRN pathway**

PL1 From Pecking Order to Ketamine – Neural Mechanisms of Social and Emotional Behaviors

17:00–18:00 | Faculty Board Room

Chair: *Ying-Shing Chan*

Hailan Hu

School of Medicine, Zhejiang University, China

17:00–18:00 **From Pecking Order to Ketamine – Neural Mechanisms of Social and Emotional Behaviors**

Emotions and social interactions color our lives and shape our behaviors. Using animal models and engineered manipulations, we aim to understand how social and emotional behaviors are encoded in the brain, focusing on the neural circuits underlying dominance hierarchy and depression. This lecture will highlight our recent discoveries on how downward social mobility leads to depression; how ketamine tames depression by blocking burst firing in the brain's anti-reward center; and, how glia-neuron interaction plays a surprising role in this process. I will also present our recent work on the mechanism underlying the sustained antidepressant activity of ketamine and its brain region specificity. With these results, we hope to illuminate on a more unified theory on ketamine's mode of action and inspire new treatment strategies for depression.

Biography

Hailan Hu is Professor and Director of School of Brain Science and Brain Medicine at Zhejiang University. She received a BA in Biochemistry from Beijing University and a PhD in neuroscience (with Corey Goodman) from UC Berkeley. After a postdoctoral training with Roberto Malinow at CSHL, she joined the faculty of Institute of Neuroscience, Chinese Academy of Sciences. Since 2015, she has been professor at Zhejiang University. Her laboratory seeks to understand how emotional and social behaviors are encoded and regulated in the brain, with a main focus on the neural circuitry underlying depression and social dominance. Her team has identified the neural mechanism underlying the winner effect, by which individuals increase their chance of winning after previous victories. Her recent work has uncovered a new model to explain the etiology of depression and the rapid antidepressant actions of ketamine, involving NMDA receptor-dependent burst activity of lateral habenular neurons. Her work has led to the identification of several molecular targets for developing new antidepressant drugs. She is a recipient of the IBRO-Kemali International Prize and the L'Oreal-UNESCO for Women in Science International award.

Monday, 24 August 2026

PL2 The New Biology of Alpha-Synuclein: From Synaptic Protein to Diverse Pathological States

09:00–10:00 | LT 3–4

Chair: *Jee Hyun Kim*

Glenda Halliday

Macquarie University, Sydney, Australia

09:00–10:00 The New Biology of Alpha-Synuclein: From Synaptic Protein to Diverse Pathological States

Alpha-synuclein (α-synuclein) is one of the most abundant proteins in the nervous system. It has traditionally been viewed as a presynaptic neuronal protein whose misfolding and aggregation drives Parkinson's disease and related synucleinopathies. However, emerging evidence indicates a much more complex biology. α-Synuclein is not highly expressed in all neuronal populations, and it is expresses in different non-neuronal cell types. Many cell types can also extrude α-synuclein, either directly or within vesicles, although its functions across diverse cell types remain incompletely understood.

α-Synuclein exists in multiple conformational and post-translationally modified states that may facilitate transitions from physiological to pathological forms, often in a cell type-specific manner. It interacts with diverse partners, including structural proteins, lipids and RNAs, contributing to substantial heterogeneity in α-synuclein pathology across Parkinson's disease, dementia with Lewy bodies and multiple system atrophy. Rather than a uniform pathological species, α-synuclein forms distinct intracellular structures and molecular states, including Lewy bodies, Lewy neurites, glial cytoplasmic inclusions and diverse intranuclear structures, some of which may be reversible. These forms vary according to disease, brain region and cell type.

This diversity may help explain why disorders sharing α-synuclein pathology produce markedly different clinical phenotypes and rates of progression. The critical question is therefore not simply whether α-synuclein aggregates, but which molecular forms accumulate, in which cells, within which subcellular compartments, and at what stage of disease. Although diverse α-synuclein aggregates occur in human brain and can propagate in experimental models, which forms initiate and drive neurodegeneration remains unresolved.

The new biology of α-synuclein therefore moves beyond a single pathogenic protein towards a spectrum of dynamic molecular states. Defining these states in human brain tissue and linking them to cellular responses, vulnerabilities and clinical phenotypes will be critical for developing biologically informed biomarkers and therapies targeting disease-driving α-synuclein species.

Biography

Professor Glenda Halliday is a career neuroscientist specialising in neurodegeneration (h-index 154, >120,000 cites, Google Scholar). She has been a Fellow of the National Health & Medical Research Council (NHMRC) since 1990 and is currently a NHMRC leadership fellow at Macquarie University. Glenda started her research in neuroscience by studying the neurochemical dopamine and its systems in a variety of animal species, including humans. Her focus on understanding the brain and its workings in people has distinguished her neuroscience career. Her research has provided the evidence base for international diagnostic criteria for neurodegenerative diseases. Recognitions include memberships to the Australian Academy of Science and the Australian Academy of Health and Medical Sciences and an Order of Australia, as well as through the following and other awards; Distinguished Achievement Awards 2025 International Parkinson's & Movement Disorders Society & 2023 Australian Neuroscience Society, 2022 NSW Scientist of the year, and 2021 Robert A. Pritzker Prize for Leadership in Parkinson's Research by the Michael J Fox Foundation.

S01 Neurochemical mechanisms underpinning complex behaviors

10:30–12:30 | LT 3–4

Chair: *Andrew Lawrence*

Session overview

This symposium examines neurochemical mechanisms that shape complex behaviour across learning, sensory processing, social interaction, affect, and empathy. It brings together circuit-level, molecular, and systems approaches to understand how neuromodulators and local network dynamics influence behavioural adaptation. The session emphasizes how integrated analysis across brain regions and cell types can clarify mechanisms relevant to both normal behaviour and neuropsychiatric illness.

Lucy Palmer

The Florey Institute of Neuroscience and Mental Health, Australia

10:30–11:00 Dynamics of serotonergic signalling in the cortex during learning

Neuromodulatory signals in the cortex play an important role in sensory processing. However, how these signals dynamically contribute to sensory-based behavior is largely unknown. Here, we investigated the role of serotonergic neuromodulation in the cortex using simultaneous calcium and serotonin imaging in pyramidal neurons within the primary somatosensory cortex in mice during learning of a tactile-association task. Throughout learning, there was a significant increase in serotonin levels during correct behavior. This serotonergic signaling was differentially correlated with changes in calcium responses in layer 2/3 pyramidal neurons during learning, with correlated and anti-correlated calcium activity in dendrites and soma respectively. Taken together, this study illustrates that serotonin and calcium activity in cortical neurons are differentially correlated during learning, highlighting a possible spatiotemporal gating role of serotonergic modulation in sensory-driven cortical signaling.

Yuki Ito

Kyushu University, Japan

11:00–11:30 Spatial proteomics uncovers presynaptic diversity across medial prefrontal circuits including a socioemotional pathway

Synaptic functional diversity is largely shaped by protein composition, which varies across neuron types, synapse subtypes and long-range neural pathways. Defining the molecular determinants of this diversity is essential for understanding normal circuit function and how it becomes dysregulated in neurological and psychiatric disorders. However, obtaining synaptic proteomes with high spatial and circuit specificity remains challenging: conventional biochemical fractionation is difficult to restrict to defined neural pathways and is prone to contamination by non-synaptic proteins. Here we present Projection-eXclusive BioID (ProX-ID), an in vivo proximity labelling strategy that selectively tags synaptic proteins within anatomically defined neural pathways for spatial proteomics. Applying ProX-ID to the medial prefrontal cortex (mPFC)-centric circuits, we reveal robust presynaptic molecular divergence across six projection-defined pathways, including efferent projections to the basolateral amygdala (BLA), nucleus accumbens, thalamus, hypothalamus and cortex, as well as the afferent projection from the BLA to the mPFC. Across these circuits, we identify >1,300 projection-enriched synaptic proteins and uncover a previously uncharacterised presynaptic protein enriched in the mPFC–BLA pathway. Functional perturbation of this protein reduces synapse density and synaptic transmission and disrupts anxiety-related, social and fear-related behaviours, linking projection-resolved proteomic features to circuit-relevant phenotypes. More broadly, ProX-ID provides a versatile framework to map the molecular architecture of defined neural pathways and to dissect circuit-selective synaptic vulnerability in disease.

Joanna Yau

University of New South Wales, Australia

11:30–12:00 The role of dopamine in safety learning

Fear is an adaptive emotion that enables us to detect and respond to threat. However, fear needs to be tightly regulated - it needs to be switched on when danger is near but switched off when danger is absent. When this regulation fails, fear can become persistent and excessive, and this is a key characteristic of anxiety and stress related psychological disorders such as phobias and PTSD. In this talk, I will present evidence for the role of dopamine in safety learning - the learning about the absence of danger. First, recording from neurochemically identified midbrain dopamine neurons reveal that activity of

dopamine neurons predicts the extent of safety learning. Next, I will present recordings of dopamine release in the amygdala and describe dopamine dynamics across fear and safety learning Together, these findings identify a key role for dopamine neuromodulatory signalling in fear regulation.

Sehoon Keum
Institute for Basic Science, Republic of Korea

12:00–12:30 **The Neurobiology of Empathy: Rodent Models and Psychiatric Implications**

Affective empathy enables individuals to detect and respond to the emotional states of others. Disruptions in empathic processing are common across a broad spectrum of psychiatric conditions, suggesting the existence of shared circuit-level and molecular mechanisms. This talk explores recent advances in understanding the neurobiological basis of observational fear, a rodent model of affective empathy. I will first present the behavioural and circuit-level mechanisms underlying empathic freezing, with particular emphasis on how specific neuronal ensembles in the anterior cingulate cortex (ACC) encode the affective states of conspecifics in distress. I will further discuss how perturbations of ACC circuit function give rise to broader impairments in socio–emotional processing. By integrating molecular, genetic, and systems-level circuit approaches, this work defines conserved neurochemical and circuit principles governing empathic behaviour and establishes a mechanistic framework for its dysregulation in neuropsychiatric conditions.

S02 Precision neuromodulation across scales: from circuit mechanisms to therapeutic translation in brain disorders

10:30–12:30 | LT 2

Chair: *Jing-Ning Zhu*

Session overview

This symposium considers precision neuromodulation across experimental and translational scales. It examines how electrical, ultrasound-based, and circuit-targeted interventions can influence neural activity, plasticity, and behaviour, and how these approaches may be adapted for brain disorders. The session highlights the need to connect mechanistic insight, controllable stimulation technologies, and clinically meaningful outcomes when developing next-generation neuromodulatory therapies.

Lei Wei Lim
Department of Biosciences and Bioinformatics
Xi'an Jiaotong-Liverpool University, Suzhou, China

10:30–11:00 High Frequency Stimulation of the Medial Prefrontal Cortex: From Antidepressant to Memory Enhancement

Depression and dementia are among the most severe global mental health challenges, affecting millions of people across all ages and regions. Current treatments for depression and dementia suffer from critical limitations, including low therapeutic efficacy and high treatment failure rates, leaving a large population of patients without effective relief. Deep Brain Stimulation (DBS), a neuromodulatory technique, holds considerable promise, yet its underlying mechanisms remain poorly understood.

We demonstrated that DBS of the medial prefrontal cortex (mPFC) elicits robust anxiolytic and antidepressant-like effects, compared with several other candidate brain stimulation targets for antidepressant therapy. Using electrophysiological and biobehavioral approaches, we showed that these effects are mediated via a brain circuit involving serotonergic, dopaminergic, and glucocorticoid receptor function in the midbrain and hippocampus. We further examined the impact of mPFC DBS on fear memories and found that mPFC DBS applied during the memory consolidation phase represents a critical window for disrupting fear memory. This effect occurs through molecular mechanisms involving hippocampal dopamine D2 receptors and specific neurotransmission responses to mPFC DBS.

Notably, we provide the first evidence that mPFC DBS can enhance learning and memory function through a mechanism involving hippocampal neurogenesis, accompanied by distinct gene expression patterns related to G protein coupled receptor pathways in both neurogenic and non-neurogenic processes. Furthermore, we demonstrated that in an aged animal model of dementia, mPFC DBS modulates DNA methylation to activate the PKA-CaMKIIa-BDNF pathway via neuroplastic and neurotransmission mechanisms. These findings suggest that mPFC DBS may represent a novel and effective intervention for dementia-related disorders. Collectively, our results support mPFC DBS as a promising novel treatment for depression and dementia-related disorders. A key limitation, however, is that our findings are based on animal models; thus, clinical translatability to humans remains to be validated.

Hyunjoo Jenny Lee
School of Electrical Engineering
Korea Advanced Institute of Science and Technology (Kaist), Daejeon, Republic of Korea

11:00–11:30 Ultrasound-mediated Neuromodulation

In the current aging society, the number of patients suffering from degenerative brain diseases is continuously increasing. However, many of these brain disorders are intractable and difficult to treat. Non-invasive brain stimulation is an attractive alternative method to a pharmaceutical approach that attempts to treat brain disorders through physical stimulation. Among the various direct brain stimulation techniques, such as electrical, magnetic, and optical, ultrasound has been proposed as a new modality for neuromodulation due to its distinct advantages such as high spatial resolution and in-depth targeting.

As ultrasound modality is still in the early stages of development, further investigations on various aspects such as neuromodulation mechanism, therapeutic effects, and safety are still required. Although ultrasound technology is a mature biomedical tool developed from ultrasound imaging, many new technological advancements such as miniaturized devices based on microelectromechanical systems (MEMS) technology have been recently introduced for the specific purpose of

neuromodulation. In this talk, I will introduce these new neurotools which are essential to uncovering the fundamental mechanisms of ultrasound brain stimulation and ultimately to developing an effective therapeutic means for brain disorders.

Lei Sun
Department of Biomedical Engineering
The Hong Kong Polytechnic University

11:30–12:00 **Ultrasound Neuromodulation and Sonogenetics**

Noninvasive and accurate control of neuronal activity in deep brain is critical for probing brain function and treating brain dysfunctions. Transcranial low-intensity ultrasound is a promising neuromodulation modality, with the advantages of non-invasiveness, deep penetration and high spatiotemporal accuracy. However, the focal spot of an ultrasound beam is still much larger than a small set of neurons, making it difficult to pinpoint a small target and precisely manipulate specific neural circuits and induce desired behaviors. In this talk, I will introduce our efforts and results in the development and refinement of the sonogenetics approach, from initial in vitro proof-of-concept demonstration, followed by in vivo validation in deep brain striatum, to a higher-order behaviors through manipulation of specific pathway. Finally, I will demonstrate the utility of sonogenetics in various neurological diseases models.

Jing-Ning Zhu
Department of Physiology, School of Life Sciences
Nanjing University, Nanjing, China

12:00–12:30 **Cerebellar rTMS Targeting the Cerebello-Nigral Circuit Improves Motor Deficits in Parkinson's Disease**

Although the cerebellum's contribution to Parkinson's disease (PD) has long been overlooked, accumulating evidence underscores its reciprocal connectivity with the basal ganglia and pivotal role in PD pathophysiology. Here, we reveal that cerebellar nuclei provide direct glutamatergic projections to dopaminergic neurons in the substantia nigra pars compacta (SNc), alleviating motor deficits in a PD rat model. To enable precise, targeted modulation, we developed a novel, portable, focused TMS instrument for facilitating enhanced circuit-specific intervention.

Strikingly, low-frequency rTMS targeting the cerebellar cortex, which exerts a potent inhibitory influence on the cerebellar nuclei, yields sustained motor improvements in both Parkinsonian rats and human patients. Mechanistically, this cerebellar rTMS likely promotes dopaminergic neuron plasticity and survival by engaging the cerebello-nigral pathway, suggesting a disease-modifying intervention that targets underlying neurodegeneration rather than mere symptomatic relief. These findings position the cerebellum as a promising non-invasive neuromodulation target in PD, establishing a novel circuit-based, disease-modifying therapeutic framework that advances beyond conventional symptom management toward potential slowing of disease progression and restoration of basal ganglia function.

SS3 Bridging Basic & Clinical Neuroscience Session 1

10:30–12:30 | LT 1

Chair: *Lin Ong*

Session overview

This translational session connects clinical problems with mechanistic neuroscience and therapeutic development. It considers how patient observations, disease models, molecular pathways, and emerging interventions can inform one another across the path from bedside to laboratory and back again. By bringing together neurological, neuromuscular, neurodegenerative, and post-stroke perspectives, the session highlights practical routes toward more precise diagnosis, prevention, and treatment.

Sophelia Chan

Department of Paediatrics and Adolescent Medicine, LKS Faculty of Medicine, The University of Hong Kong; Department of Paediatrics and Adolescent Medicine, The Hong Kong Children's Hospital, Hospital Authority; Paediatric Neurology, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital

10:30–11:00 Translational Research for neurological diseases: BBB - Bedside to Bench and Back or Bench to Bedside and Back?

The current sharing highlights how clinical insights guide laboratory research and vice versa, advancing personalized treatment, through the illustration of two pediatric onset neurological diseases.

'Bedside to bench and back': Our patient with Congenital Insensitivity to Pain with Anhidrosis (CIPA), caused by NTRK1 mutations, initially presented with pain insensitivity and anhidrosis. Her severe skeletal issues notably paraplegia and total knee destruction due to Charcot spine and Charcot joint, highlighted the aggressive osteoarthropathy and prompted our deeper investigation. Our extensive literature review found skeletal complications, previously not recognised, are common in NTRK1 mutation cases. Through molecular studies, our collaborative team found NTRK1 mutations impair TrkA interactions with GRB2/PLCG, impairing bone modelling signals. This ongoing work links clinical phenotypes with molecular pathophysiology in NTRK1-related CIPA, emphasizing the importance of multi-disciplinary research to advance care.

'Bench to bedside and back': Using patient-derived iPSC cardiomyocytes, we modelled dystrophinopathy-related cardiomyopathy to test Givinostat, an FDA-approved drug for Duchenne muscular dystrophy – a most common and severe childhood onset muscular dystrophy. While Givinostat' s benefit on skeletal muscle is well documented, its effects on the heart are unclear. Our research found Givinostat improved calcium handling and reduced cell fragility in cardiac cells, indicating its potential cardio-protection effect. However, higher doses caused arrhythmias, underscoring the need for careful dose titration and monitoring. These findings prompt further research into epigenetic mechanisms, dose optimization, and therapeutic potential of more selective epigenetic therapies.

Chi Wai Lee

Hong Kong Baptist University

11:00–11:30 Spatially restricted BDNF–TrkB signaling drives postsynaptic differentiation at neuromuscular synapses

Efficient neurotransmission at neuromuscular junctions (NMJs) requires the formation of densely packed acetylcholine receptor (AChR) clusters at the postsynaptic membrane. While the agrin–Lrp4–MuSK pathway is central to this process, emerging evidence indicates that brain derived neurotrophic factor (BDNF) and its receptor TrkB also contribute to NMJ development. Notably, the spatial pattern of BDNF stimulation leads to distinct effects on presynaptic and postsynaptic cells: localized BDNF promotes axonal outgrowth, growth cone turning, and synaptic maturation, whereas global BDNF application suppresses agrin synthesis and AChR clustering. Here, we investigated how spatially restricted BDNF–TrkB signaling regulates postsynaptic differentiation using recombinant BDNF coated beads applied to cultured Xenopus muscle cells. Local BDNF stimulation robustly induced AChR clustering, an effect diminished by global BDNF stimulation or TrkB knockdown, indicating the necessity of spatially confined TrkB activation. The postsynaptic effects of BDNF occurred independently of Lrp4, distinguishing them from agrin mediated mechanisms. Using live cell imaging with an ERK KTR biosensor, we observed localized enrichment of activated ERK at BDNF bead–muscle contact sites, along with increased cytoplasmic translocation of phosphorylated ERK in bead-contacted cells. Pharmacological inhibition of MAPK/ERK signaling impaired BDNF induced, but not agrin induced, AChR clustering and disrupted nerve induced AChR cluster formation during NMJ development. Together, our findings identify a distinct mechanism in which localized BDNF–TrkB

signaling drives postsynaptic differentiation at developing NMJs, contrasting with the effects of global BDNF stimulation and operating independently of the agrin–Lrp4–MuSK pathway.

Lin Ong
University of Southern Queensland, Australia

11:30–12:00 **Mechanisms and Therapeutic Targeting of Secondary Neurodegeneration in Post-Stroke Cognitive Impairment**

Post-stroke cognitive impairment is a major long-term complication of stroke, affecting up to 60% of survivors and substantially increasing the risk of dementia. Accumulating clinical and experimental evidence implicates secondary neurodegeneration (SND), the progressive degeneration of structurally and functionally connected brain regions remote from the primary infarct as a key contributor to cognitive decline after stroke. This presentation will examine the neuropathological mechanisms underlying SND, including chronic neuroinflammation, neuronal and synaptic loss, cerebrovascular dysfunction, blood–brain barrier disruption and the accumulation of neurotoxic proteins. Emerging therapeutic strategies aimed at limiting SND will be discussed, including immunomodulatory interventions targeting neuroinflammatory pathways and cell-based therapies that promote neuroplasticity and vascular repair. This presentation will highlight novel therapeutic opportunities to mitigate cognitive decline and improve long-term outcomes after stroke.

Koon Ho Chan
The University of Hong Kong

12:00–12:30 **Anti-amyloid therapy for Alzheimer Disease**

Alzheimer disease has been actively studied for recent decades. Since 2023, anti-amyloid antibodies (lecanemab and donanemab) are available for patients with mild cognitive impairment and early dementia due to AD as disease modifying treatments. They confer modest slowing of cognitive decline demonstrated in randomized control trials of 18-month duration and also importantly risk of adverse effects, typically amyloid related imaging abnormalities (ARIA) which can symptomatic and rarely causing severe manifestations of cerebral edema, seizures, hemorrhage and even mortality. Open label extension of clinical trials and real world post-marketing observational data are accumulating to confirm their long-term efficacy and safety/adverse effects. Interestingly and also importantly, efficacy and risk of adverse effects are affected by a number of clinical and genetic factors. Careful and adequate workup and selection of patients for these anti-amyloid antibodies are likely needed for precision/personalized medicine practice.

SS4 Forum on Neuroethics

10:30–12:30 | Seminar Room 1, 3rd Floor

Chair: *Tamami Fukushi; Sung-Jin Jeong*

Session overview

This forum examines ethical questions that arise as neuroscience advances into increasingly powerful clinical, computational, and societal domains. It provides a space for interdisciplinary discussion on responsibility, consent, privacy, equity, and the appropriate translation of new knowledge and technologies. The session encourages thoughtful dialogue between neuroscience, medicine, law, policy, and the wider public.

Participants

Kun Ho Lee • *Kensaku Kasuga* • *Glenda Halliday* • *Jialin Zheng* • *Hitoshi Shimada* • *Gilberto Leung* • *Fumie Arie*

OS1 Oral presentation session 1

10:30–12:30 | Seminar Room 2, 3rd Floor

Lei Han
BGI Research, China

10:30–10:54 Single-nucleus multi-omics profiling uncovers pathological features driving hippocampal vulnerability in Alzheimer's disease

Alzheimer's disease (AD) exhibits region- and cell-type-specific hippocampal vulnerability, but the underlying regulatory mechanisms remain unclear. We applied Stereo-seq spatial transcriptomics with integrated single-nucleus RNA-seq and ATAC-seq of human hippocampus to link gene expression, chromatin accessibility, and spatial pathology. Spatially, we uncovered AD-associated alterations with single-cell precision: (1) elevated synapse pruning gene expression in the fimbria, with disrupted microglia-astrocyte communication; (2) globally increased energy generation across CA subregions; (3) significant CA1 neuron loss while CA4 neurons remained largely unaffected, suggesting resilience-conferring gene alterations; and (4) aggravated amyloid-beta plaques in CA1 and SLRM, with Stereo-seq revealing sequential microglia and astrocyte enrichment around plaques. To uncover epigenetic dysregulation in hippocampus in the context of AD, we identified over 1,000 disease-associated cis-regulatory interactions, revealing coordinated epigenomic–transcriptomic remodeling. EX.CA neurons showed disproportionate regulatory disruption with increased chromatin accessibility coupled to apoptosis activation, whereas EX.DG neurons were more resistant. In glia, regulatory networks uncovered activation of SPI1/KLF4 in microglia and STAT3 in astrocytes, defining epigenetic programs driving inflammatory and metabolic transitions. Cross-species integration showed many AD-associated regulatory elements are human-specific, with risk variants enriched in microglial cis-elements at BIN1 and APOE. Together, these findings establish a mechanistic framework linking chromatin remodeling, spatial pathology, and cell-type-specific dysfunction, revealing human-specific regulatory architecture as a key determinant of AD vulnerability.

Christy Hung
City University of Hong Kong, Hong Kong SAR

10:54–11:18 Evaluating APP-targeting antisense oligonucleotides in human stem cell models of Alzheimer's disease

Alzheimer's disease is characterized by progressive neurodegeneration and accumulation of amyloid-β peptides generated from amyloid precursor protein (APP). Although antibody-based therapies have shown clinical promise, complementary strategies that directly modulate APP expression may provide an alternative approach to reduce amyloid burden. In this study, we use human induced pluripotent stem cell (iPSC)-derived neural models to evaluate antisense oligonucleotides designed to lower APP expression. Treated cultures are assessed for changes in APP transcript and protein levels, amyloid-β production, and disease-relevant cellular phenotypes. By testing APP-targeting antisense oligonucleotides in human iPSC-derived neurons, this work provides a translational platform for evaluating RNA-based therapeutic strategies in Alzheimer's disease.

Yong-Seok Oh
Brain Sciences Dep., DGIST (Daegu-Gyungbuk Institute of Sci. & Tech.), Republic of Korea
Brain Convergence Center (BCC), DGIST (Daegu-Gyungbuk Institute of Sci. & Tech.), Republic of Korea

11:18–11:42 Anterior Claustrum Dopamine D1 Receptor Confers Resilience to Helpless Behavior via Stress Relief

Stress resilience varies among individuals and reduces the risk of developing mental illness. While the dopaminergic system has been implicated, its precise role in fostering resilience remains unclear. Here, we uncovered a novel mechanism centered on dopamine D1 receptor (Drd1) signaling in the anterior claustrum (aCLA). Using a learned helplessness paradigm, we found that inescapable stress reduces Drd1 expression in the aCLA of the stress-susceptible subgroup of mice. Targeted depletion of Drd1 in the aCLA was sufficient to increase vulnerability to helpless behavior. Strikingly, in vivo Ca2+ recordings revealed that Drd1-expressing neurons in the aCLA (aCLADrd1) showed no significant phasic activation during inescapable stress but became robustly activated upon stress cessation. This relief-associated activation was abolished by Drd1 silencing. Critically, chemogenetic inhibition of aCLADrd1 during the stress induction phase, but not during subsequent testing, aggravated helplessness. Circuit mapping revealed that aCLADrd1 projects to the prelimbic cortex, mediating resilience by activating local parvalbumin interneurons. These findings establish the Drd1-dependent, relief-activated claustro-cortical pathway as a key neural substrate for conferring resilience to stress. National Research Foundation

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Bo Gao

School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China.
Department of Orthopaedics and Traumatology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China.

11:42–12:06 Genetic evidence links synaptic dysfunction and neural circuit dysregulation to adolescent idiopathic scoliosis

Adolescent idiopathic scoliosis (AIS) is the most common skeletal disorder in adolescent, yet its etiopathogenesis remains poorly understood. Current clinical management largely depends on bracing or surgery after spinal curvature becomes evident, highlighting the need to define its early causal mechanisms. We previously identified pathogenic variants in SLC6A9, encoding glycine transporter 1, in AIS families and sporadic patients. Functional studies showed that SLC6A9 variants impair glycine uptake, increase extracellular glycine, disrupt bilateral spinal central pattern generator (CPG) activity, and induce scoliosis-like phenotype in zebrafish, supporting a neuropathic origin of AIS driven by abnormal inhibitory neurotransmission.

Extending this concept, we further identified rare variants in two neural genes, SYN3 and LHX8, from AIS patients. SYN3 encodes a synaptic vesicle-associated phosphoprotein involved in dopamine release, while LHX8 is essential for cholinergic interneuron development in the striatum. SYN3 variants reduced protein phosphorylation and impaired synaptic vesicle recruitment, leading to increased dopamine release in cellular models. Loss of syn3 or pharmacological activation of dopamine signalling induced scoliosis-like phenotypes in zebrafish. In parallel, LHX8 variants affected nuclear localization, and lhx8 mutant zebrafish showed reduced cholinergic interneurons and increased scoliosis incidence. Mouse retrograde tracing further suggested that paraspinal muscles are regulated by neural circuits involving SYN3-positive dopaminergic neurons in the substantia nigra and LHX8-positive cholinergic neurons in the striatum.

Together, these findings support a unified model in which genetic disruption of neurotransmitter homeostasis and motor circuit regulation, from supraspinal nigrostriatal pathways to spinal CPGs, contributes to AIS pathogenesis. This work provides new insight into the neurobiological basis of AIS and suggests potential opportunities for pre-onset risk prediction and mechanism-based intervention.

Shen Gu

The Chinese University of Hong Kong

12:06–12:30 Selective neuronal vulnerability caused by disrupted endolysosomal dynamics and impaired mitochondria clearance

Selective neuronal vulnerability is a defining feature of all neurodegenerative diseases, yet the underlying mechanisms remain poorly understood. Inspired by hereditary spastic paraplegia (HSP) patients with corticospinal upper motor neurons (CSMN)-specific degeneration, we generated mice carrying patient-specific heterozygous mutations in the Ubap1 (ubiquitin-associated protein 1) gene. These mice exhibited progressive motor deficits and selective CSMN degeneration, recapitulating patients' clinical phenotype. Using super-resolution microscopy and single-nucleus transcriptomic profiling, we identified endosomal accumulation, lysosomal deficiency, and mitochondria defects with impaired mitophagy as key contributors to CSMN degeneration. These abnormalities were further validated in human neurons. By studying mice with different types of Ubap1 mutations, we confirmed a dominant-negative mechanism of pathogenicity, ruling out loss-of-function effects. Based on these findings, we developed genetic and pharmacological interventions that successfully rescued disrupted endolysosomal dynamics and mitochondria functions. Our study provides a mechanistic understanding of cell type-specific vulnerability in HSP and establishes promising therapeutic strategies.

OT1 Open Theatre on Neurotechnology

13:30–14:15 | LT 1

Yulong Li

School of Life Sciences; PKU-THU Center for Life Sciences; IDG/McGovern Institute for Brain Research, Peking University, China

13:30–14:15 Quantitative Imaging of Neuromodulator Dynamics in vivo by Constructing New GRAB sensors

Biography

Professor Yulong Li is a Chair Professor at the School of Life Sciences and a principal investigator at the PKU-THU Center for Life Sciences and the IDG/McGovern Institute for Brain Research at Peking University. He received his B.S. from Peking University, his Ph.D. in Neurobiology from Duke University, and completed his postdoctoral training at Stanford University. Professor Li is internationally renowned for his pioneering work in developing advanced molecular tools and genetically encoded optical biosensors to study neural communication. His laboratory is widely celebrated for creating the groundbreaking GPCR-Activation-Based (GRAB) sensor family, which has revolutionized the real-time, in vivo visualization of neuromodulators such as dopamine, acetylcholine, and neuropeptides with exceptional spatial and temporal resolution. His innovative toolkit has profoundly transformed how the global neuroscience community investigates complex chemical signaling in the brain.

S03 Network rebalancing and therapeutic targets in severe neuropathological disorders

14:30–16:30 | Seminar Room 1, 3rd Floor

Chair: *Dan Ohtan Wang*

Session overview

This symposium focuses on restoring network stability and identifying therapeutic targets in severe neurological and neuropsychiatric disorders. It brings together work on seizures, acquired brain injury, astrocyte-mediated plasticity, and RNA-linked disease mechanisms to examine how disrupted circuits can be rebalanced. Across diverse disease contexts, the session highlights mechanistic routes toward resilience, repair, and more targeted intervention.

Geoffrey Lau
City University of Hong Kong

14:30–15:00 Long-range modulation of brain activity alleviates seizures in temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is characterized by disrupted excitation–inhibition (E–I) balance and recurrent seizures. The anterior piriform cortex (APC), a limbic structure closely linked to TLE, relies on parvalbumin-expressing (PV+) interneurons to provide strong inhibitory control. Using the pilocarpine mouse model, electrophysiology, and histology, we identified impaired synaptic inhibition and a loss of PV synapses in the APC. However, the causal contribution of APC-PV neurons to seizure dynamics remained unresolved. To address this, we employed chemogenetic activation combined with multi-site local field potential recordings in the intrahippocampal kainic acid (KA) model. In this model, activation of APC-PV neurons reduced hippocampal seizure recurrence. Notably, APC-PV neurons broadly modulated functional connectivity across the seizure network. Furthermore, seizure frequency was strongly and negatively correlated with inter-regional functional connectivity, suggesting that large-scale connectivity serves as a biomarker of seizure severity. These findings highlight APC-PV neurons as critical regulators of network-wide E–I balance and underscore the APC's role in shaping seizure dynamics. By establishing functional connectivity as a readout of seizure severity, our work provides a foundation for developing circuit-based therapeutic strategies for TLE.

Winnie Tso
University of Hong Kong

15:00–15:30 Repairing the Young Injured Brain: Understanding Risk and Advancing Rehabilitation Strategies in Paediatric Brain Tumor Survivorship

Survival rates for paediatric brain tumors have improved significantly over the past decades. However, survivors have increased risk of neurodevelopmental and neurocognitive sequelae due to the tumor and the effects of treatment modalities such as chemotherapy and radiotherapy. Prof Tso will examine the spectrum of neurocognitive and developmental sequelae in this population. She will analyze key risk factors—including age at diagnosis, tumor localization, treatment intensity, and socioeconomic determinants—and will highlight emerging evidence that supports healthy lifestyle habits as modifiable protective factors to improve physical and cognitive outcomes in pediatric brain tumor survivors.

Prof Tso will present novel interventions aiming to improve the physical and cognitive outcomes of paediatric brain tumour survivors. Drawing on both pre-clinical studies and results from randomized controlled trials, she will discuss promising strategies—including non-invasive brain stimulation, cognitive remediation and pharmacological interventions with implications for clinical practice and future research.

This session aims to synthesize current evidence and provide insights for researchers and clinicians committed to optimizing long-term neurocognitive health and quality of life in pediatric brain tumor survivors.

Joo Min Park
Institute for Basic Science, Republic of Korea

15:30–16:00 Ultrasound-Driven Network Rebalancing: From Astrocytic Mechanotransduction to Long-Term Plasticity

Non-invasive ultrasound neuromodulation is emerging as a powerful approach for regulating brain circuits, yet the mechanisms underlying its long-term effects remain poorly understood. Here, we present brain-rhythm–inspired ultrasound stimulation as a strategy to reshape neural networks through frequency-specific entrainment and sustained synaptic plasticity. Patterned ultrasound induces bidirectional modulation of circuit activity by engaging canonical plasticity pathways, including NMDAR-dependent signaling, BDNF/TrkB activation, and activity-dependent protein synthesis. Beyond

neuronal responses, our work highlights a central role for astrocytes in mediating ultrasound-induced plasticity. Mechanosensitive astrocytic channels, particularly TRPA1, translate mechanical energy into biochemical signals, enabling coordinated astrocyte–neuron communication and long-range circuit remodeling. These astrocyte-centered mechanisms support persistent changes in network dynamics and may contribute to stabilizing maladaptive or unstable brain states. Together, these findings provide mechanistic insight into how patterned ultrasound drives durable neuromodulatory effects across both healthy and diseased circuits. By integrating neural oscillations, mechanobiology, and glial modulation, this work proposes a framework in which ultrasound may help restore circuit homeostasis and promote adaptive neuroplasticity.

Dan Ohtan Wang

16:00–16:30 RNA Modifications in Ischemic Injury, and Neuropsychiatric Risk

RNA modifications provide a dynamic regulatory layer essential for brain development, functional plasticity, and neurological health. This talk highlights emerging epitranscriptomic mechanisms that shape neuronal function in acute injury responses and genetic susceptibility to psychiatric disorders. We performed a systematic functional-genomic survey to prioritize RNA modifying proteins (RMPs) underlying risks for major neuropsychiatric conditions. This integrative analysis identifies the tRNA methyltransferase NSUN2 as a shared risk gene for Bipolar I Disorder and Schizophrenia alongside other tRNA modifying enzymes, pointing to tRNA expression as a convergent molecular mechanism in psychiatric pathology. We discuss a potential cellular pathway being impacted by aberrant signaling of N6-methyladenosine (m6A) in axonal development. The m6A/YTHDFs/APC pathway is shown to regulate β-actin mRNA transport and local translation in growth cones, a process essential for structural integrity. Notably, human missense mutations in the methyltransferase METTL14 associated with autism and schizophrenia disrupt this pathway and compromise axonal outgrowth of hippocampal neurons.

Finally we explore the role of epitranscriptomics in acute brain injury. In models of cerebral ischemia/reperfusion, the m6A reader YTHDF1 is upregulated and promotes the translation of p53, which exacerbates oxidative stress and induces ferroptosis. Conversely, neuron-specific knockdown of YTHDF1 is neuroprotective, significantly reducing infarct volume. Together, these findings establish RNA modifications as critical regulators of the brain's structural and pathological landscapes, nominating the epitranscriptomic machinery as a strategic avenue for novel therapeutic interventions.

S04 Organoid, transgenic, and environmental models of neurochemistry to understand developmental brain disorders

14:30–16:30 | Seminar Room 3, 3rd Floor

Chair: *Jee Hyun Kim*

Session overview

This symposium explores how organoid, transgenic, and environmental models can reveal mechanisms of developmental brain disorders. It considers how complementary experimental systems capture molecular, cellular, circuit, and behavioural phenotypes, while also enabling the testing of potential interventions. The session emphasizes the value of combining human-relevant models with in vivo approaches to understand developmental vulnerability and identify therapeutic opportunities.

Jacque Ip

The Chinese University of Hong Kong

14:30–15:00 Functional and Molecular Dissection of CDKL5 Deficiency Disorder

CDKL5 deficiency disorder (CDD) is a neurodevelopmental disorder linked to the X chromosome and caused by genetic deficits in Cyclin Dependent Kinase-like 5 (CDKL5). Previously classified as the early-onset-seizure variant of Rett syndrome due to overlapping clinical presentation, CDD is now considered an independent condition. CDD remains relatively understudied compared to other X-linked neurodevelopmental disorders. Notably, cortical visual impairment is a common clinical feature observed in at least 75% of CDD patients. Although cortical visual impairment has been suggested as a potential functional biomarker, the developmental and specific mechanisms underlying sensory processing impairments caused by CDKL5 deficits are not well understood. To address this, our study utilizes a CDD transgenic mouse model and employs in vivo two-photon calcium imaging to investigate how CDKL5 deficiency in the primary visual cortex contribute to developmental and functional deficits. Our findings revealed that Cdkl5 mutant mice exhibit impaired orientation selectivity, binocular integration, reduced neural coding ability, and network dysfunction, as observed through in vivo two-photon calcium imaging. Through a phospho-proteomics screen, we identified novel CDKL5 substrates. We further demonstrated that the absence of CDKL5 phosphorylation on the novel substrates leads to abnormal formation of RNA granules by affecting the dynamic process of phase separation. In summary, our study highlights circuit-specific cortical impairments in a CDD mouse model and uncovers a novel RNA granules-mediated mechanism involving CDKL5. These findings provide insights into potential therapeutic strategies for CDD and shed light on the understanding of this complex neurodevelopmental disorder.

Woong Sun

Department of Anatomy, Korea University College of Medicine, Republic of Korea

15:00–15:30 Modeling Cohen Syndrome with Scalable Human Anterior Neural Organoids

Loss-of-function variants in the VPS13B gene cause Cohen syndrome (CS), a rare neurodevelopmental disorder clinically characterized by postnatal microcephaly and neurological deficits. Investigative progress has been limited because animal models do not fully mimic human-specific phenotypes, and conventional brain organoids often exhibit batch-dependent variability. To address these limitations, we established a scalable, 2D neural induction-based culture platform that produces uniform human anterior neural organoids (hANOs). Using this platform, we modeled CS pathogenesis via CRISPR/Cas9-mediated VPS13B knockout. VPS13B-deficient hANOs developed a secondary microcephaly-like phenotype characterized by reductions in organoid size, neuronal soma size, and axonal elongation, which were mechanistically linked to a global suppression of protein synthesis as revealed by transcriptome at single-cell level and O-propargyl-puromycin (OPP) translation assays. Furthermore, network-level MEA recordings identified an emergent neural network hyperexcitability that aligns with the clinical epileptogenesis observed in a subset of CS patients. Together, our scalable hANO platform models key features of CS, identifying translation-dependent maturation deficits and network hyperexcitability as potential targets for therapeutic intervention.

Hovy Wong
The Chinese University of Hong Kong

15:30–16:00 **Local mRNA translation in axons sustains neurotransmission**

For more than 60 years, memory formation has been linked to protein synthesis, with the prevalent view that nascent proteins originate from the cell body. Yet recent omics studies have found hundreds of mRNAs in axons, challenging the decades-old view.

Using quadruple whole-cell recordings, we found that burst neurotransmission depends on protein synthesis linked to NMDA receptors and mTOR. We localized protein synthesis to axons with 2-photon laser microsurgery and nascent protein live imaging. Live imaging of axons revealed sparsely docked RNA granules, suggesting synapse-specific regulation. In agreement, translation boosted neurotransmission onto excitatory but not inhibitory cells. Local axonal mRNA translation is thus a hitherto unappreciated principle for sustaining burst neural coding at specific synapse types.

Protein synthesis has emerged as a promising candidate target for treating neuropathologies like autism and Alzheimer's, yet the focus has historically been postsynaptic. Our results highlight intervention potential that relies on synapse-type-specific local translation in axons.

Jee Hyun Kim
Deakin University, Australia

16:00–16:30 **Sex differences in susceptibility to early life adversity: neurochemical answers**

Prevalence of neuropsychiatric conditions are sex-specific. While there is strong evidence of sexual dimorphism of brain development, most of the differences described are anatomical and potential sex differences in neurochemistry, especially in response to early life adversity, are poorly understood. In response, we exposed rats in their neonatal period to maternal abuse by housing the dam and her litter with limited bedding and nesting, which is a model of receiving caregiver stress due to resource deprivation. Such adversity did not affect basal plasma corticosterone levels but it did elevate fear conditioning-induced corticosterone in male and not female offspring, indicating male susceptibility to altered hypothalamic-pituitary-adrenal (HPA) axis reactivity. Expression of HPA axis-related genes, namely Crhr1 and Crhr2 encoding corticotropin-releasing hormone receptors, Nr3c1 and Nr3c2 encoding glucocorticoid and mineralocorticoid receptors, and Fkbp5 encoding FK506 binding protein 5 was assessed. Crhr1 expression was significantly higher in males compared to females in all brain regions examined (dorsal and ventral hippocampus, prelimbic and infralimbic cortices of the prefrontal cortex, p's < 0.05), regardless of adversity condition. Nr3c1 expression was also higher in males than females in the ventral hippocampus and the infralimbic cortex (p's < 0.05), regardless of adversity. There were trends (sex x adversity interaction, p's < 0.1) of reduced gene expression of Nr3c1 in the dorsal hippocampus and of the Nr3c2 in the ventral hippocampus due to adversity in males but not in females. Juvenile males showed precocious emergence of conditioned fear relapse following extinction due to adversity. Taken together, females appear more resilient than males against early life stress effects measured by gene expression, HPA axis reactivity corticosterone and extinction of fear. These findings are consistent with emerging neurochemical evidence of female resilience before puberty (Perry et al., 2021, J Neurochemistry).

S05 Advancing stem cell technologies for neurological disorders

14:30–16:30 | LT 3–4

Chair: *Ralf Jauch*

Session overview

This symposium examines advances in stem-cell technologies for understanding and treating neurological disorders. It considers how patient-derived cells, engineered neural systems, and scalable differentiation platforms can model disease mechanisms, identify cellular vulnerabilities, and support therapeutic discovery. The session highlights the opportunities and limitations of translating stem-cell-based science into robust disease models and clinically relevant interventions.

Alfred Xuyang Sun

14:30–15:00 Benchmarking human midbrain culture for cell therapy for Parkinson's disease

Protocols for deriving midbrain dopaminergic (mDA) neurons for Parkinson's disease (PD) modeling and therapy remain incompletely benchmarked against in vivo references. To establish transcriptomic standards, we generated an integrated human fetal whole-brain atlas and a midbrain subatlas. Whole-brain analysis revealed strong region-specific signatures, underscoring the need for global mapping before refined midbrain annotation. We implemented this two-tier strategy, BrainSTEM (Brain Single-cell Two tiEr Mapping), to systematically reassess published single-cell datasets of human midbrain culture models. BrainSTEM confirmed the presence of bona fide midbrain cell types ("on-target"), but also revealed substantial populations aligning with nonmidbrain regions ("off-target"), inflating reported mDA yields across protocols. This unbiased framework enables rigorous evaluation of differentiation outcomes, clarifies current limitations of midbrain-directed models, and provides a foundation for refining protocols toward more faithful in vitro systems for PD research and regenerative applications.

Ping Hu

Guangzhou Laboratory, China

15:00–15:30 Profound cellular defects contribute to muscular pathogenesis in the rhesus monkey model of Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease caused by mutations in the DMD gene. Multiple disorders including decline of neuromuscular junctions (NMJ) and muscle functions were attributed to the progression of the disease. Muscle fibers rely on the coordination of multiple cell types for repair and regenerative capacity. To elucidate the cellular and molecular changes in these cell types under pathologic conditions, we generated a rhesus monkey model for DMD that displays progressive muscle deterioration and impaired motor function, mirroring human conditions. By leveraging our newly developed DMD monkeys, we analyzed freshly isolated muscle tissues using scRNA-seq. Our analysis revealed changes in immune cell landscape, reversion of lineage progressing directions in fibrotic fibro-adipogenic progenitors (FAPs), and TGF-β resistance in FAPs and muscle stem cells (MuSCs). Furthermore, muscle stem cells displayed cell-intrinsic defects, leading to differentiation deficiencies. These findings provide new insights into the pathogenesis of DMD.

Zhefan Stephen Chen

Chinese University of Hong Kong

15:30–16:00 Modeling repeat expansion diseases with stem cells: from mechanism to therapy

Repeat expansion diseases represent a group of inherited disorders caused by the expansion of tandem repeat sequences. To date, more than 50 such conditions have been reported, including amyotrophic lateral sclerosis, Huntington's disease, and myotonic dystrophy type 1. These diseases predominantly affect the nervous system, leading to progressive neuronal dysfunction and loss. However, the underlying mechanisms remain elusive, which significantly impacts the development of effective therapeutic strategies. My research group uses patient-derived induced pluripotent stem cell (iPSC) models to investigate the mechanisms of repeat expansion diseases. By directing the differentiation of patient iPSCs into disease-relevant neuronal subtypes, we recapitulate key pathological hallmarks, including RNA foci formation, expanded repeat protein production, and neuronal dysfunction and death. Through an integrated approach combining transcriptomic profiling, functional characterization, and molecular validation, we have dissected out the pathogenic pathways triggered by repeat RNAs, and evaluated the efficacy of potential therapeutic agents. Collectively, iPSC-derived neuronal models offer a

powerful platform for uncovering critical pathogenic mechanisms in repeat expansion diseases, and provide a robust, scalable system for preclinical drug discovery for these devastating disorders.

Anna Maria Blocki
Chinese University of Hong Kong

16:00–16:30 **Harnessing Positive Charges: Chitosan-Enhanced Laminin for Neuronal Cell Culture**

Human motor neuron (MN) cultures are invaluable tools in biomedical research, particularly for studying neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). To promote neuronal adhesion in vitro, synthetic cationic polymers such as poly-lysine and poly-ornithine are commonly employed, often in combination with laminin. However, these substrates present significant drawbacks: high solubility leads to unstable coatings, and neurons frequently detach and aggregate, forming fragile clusters with abnormal axonal branching and restricted neurite outgrowth. Such clumping destabilizes cultures and obscures single-cell resolution, limiting the study of neuronal physiology, synaptic activity, and disease-specific phenotypes in advanced microphysiological systems (MPS). These limitations highlight the need for biomimetic substrates that support robust adhesion, maturation, and functional network formation.

Chitosan, a naturally derived, positively charged polysaccharide obtained through the deacetylation of chitin, offers a promising alternative. Its pH-dependent solubility, biocompatibility, and ability to form stable films make it particularly attractive compared to conventional synthetic polymers. We developed a simple and adaptable method for fabricating chitosan films and evaluated their ability to support MN differentiation from human neural stem cells (hNSCs).

Uniform chitosan films formed on polystyrene and glass exhibited smooth surfaces and superior laminin-binding compared to polycationic coatings. hNSC-derived MNs cultured on these films showed enhanced survival, reduced clustering, and improved neurite extension, with strong expression of MN markers (MAP2, CHAT, HuC/D). Transcriptomic profiling revealed upregulation of genes involved in cell adhesion, axon guidance, and synapse formation, underscoring the unique molecular environment provided by chitosan. This robust, biocompatible substrate minimizes variability and can be integrated into advanced MPS, such as the neuromuscular junction (NMJ)-on-a-chip. In this platform, axons extend through microchannels to interact with three-dimensional myotubes formed in collagen I hydrogels. Functional NMJs induce myotube contraction, with contractile force quantified by post deflection, enabling precise evaluation of MN functionality in physiologically relevant contexts.

S06 Dynamic control of AMPA receptor trafficking across scales in synaptic plasticity

14:30–16:30 | LT 1

Chair: *Victor Anggono*

Session overview

This symposium investigates how the trafficking and regulation of AMPA receptors shape synaptic plasticity across molecular, cellular, and circuit scales. It considers mechanisms that control receptor movement, synaptic strength, memory formation, and vulnerability to disease. By connecting fundamental receptor biology with network function, the session offers an integrated view of how dynamic synaptic signalling supports adaptive brain function.

Deepak Nair
Centre for Neuroscience
Indian Institute of Science, Bangalore, India

14:30–15:00 **A self-organizing AMPA receptor landscape underlies nanoscale synaptic plasticity**

Synaptic plasticity, the process by which experience modifies neural connections, is shaped in part by nanoscale organization within the postsynaptic density (PSD). Over the past decade, studies have shown that AMPA-type glutamate receptors (AMPARs) and their scaffold protein PSD95 assemble into dynamic nanodomains that govern the precision and efficacy of synaptic signaling. Using multimodal super-resolution microscopy, correlative electron microscopy, and computational reconstruction, we show that AMPARs are not uniformly distributed but instead cluster into discrete nanodomains (~70 nm in diameter, ~20 receptors per domain). These nanodomains merge, drift, and dissolve over minutes, yet remain sufficiently stable to exert sustained influence on synaptic transmission. To resolve this hidden spatial organization, we employed Voronoi tessellation, a geometric framework that partitions molecular space based on local proximity rather than pixel intensity. Unlike conventional segmentation approaches, Voronoi analysis assigns each molecule a domain of influence, generating adaptive boundaries that reflect local crowding and spatial constraints. We rely on these approaches to show that receptor clustering as a continuum of densities that evolve in real time, rather than as static, threshold-defined puncta. Viewed through this geometric lens, the PSD emerges as a living mosaic, fluid and entropic yet constrained by thermodynamic balances between diffusion and molecular anchoring. The continual formation, dissolution, and redistribution of nanodomains enables neurons to dynamically tune synaptic responsiveness while preserving transmission reliability. This geometry-driven analytical framework provides a high-precision route to visualize and quantify nanoscale molecular dynamics underlying synaptic plasticity, signaling, and adaptive network function.

Jiajia Liu
Institute of Genetics and Developmental Biology
Chinese Academy of Sciences, Beijing, China

15:00–15:30 **Plasma membrane PI4P facilitates activity-induced exocytosis of AMPA receptor**

The AMPA-type glutamate receptors (AMPARs) mediate the majority of fast excitatory synaptic transmission in the brain and are central to synaptic plasticity in excitatory neurons. Although much has been learned about active transport of AMPAR vesicles to the postsynaptic site, mechanism(s) underlying neuronal activity-dependent AMPAR exocytosis at the plasma membrane (PM) remains largely unexplored. Here we report that PI4P, a low abundance membrane lipid, is essential for AMPAR exocytic trafficking during NMDA receptor-mediated long-term potentiation (LTP). We found that in hippocampal pyramidal neurons, LTP signal-triggered elevation in cytosolic Ca2+ causes translocation of PI4KIIIa to the dendritic PM to enhance synthesis of PI4P. PI4P, not PI(4,5)P2, is required for activity-induced AMPAR surface expression, LTP expression and hippocampus-dependent long-term memory. We further found that the interaction between the endoplasmic reticulum (ER) and the PM undergo dynamic changes during LTP induction and expression. In response to elevated cytosolic Ca2+ E-Syt1, a membrane tethering protein, recruits PI4KIIIa to ER-PM membrane contact sites to increase PI4P levels, and PM-enriched PI4P promotes SNARE-mediated membrane fusion of AMPAR transport vesicles. Collectively, these findings provide insights into the regulatory mechanisms and functions of lipid metabolism and ER-PM contact in synaptic plasticity.

Victor Anggono
Queensland Brain Institute, Australia
The University of Queensland, Brisbane, Australia

15:30–16:00 Copine-6 binding to phosphatidylinositol 3-phosphate and Rab11 promotes endosomal sorting of AMPA receptors during synaptic activity

The endosomal trafficking pathway is essential for the sorting and recycling of membrane receptors during synaptic function and plasticity. We have previously identified a Ca2+-dependent lipid-binding protein, Copine-6, as a postsynaptic Ca2+-sensor that mediates the activity-dependent exocytosis of AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, a process triggered by NMDA (N-methyl-D-aspartate) receptor-dependent calcium (Ca2+) influx. The binding of Ca2+ triggers Copine-6 translocation to the plasma membrane as well as the endosomes. However, the role of Copine-6 in the endosomes is not well characterised. Here, we show that Copine-6 binds directly to the recycling endosomal Rab11 small GTPase protein and the endosomal enriched phosphatidylinositol 3-phosphate (PI3P). Mutations of the conserved lipid-binding residues in Copine-6 C2B domain impair the activity-induced translocation of Copine-6 to the PI3P-positive endosomes and accumulated Copine-6 at the recycling endosomes. Loss of Copine-6 expression not only reduces the association between the early and recycling endosomes but also blocks the activity-induced AMPA receptors trafficking to the plasma membrane in primary neurons. These defects can be restored by wild-type Copine-6, but not the C2B lipid-binding mutant. Our findings demonstrate that Copine-6 acts as a molecular bridge by coupling the early and recycling endosomal membranes during synaptic potentiation to promote glutamate receptor exocytosis.

Yong Zhang
Department of Neurobiology
Peking University School of Basic Medical Sciences & Idg/McGovern Institute for Brain Research, Beijing, China

16:00–16:30 Dynamic changes of AMPA receptors in memory-related neuronal ensemble during sensory learning

Understanding the dynamic processes of sensory learning and memory is essential for comprehending cognitive function. How neurons undergo synaptic changes at the receptor level in vivo to form a memory engram remains unclear. Here, we employed a genetic approach and identified memory-related (Robust Activity Marking [RAM+]) neuronal ensembles in the barrel cortex following a sensory detection task. Manipulation of RAM+ neurons replicated licking behavior, demonstrating their role in memory encoding. We observed a layer-selective activation pattern during learning with L2/3 excitatory neurons as primary targets. Two-photon in vivo imaging revealed distinct changes in spine surface GluA1 in L2/3 RAM+ and RAM- neurons during learning; both correlate with learning performance. Furthermore, connections between L4 and L2/3 RAM+ neurons were selectively strengthened during learning. Together, these results reveal a learning-induced a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) redistribution toward active neuronal ensembles in a layer-selective manner, which advances our understanding of cellular and synaptic mechanisms underlying sensory memory formation.

OS2 Oral presentation session 2

14:30–16:30 | LT 2

Muhammad Zulfadli Mehat
Universiti Putra Malaysia
Universiti Sultan Zainal Abidin
Ajman University, United Arab Emirates

14:30–14:50 Ficus deltoidea improves spatial memory and reduces amyloid-β and phosphorylated tau in an Alzheimer's disease-like rat model

Introduction: Alzheimer's disease (AD) is the most common cause of dementia in the elderly population due to its progressive nature in causing neurodegeneration, affecting cognition and memory. The accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles, together with neuroinflammation and oxidative stress, are key pathological features of AD. Hyperphosphorylated tau leads to the accumulation of neurofibrillary tangles, while increasing evidence indicates that AD pathology involves a complex interaction between Aβ and tau. Ficus deltoidea (FD), a medicinal plant traditionally used in Southeast Asia, exhibits antioxidant and anti-inflammatory properties, but its multitarget effects on Aβ- and tau-associated pathways in AD remain unclear. This study investigated the neuroprotective effects of FD on spatial memory, hippocampal histology, and hippocampal levels of Aβ and phosphorylated tau (p-tau). Methods: Male Albino Wistar rats were administered D-galactose (60 mg/kg) and aluminium chloride (200 mg/kg) to induce AD-like characteristics. The rats were co-treated with FD extract (50, 100, or 200 mg/kg) and donepezil (1 mg/kg) for 10 weeks. Behavioural assessments were conducted using the Morris water maze and T-maze, while histological analysis was conducted using hematoxylin and eosin (H&E) staining. Enzyme-linked immunosorbent assay (ELISA) and Western blot were performed to quantify hippocampal Aβ (1-42) and p-tau at threonine 181 (T181), respectively. Results: FD significantly improved spatial learning and memory and preserved the pyramidal neurons in the hippocampal subregions. FD administration led to a marked reduction of hippocampal Aβ (1-42) and p-tau T181 levels. These reductions in Aβ (1-42) and p-tau may have contributed to the preservation of hippocampal pyramidal neurons and enhanced memory performance. Conclusion: These findings suggest that FD exhibits neuroprotective properties in an AD-like rat model, potentially through its multitarget effects on the Aβ- and tau-associated pathology. Further mechanistic studies are required to support its potential use in AD intervention.

Sopak Supakul
Fujita Health University, Japan
Keio University Regenerative Medicine Research Center, Japan

14:50–15:10 Human iPSC-Derived D1R- and D2R-Specific Medium Spiny Neurons for Modeling Corticostriatal Circuit Function and Neuropsychiatric Disorders

Medium spiny neurons (MSNs) are the principal output neurons of the striatum and form the direct (dopamine D1 receptor; D1R) and indirect (dopamine D2 receptor; D2R) pathways that regulate motor control, reward processing, and adaptive behavior. Dysregulation of these pathways has been implicated in neuropsychiatric disorders, including schizophrenia. However, human pathway-specific MSN models with defined circuit-level functionality remain limited. Here, we established a transcription factor-guided differentiation strategy to generate D1R- and D2R-enriched MSNs from human induced pluripotent stem cells (iPSCs). Tet-On-mediated transcription factor induction yielded DARPP-32+ MSNs by post-induction day 28, with high neuronal purity confirmed by single-cell RNA sequencing. Modulation of transcription factor combinations enabled selective enrichment of D1R- or D2R-expressing populations. Functionally, microelectrode array recordings and calcium imaging demonstrated low spontaneous firing activity characteristic of striatal MSNs. Pharmacological analyses revealed pathway-specific dopaminergic responses, with D1R activation enhancing neuronal activity in D1R MSNs and D2R stimulation suppressing activity in D2R MSNs. To model corticostriatal interactions, we established a co-culture system comprising iPSC-derived MSNs and glutamatergic neurons. Co-culture significantly increased dendritic spine density and enhanced neuronal activity, supporting structural and functional maturation through glutamatergic input. Together, these findings establish a human D1R/D2R striatal microcircuit model for investigating dopamine-dependent regulation of corticostriatal signaling. The platform is currently being applied to investigate pathway-specific mechanisms underlying antipsychotic responsiveness in patient-derived schizophrenia iPSC models and provides a framework for studying corticostriatal circuit dysfunction in schizophrenia and related basal ganglia disorders. Funding: This work was supported by the Fujita Mind-Brain Research & Innovation Center for Drug Generation (Fujita Mind-BRIDGe) of the Japan's Peak Research Universities (J-PEAKS) Program (Grant No. JPJS00420240019), funded by the Japan Society for the Promotion of Science (JSPS), and by the Japan Society for the Promotion of Science KAKENHI/Grants-in-Aid for Scientific Research (Grant No. 26K18814).

Sunil Dhungel
Medical University of Americas
Nepalese Army Institute of Health Sciences, Nepal
Neuroscience Society of Nepal

15:10–15:30 Altitude-Dependent Neurocognitive Impairment in the Nepal Himalayas: Frontal Lobe Susceptibility Across Progressive Hypoxic Exposure

The Nepal Himalayas contain over 1,300 peaks exceeding 6,000 meters, with 42% of the national landmass classified as high altitude. Hypobaric hypoxia at high altitude (HA) alters cerebral oxygen delivery, potentially disrupting cerebral cortex network function. However, lobe-specific vulnerability and predictive neurocognitive markers remain insufficiently defined. This cross-sectional cohort study evaluated altitude-dependent cerebral lobe dysfunction across eleven stations ranging from low altitude (LA)—Pokhara (800 m) and Kathmandu (1,400 m)—to HA locations including Jomsom (2,700 m), Manaslu Base Camp (4,800 m), Kanchanjanga Base Camp (5,457 m), and Everest Base Camp (5,500 m). Assessments were conducted from February to May 2022 during the "Safa Himal Aviyan" Mountain Cleaning Campaign (MCC-22) involving Nepalese Army personnel. Standardized cerebral function test (CFT) batteries selectively targeting frontal (11 tests), parietal (10 tests), temporal (5 tests), and occipital (2 tests) domains were administered. Frontal lobe functions demonstrated the greatest altitude-related decline, particularly in executive control, inhibitory processing, sustained attention, and social cognition—functions mediated by prefrontal cortical networks highly sensitive to hypoxic stress. Parietal lobe performance showed modest impairment, whereas temporal and occipital functions remained comparatively preserved across altitude gradients. Notably, cognitive decline was more pronounced at Manaslu Base Camp compared to Everest and Kanchanjanga Base Camps, suggesting differential hypoxic burden or acclimatization dynamics. The findings support selective vulnerability of prefrontal cortical circuits to hypobaric hypoxia, likely mediated by altered cerebral perfusion, metabolic stress, and network-level dysregulation. In conclusion, our results show lobe-specific cerebral function testing provides a sensitive framework for predicting altitude-related neurocognitive dysfunction and may aid in early identification, prevention planning, and management of high-altitude cerebral impairment in climbers and military personnel

Yingjun Liu
School of Biomedical Sciences, The Chinese University of Hong Kong
Gerald Choa Neuroscience Institute, The Chinese University of Hong Kong

15:30–15:50 Direct in vivo AAV-mediated CRISPR screening reveals shared and selective neuronal vulnerabilities

Progressive neuronal death is a common feature of fatal brain disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD). It underlies the symptomatic manifestations of affected patients and serves as a primary target for disease-modifying interventions. However, the genes and genetic networks governing the survival and maintenance of adult neurons in the mammalian brain remain largely unknown, hindering the development of effective neuroprotective therapies.

Here, we developed a flexible and broadly applicable direct in vivo AAV-mediated genome-scale CRISPR screening method, designated DIVAS, which enables minimally invasive systemic delivery of guide RNA (gRNA) libraries via intravenous AAV injection and high-throughput interrogation of gene functions in the adult mouse brain. Applying DIVAS, we screened the entire mouse genome to identify essential genes and genetic networks that support neuronal survival directly in vivo across various brain regions, revealing both known and novel mechanisms related to neurodegenerative processes and a crucial role of vesicle-mediated transport in neuronal maintenance.

Notably, among the more than 800 screening hits, we identified a single gene encoding a core component of the cellular malate-aspartate shuttle, loss of which leads to selective neuronal death and robust glial responses in the thalamus, uncovering a unique and region-specific dependence of thalamic neurons on this metabolic pathway. These data highlight the power of DIVAS in discovering novel biology directly in vivo and point to amino acid metabolism as a potential therapeutic target against thalamic neurodegeneration in AD, PD, and other brain disorders with thalamic involvement.

Sze Wa Chan
School of Health Sciences, Saint Francis University, Hong Kong SAR
School of Biomedical Sciences, The Chinese University of Hong Kong

15:50–16:10 Hypothalamic Glucagon-Like Peptide-1 Receptors are Involved in Exendin-4-Induced Emesis in Suncus murinus

Introduction. The hypothalamus is crucial in coordinating neuroendocrine and autonomic function however, its role in emesis remains underexplored. Using Suncus murinus, we previously demonstrated that the paraventricular hypothalamic

nucleus (PVH) mediates exendin-4 induced emesis and anorexia. In the present studies, we used the GLP-1 receptor antagonist, exendin (9-39), to confirm if these effects are mediated via GLP-1 receptors. Methods. Animals were anaesthetized and then stereotaxically implanted with a guide cannula into the lateral ventricle or PVH. After 7-days recovery, fasted animals were pretreated with saline (5 µl, i.c.v.) or the GLP-1 receptor antagonist, exendin (9-39), (3-30 nmol, i.c.v.) 15 min prior to subcutaneous administration of exendin-4 (10 nmol/kg). In other studies, fasted animals were pretreated with saline (2 µl, iPVH) or exendin (9-39) (3-30 nmol, iPVH) 15 min prior to exendin-4 (10 nmol/kg, s.c.). Emesis and food and water intake were recorded for 6 h. Results. Exendin-4 induced 8.4 ± 1.3 episodes of emesis following a median latency of 62.7 min. The i.c.v. administration of exendin (9-39) at 10 and 30 nmol significantly reduced exendin-4-induced emesis by 57.1% ($P<0.05$) and 71.9% ($P<0.01$, $n = 8 - 9$), respectively. In another set of experiments, exendin-4 induced 10.3 ± 1.3 episodes of emesis following a median latency of 40.3 min. iPVH administration of exendin (9-39) at 10 and 30 nmol significantly reduced exendin-4-induced emesis by 50.0% ($P<0.05$) and 63.4% ($P<0.01$, $n = 8$), respectively. Exendin (9-39) did not affect the exendin-4-induced inhibition of food and water intake. Conclusion. Our study reveals that exendin-4 induces emesis via GLP-1 receptors in the PVH. This emetic action appears functionally dissociated from mechanisms of appetite suppression following a subcutaneous administration of exendin-4. These studies were fully supported by a grant from the Research Grants Council of the Hong Kong SAR, China (Project no. UGC/FDS11/M03/22).

Theodore Cheung

Department of Applied Psychology & Human Development, Ontario Institute for Studies in Education, University of Toronto, Canada
Department of Psychiatry & SickKids Research Institute, The Hospital for Sick Children, Canada
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The Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong
Music Children Foundation Limited, Hong Kong SAR
Department of Paediatric and Adolescent Medicine, Hong Kong Children's Hospital

16:10–16:30 **Musical training for survivors of pediatric brain tumors: A feasibility pilot study**

Introduction: Cancer and its treatment can have lasting adverse effects among survivors of pediatric brain tumors, particularly impairing neurocognitive functions such as attention, processing speed, and executive functions. Such adverse effects can severely affect survivors' academic achievement and abilities to perform daily and recreational activities. Musical training is a potential avenue for neuroplasticity, but its efficacy in promoting neuroplasticity among survivors of pediatric brain tumors is uncertain. The aim is to examine the feasibility, acceptability, and potential efficacy of implementing a musical training program for survivors of pediatric brain tumors. Methods: An open-label, repeated measure within-subject design was conducted in Hong Kong's Children Hospital. Forty Hong Kong pediatric brain tumor survivors who had completed cancer treatment at least 2 months previously and aged between 7 and 16 years were invited to participate in the study. All participants were scheduled to receive 45 minutes of 1:1 music training per week for 12 months, conducted by a qualified Orchestral Performer. Primary outcomes were rates of recruitment, response, and retention, and the process evaluation outcome. Secondary outcomes were nonverbal intelligence, attention, processing speed, and executive functions at baseline and after 12 months. Results: Rates of recruitment (82.3%), response (78.4%), and retention (82.5%) were high. The process evaluation supported the feasibility and acceptability of the intervention in the target cohort. The t-test results showed statistically significant improvements in participants' digital span ($p < .001$) and the Children's Color Trails Test ($p < .001$) but not nonverbal intelligence ($p = .060$) comparing pre- and post-intervention. Conclusion: This study demonstrated the feasibility, acceptability, and potential efficacy of implementing a weekly musical training program for promoting neuroplasticity among survivors of pediatric brain tumors. A fully powered randomized controlled trial of musical training is needed to provide a rigorous empirical evaluation of its efficacy in this population.

PL3 Dysregulated Synaptic Plasticity: From Alzheimer's Disease to Autism

16:50–17:50 | LT 3–4

Chair: *Michael Hausser*

Graham Collingridge

Tanz Centre for Research in Neurodegenerative Diseases; Physiology Department, University of Toronto; Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

16:50–17:50 Dysregulated Synaptic Plasticity: From Alzheimer's Disease to Autism

Synapses are highly complex molecular machines with thousands of components; genetic, epigenetic of environmental impacts upon which result in a diverse array of brain disorders. We study the molecular basis of long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus and its dysregulation in disease, with a current focus on glutamate receptors (NMDARs, AMPARs, mGluRs), protein kinases (PKA, PKB, PKC, GSK3) and tau. I will make the case that LTD gone awry is the principal cause of Alzheimer's disease and that altered LTP and LTD are involved in the core features of autism.

Biography

Professor Graham L. Collingridge, FRS, CBE, graduated with a BSc in Pharmacology at the University of Bristol (UK) in 1977. After postdoctoral positions in Vancouver (Canada) and Sydney (Australia) he returned to Bristol in 1983 to become a lecturer (Assistant Professor) in the Department of Pharmacology. From 1990 to 1994 he was the Chair of Pharmacology at the University of Birmingham (UK) and since 1994 he has held the position of Professor of Neuroscience in Anatomy at the University of Bristol. He served as Chair of the Department of Anatomy from 1997 to 1999 and then became the founding Director of the MRC Centre for Synaptic Plasticity from 1999 to 2012. In 2016 he was a co-recipient of The Brain Prize (with Tim Bliss FRS and Richard Morris CBE, FRS) and in 2019 received a CBE for services to Biomedical Sciences. Collingridge is currently the Director of the Tanz Centre for Research in Neurodegenerative Diseases, the inaugural holder of the Krembil Family Chair of Alzheimer's Research and an Affiliated Scientist at the Krembil Research Institute. He is also a Professor in the Department of Physiology at the University of Toronto, Canada and a Senior Investigator at the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital, Toronto, Canada.

Tuesday, 25 August 2026

PL4 From Genetic Tools to Motor Recovery, Blindsight, Decision and Neuropsychiatric Disorder in Nonhuman Primates

09:00–10:00 | LT 3–4

Chair: *Wing Ho Yung*

Tadashi Isa

National Institute for Physiological Sciences, Japan
Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Japan

09:00–10:00 From Genetic Tools to Motor Recovery, Blindsight, Decision and Neuropsychiatric Disorder in Nonhuman Primates

What are unique to primates include (1) fine hand motor skill which is often affected by stroke or spinal cord injury, and (2) high level cognition, including flexible decision making, which is often affected in neuropsychiatric disorders. Both of them are difficult to replicate in rodent models. During the past 2-3 decades, our group has been working on the neural mechanisms of recovery of dexterous hand movements after partial spinal cord injury by applying multi-disciplinary approaches including electrophysiology, neuroanatomy, non-invasive brain imaging, pharmacological intervention, and chemogenetic or optogenetic pathway-selective manipulation techniques with viral vectors in macaque monkeys. Using these techniques, we are also extending our research to understanding the neural mechanisms underlying visuomotor systems preserved after damage to the primary visual cortex (blindsight), and flexible decision making based on motivation or risk preference. Furthermore, we are applying our disciplines to understand the neural mechanisms of neuropsychiatric disorder phenotypes created by genome editing in macaques. I will also talk about all these studies on nonhuman primates and also on the future perspectives of our studies.

Biography

Tadashi Isa graduated from the Faculty of Medicine, the University of Tokyo (UT) in 1985 and obtained PhD from UT in 1989. He worked as a visiting scientist in the University of Göteborg in Sweden from 1988 to 1990. He returned to Japan and became an assistant professor in the University of Tokyo. During these periods, he had been working on the descending pathways controlling eye, head and forelimb movements in cats. Then, he switched his target to molecular physiology of AMPA type glutamate receptors in Gunma University in 1993-1995. He was appointed to be a professor of the National Institute for Physiological Sciences in 1996. There he returned to the systems neuroscience studies, particularly on the neural mechanism of motor recovery after the spinal cord injury and that visual cognition following the lesion of the primary visual cortex (the animal model of blindsight). He moved to Kyoto University in 2015. More recently, he is studying the neural mechanism of decision making and primate model of neuropsychiatric disorders. Since 2025, he has been appointed to be the Director General of the National Institute for Physiological Sciences.

S07 Neuroimmune interactions – new tools and discoveries

10:30–12:30 | LT 3–4

Chair: *Yulong Li*

Session overview

This symposium examines emerging tools and discoveries in neuroimmune interactions. It considers how immune cells, glia, inflammatory mediators, and neural circuits communicate across physiological and disease contexts, and how new measurement and manipulation approaches are refining this picture. The session highlights the importance of neuroimmune mechanisms for understanding brain resilience, dysfunction, and therapeutic opportunity.

Yulong Li
Peking University, China

10:30–11:00 Spying on Neuromodulator Dynamics in Neuroimmune Crosstalk by Constructing Multi-Color GRAB Sensors

The human brain consists of billions of neurons, most of which communicate with each other by releasing different kinds of neuromodulators through chemical synapses, and therefore is able to control different physiological functions like perception, motion, learning and memory. To dissect the mechanism underlying how brain take part in different physiological functions and pathological conditions, it's important to monitor the dynamics of neuromodulators in vivo. In the past few years, we and others have developed a series of multi-color GPCR-activation–based (GRAB) sensors for monitoring extracellular neuromodulator dynamics with high sensitivity, specificity, and spatial-temporal resolution in living animals. In this talk, I will share our recent progress in developing sensors for monitoring key signals involved in neuroimmune crosstalk, including monoamines, nucleotides, neurolipids and neuropeptides. With these GRAB sensors, we have monitored the dynamics of neuromodulators in mice in a wide range of physiological processes and pathological conditions.

Miao Jing
Chinese Institute for Brain Research, China

11:00–11:30 Decoding Injury Signals: Imaging Spatiotemporally-Selective ATP Dynamics in Neuron–Glial crosstalk

Brain injury triggers highly organized, multicellular response programs aimed at limiting damage and restoring tissue integrity, yet how chemical signals dynamically orchestrate these processes in time and space remains poorly understood. Focusing on extracellular ATP as an injury-related signal, we used genetically encoded fluorescent sensors to track ATP dynamics in real time during brain injury. We identified a previously unrecognized, spatiotemporally selective mode of astrocytic ATP release, termed Inflares, which represents an internal encoding of injury. Individual Inflares are digitized with stereotyped amplitudes, whereas injury severity is encoded at the population level through frequency modulation across astrocyte networks. Functionally, Inflares act as a programmed injury signal that coordinates microglial reactivity. A mismatch between injury severity and Inflares output disrupts microglial responses and leads to worsened tissue damage. In a complementary direction, microglia actively stabilize Inflare dynamics through a negative-feedback mechanism, which involve their IL-1β release that activate astrocytic IL-1 receptors to suppress Panx1-dependent Inflares, forming a astrocyte–microglia circuit that tunes purinergic signaling to maintain a balanced injury response. Together, these findings extend the role of extracellular ATP from a passive damage-associated molecular pattern released by dying cells to an active, structured signal that transmits injury information, and highlight non-neuronal signaling circuits as potential therapeutic entry points for injury-related neurological diseases.

Ji Hu
ShanghaiTech University, China

11:30–12:00 Anti-NMDAR Autoantibodies: Circuit Mechanisms of Pathology and Therapeutic Applications

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune brain disorder characterized by prominent psychiatric and cognitive symptoms, yet its circuit-level mechanisms remain incompletely understood. In this talk, I will present evidence that parvalbumin (PV) interneuron-centered circuits represent a critical substrate for anti-NMDAR antibody–mediated dysfunction. Using passive transfer of patient-derived anti-NMDAR IgG into discrete brain regions, we demonstrate that PV interneurons in the medial prefrontal cortex and hippocampus undergo marked structural

degeneration, reduced intrinsic excitability, impaired synaptic output, and disruption of NMDAR-dependent gamma oscillations. These cellular and network alterations closely mirror the reversible cognitive deficits observed in both patients and animal models, establishing a direct mechanistic link between antibody action, circuit disorganization, and behavioral impairment.

Importantly, circuit-level causality is supported by rescue experiments showing that selective optogenetic or chemogenetic activation of medial prefrontal PV interneurons restores gamma oscillatory activity and reverses anti-NMDAR IgG–induced cognitive deficits, despite the continued presence of pathogenic antibodies. Beyond mechanistic insight, I will also discuss a novel therapeutic strategy using nanobubble-actuated focused ultrasound to transiently and precisely open the blood–brain barrier, enabling localized delivery of patient-derived anti-NMDAR autoantibodies into small brain regions such as the lateral habenula. This approach achieves sustained regional antibody retention for more than ten days and unexpectedly alleviates depression-like behaviors in mice for at least two weeks. Together, these findings reveal circuit-specific mechanisms of anti-NMDAR antibody pathology and suggest that autoantibodies from autoimmune encephalitis patients may represent an unexpected source of inspiration for novel circuit-targeted therapeutic development.

Danyang He
Westlake University, China

12:00–12:30 **A Meningeal Neural Circuit Enforces Brain Immune Privilege and Limits B-ALL CNS Metastasis**

As a critical interface between the brain and immune system, the dura mater faces the fundamental challenge of maintaining robust CNS immunosurveillance while simultaneously preserving the brain's unique immune privilege. Yet, the mechanisms that allow for homeostatic immune cell trafficking without permitting pathological infiltration remain poorly understood. To address this, we focused on meningeal B cells, which routinely migrate from the skull marrow to the meninges through specialized vascular channels that are hijacked during leukemic invasion of the CNS. Using this system, we identified a peripheral-to-brain neural circuit that, when activated, suppresses the migration of B cell progenitors from the skull marrow to the dura mater under normal conditions. Remarkably, this same circuit is engaged during B-cell acute lymphoblastic leukaemia (B-ALL) invasion. Activation of the circuit blocks B-ALL cells from entering the CNS, while silencing it facilitates leukemic infiltration. Our findings establish this neural circuit as an activation dependent checkpoint that preserves brain immune privilege by restricting immune cell recruitment at the skull marrow-dura interface. This mechanism not only advances our understanding of CNS immune regulation but also points to promising strategies for preventing leukemic brain metastasis and other neuroinflammatory conditions.

S08 Neuronal and neurochemical remodelling in pathological states

10:30–12:30 | LT 2

Chair: *Ying Huang*

Session overview

This symposium explores neuronal and neurochemical remodelling in pathological states. It considers how injury, disease, stress, and altered cellular environments reshape synapses, circuits, signalling pathways, and behaviour. By integrating molecular, cellular, and systems perspectives, the session seeks to identify the processes that drive maladaptation as well as the mechanisms that may support recovery and restoration.

Ewan St. John Smith

Department of Pharmacology
University of Cambridge; Corpus Christi College, United Kingdom

10:30–11:00 Non-neuronal cells in joint pain: provocation and prevention

Joint pain is highly prevalent, osteoarthritis affecting ~600 million individuals globally and pain being the main driver of clinical decision making. However, joint pain often remains poorly managed, current medications often lacking efficacy or generating unwanted side effects. Identifying mechanisms of joint pain could lead to better therapies. In mouse models of joint pain, retrograde tracing enables recording from sensory nerves that innervate the site of injury. However, Nerves do not innervate empty space, but rather interact with different cell types: non-neuronal cells, and the mediators they release, are key regulators of sensory neuron activity and thus pain. Fibroblast-like synoviocytes (FLS) are not quiescent synovial cells, instead contributing to arthritis pathogenesis. We find that activation of FLS by tumour necrosis factor causes release of mediators that sensitise knee-innervating neurons. Moreover, we have identified a key role for the proton-sensing G protein-coupled receptor GPR65 in FLS. Conditioned medium from GPR65 stimulated FLS sensitises sensory neurons in a similar manner to the sensitisation of knee-innervating neurons that occurs in vivo following GPR65 activation. Inhibiting GPR65 could therefore be beneficial for treating joint pain.

However, some cell-cell interactions may be important in preventing pain. Mesenchymal stem cells (MSCs) relieve pain in humans with osteoarthritis, which we find also occurs in murine osteoarthritis due to prevention of knee-innervating neuron sensitisation. Extracellular vesicles released by MSCs (MSC-EV) act directly on sensory neurons to prevent sensitisation induced by the osteoarthritis-associated mediator, nerve growth factor (NGF). Further experiments show that MSC-EV internalisation into sensory neurons is required for their anti-NGF effects, which suggests delivery of a biomolecular cargo is required for their analgesic effect. We find that a cocktail of microRNAs reproduces the ability of MSC-EVs to prevent NGF-induced sensitization, further analysis being required to identify the molecular mechanisms involved.

Jessica Liu

Department of Neuroscience, College of Biomedicine, City University of Hong Kong, Hong Kong SAR

11:00–11:30 Plasma cytokines induced astrocytic P21-activated kinases (PAK1) activation alters blood-spinal cord barrier in promoting neuropathic pain

Neuropathic pain is a debilitating condition driven by chronic central sensitization, yet its underlying mechanisms remain incompletely understood, significantly limiting effective therapeutic options. Here we identified distinct astrocyte subpopulations in the dorsal horn, among which an emergence of a PAK1-expressing subset was found to be critically associated with blood-spinal cord barrier (BSCB) disruption during neuropathic pain development. Following peripheral nerve injury, PAK1 was activated in astrocytes, impairing astrocyte-endothelial cell coupling and disrupting BSCB integrity. This barrier dysfunction facilitated peripheral monocyte infiltration into the central nervous system (CNS), thereby exacerbating neuroinflammation and chronic pain states. To establish clinical relevance, we analyzed plasma from neuropathic pain patients and detected significantly elevated levels of phosphorylated PAK1 (p-PAK1), which positively correlated with established pain-associated biomarkers, including glial fibrillary acidic protein (GFAP) and S100β. Mechanistically, patient-derived plasma directly induced PAK1 phosphorylation in astrocytes, an effect sustained by elevated tumor necrosis factor-alpha (TNF-α) signaling, thereby identifying a clinically relevant inflammatory axis driving astrocytic dysfunction. Collectively, these findings demonstrate that pathological factors present in patient plasma drive PAK1 hyperactivation, disrupting astrocyte-endothelial coupling and amplifying central neuroinflammation.

Ying Huang
Laboratory of Neuronal Circuit & Neuroplasticity
School of Medicine, Tongji University, China

11:30–12:00 **5-HT3 Receptor-Dependent Nigro-Hippocampal Circuit Remodeling Mediates Exercise-Enhanced Cognition in Parkinson's Disease**

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal degeneration, leading to motor deficits and non-motor symptoms such as cognitive dysfunction. While aerobic exercise offers benefits for cognitive impairment in PD, the underlying mechanisms remain unclear. Here, we investigated the role of 5-HT3R in exercise improving cognition in a PD mouse model. Behavioral tests demonstrated that aerobic exercise alleviated deficits in exploratory learning and working memory via 5-HT3R in PD mice. Exercise enhanced impaired hippocampal dentate gyrus neurogenesis, promoted astrocyte proliferation, and suppressed pathological microgliosis in a 5-HT3R-dependent manner. In vitro electrophysiology revealed that 5-HT3R is required for exercise-induced rescue of long-term potentiation (LTP) impairment in the hippocampal CA3 region. Viral tracing identified a dopaminergic projection from the substantia nigra pars compacta (SNc) to the CA3. Chemogenetic activation of this nigro-hippocampal pathway rescued CA3 LTP impairment in PD mice, whereas pathway inhibition abolished exercise benefits.

Mechanistically, exercise promoted hippocampal dopamine release via this pathway, ameliorating LTP impairment through D1 receptors. Exercise upregulated 5-HT3R expression in the SNc and reduced nigral dopaminergic neuron loss as well as aberrant microglial proliferation in PD mice. Notably, AAV-mediated 5-HT3R upregulation in the SNc, independent of exercise, was sufficient to improve memory and alleviated CA3 LTP impairment in PD mice. RNA-seq analysis of the SNc with 5-HT3R overexpression revealed suppression of neuroinflammatory pathways, activation of cAMP signaling, and upregulation of neurotrophic factors including BDNF. Collectively, these findings demonstrate that aerobic exercise enhances nigro-hippocampal dopaminergic transmission by upregulating 5-HT3R, thereby restoring hippocampal synaptic plasticity and cognitive function in a preclinical model of PD. This work identifies 5-HT3R as a critical mediator of exercise benefits and a potential therapeutic target for cognitive dysfunction in PD.

Cheng Cen
Department of Neurobiology
Peking University School of Basic Medical Sciences, Beijing, China

12:00–12:30 **Decoding the Pathophysiology of Trigeminal Neuralgia and Its Emotional Comorbidities**

Trigeminal neuralgia (TN) is a common chronic pain syndrome affecting the orofacial region, often accompanied by psychiatric comorbidities such as anxiety and depression. Currently, the central mechanisms underlying TN remains elusive. Analysis of fMRI data from TN patients identified the parafascicular nucleus (PF) as a candidate region. Using a TN mouse model, we revealed an increase in intrinsic excitability of glutamatergic neurons in the PF and an imbalance in the excitatory-inhibitory synaptic transmission. We uncovered two spatially and functionally distinct PF neuronal ensembles that separately encode sensory and affective dimensions of TN. Single-nucleus RNA sequencing identified Col25a1 and Syn2 as markers of the anxiety-encoding ensemble. This work aims to provide potential targets and novel strategies for clinical intervention of TN and other refractory thalamic pain conditions.

YIC1 ISN-APSN Young Investigators Colloquium Session 1

10:30–12:30 | Seminar Room 1, 3rd Floor

Chair: *Yuuki Fujiwara*

Xuan Ling Hilary Yong
University of Queensland, Australia

10:30–10:54 **Tau controls the homeostasis of synaptic NMDA receptors**

Dysregulation of the microtubule-associated protein tau causes synaptic deficits associated with a range of neurodegenerative diseases. However, the physiological function of tau at the postsynaptic compartment of neurons remains unclear. Here, we show that tau phosphorylation, distinct from its pathological form, controls the subunit-specific expression of N-methyl-Daspartate (NMDA) receptors during homeostatic plasticity. Upon chronic neuronal inactivity, tau is phosphorylated at Ser-235 by cyclin-dependent kinase 5, which helps retain active fyn kinase at the synapse. This promotes the phosphorylation of the GluN2B subunit of NMDA receptors at Tyr-1472,

thereby increasing receptor availability at synapses during homeostatic adaptation. Disease-associated tau mutations cause an aberrant increase in surface NMDA receptor levels, which can be restored by blocking tau phosphorylation at Ser-235. Together, our findings identify that site-specific tau phosphorylation, which enables the tau protein to differentiate between physiological and pathological conditions, is essential for maintaining neuronal network homeostasis.

Ami Kobayashi
Tohoku University, Japan

10:54–11:18 **tRNA-derived fragments function as tau binders, promoting Tau aggregation**

Tauopathies, including Alzheimer's disease (AD), are characterized by the pathological aggregation of tau, a process that requires specific co-factors. Recent studies suggest that tRNA-derived fragments (tRFs) may play a role as tau-binding partners, though their involvement in tau pathology remains poorly understood. In this study, we explore the contribution of tRFs to tau aggregation. Our preliminary data indicate that aging and persistent neuronal stress, key factors in tauopathies, induce tRNA cleavage, resulting in the accumulation of specific tRFs in neurons and conditioned media from stress-enduring neuronal cultures. We observed elevated levels of these tRFs in the hippocampus of wild-type (WT) mice, Tau P301S transgenic mice, Tau P301S human iPS-derived neurons (hiNs), and stressed WT hiNs. Additionally, these tRFs were upregulated in the temporal lobe of AD, Frontotemporal Lobar Degeneration (FTLD), Progressive Supranucelar Palsy (PSP) patients but not in Parkinsons disease dementia patients. Using in situ hybridization (FISH), we confirmed the intracellular localization and upregulation of tRFs, which co-localized with tau aggregates in both animal models and AD, FTLD, and PSP patients. Crosslinking and immunoprecipitation sequencing revealed the specific binding of certain tRFs to phosphorylated tau. Notably, tRFs which were elevated in all tauopathy models, significantly enhanced tau seeding in FRET biosensor cell lines. This was further supported by Thioflavin T assays, nuclear magnetic resonance spectroscopy, and Transmission Electron Microscopy, which confirmed tau fibril formation. Furthermore, specific tRFs were highly secreted by neurons and were taken up by recipient cells. Horizontal transfer of these tRFs was associated with Tau aggregation in the recipient cells, implicating the propagation of tau pathology. Our findings suggest that specific tRFs, increased with aging, are critical regulators of tau aggregation, enhancing fibril formation and propagation. These tRFs represent potential therapeutic targets for tauopathies, offering new insights into the molecular mechanisms driving AD and related tau diseases.

Keita Kakuda
The University of Osaka, Japan

11:18–11:42 **Lysosomal resilience as a central regulator of pathogenic protein propagation in neurodegenerative diseases**

The propagation of pathogenic protein aggregates across neural networks is a central mechanism underlying the progression of neurodegenerative diseases, including Parkinson's disease and other synucleinopathies. Although lysosomal dysfunction has been widely implicated in these disorders, how lysosomal damage responses influence aggregate propagation and their relevance to human disease remain incompletely understood. Our recent study demonstrated that rupture of lysosomal membranes serves as a critical route through which pathogenic α-synuclein propagates aggregation between neurons, while lysosomal damage responses—including membrane repair and lysophagy—act to counter this process (PNAS, 2024). These findings highlight lysosomal resilience as a decisive factor regulating the intercellular spread of pathogenic aggregates. Building on this discovery, we have expanded our investigation of lysosomal damage responses across molecular, in vivo, and clinical contexts. First, through proteomic analysis of lysosomes isolated from aggregate-accumulating cells followed by

siRNA screening, we identified a novel lysosomal damage response in which recruitment of lysosomal proteolytic activity to damaged lysosomes modulates aggregate accumulation. Second, using mouse models, we demonstrated that intranasal exposure to environmental factors induces lysosomal damage and accelerates the propagation of pathological aggregates in vivo, highlighting a potential mechanistic link between environmental stressors and disease progression. Third, we are currently extending these findings toward translational applications by exploring candidate cerebrospinal fluid biomarkers reflecting lysosomal damage and initiating therapeutic exploration aimed at modulating lysosomal resilience. Together, these findings position lysosomal damage responses as a central regulatory system governing the propagation of pathogenic protein aggregates across neurodegenerative diseases. Elucidating and modulating lysosomal resilience may open new avenues for mechanism-based, disease-modifying strategies.

Yuek Ling Chai
National University of Singapore

11:42–12:06 Unique inflammasome activation patterns in mice models of β-amyloid accumulation and tauopathy

Neuroinflammation plays an important pathophysiological role in the development of Alzheimer's disease (AD), whose pathological hallmarks of aggregated, insoluble proteins include β-amyloid forming senile plaques and abnormally phosphorylated tau forming neurofibrillary tangles. Within the innate immune system, large cytosolic multiprotein complexes called inflammasomes are proposed to sustain a feed forward loop in AD: amyloid and tau activate inflammasomes, which in turn further promote amyloidogenesis, tauopathy, synaptic dysfunction and cognitive decline. While several preclinical studies have explored associations between inflammasomes and amyloid or tau, most have focused on either amyloid-driven or tau-driven pathology, but no study to date has compared and contrasted potential differences in affected inflammasome pathways between these processes. In this study, we performed a head-to-head comparison of various inflammasome-related markers using two animal models: APPNLGF mice with amyloid pathology and P301S mice with tauopathy. We compared animals from different ages and correlated their neuropathological burden of amyloid or tau with gene expression levels of inflammasome markers. Our studies revealed that inflammasome sensor NLRP3 was upregulated in older mice with heightened amyloid and tau pathology. Other inflammasome sensor AIM2 and adaptor protein ASC/PYCARD were both upregulated in older P301S mice, but not in APPNLGF mice. Downstream caspases were involved as well, with CASP1 upregulated in older P301S mice, whereas CASP8 was upregulated in older APPNLGF mice. Downstream effectors such as IL1B and GSDMD were upregulated in both P301S and APPNLGF mice, suggesting involvement of inflammation and pyroptosis during amyloid and tau pathology in these disease models. Our findings indicate that inflammasome activation is a shared feature of both amyloid and tau driven AD mouse models, but distinct inflammasome components are differentially engaged, with NLRP3 broadly responsive to amyloid and tau pathology and AIM2-ASC signaling more prominently associated with tauopathy. This highlights NLRP3 and AIM2-ASC as potential, pathology selective therapeutic targets in AD.

Dhirendra Pratap Singh
Neurotoxicology and Immunotoxicology Laboratory, Division of Biological Sciences
Icmr-National Institute of Occupational Health, Ahmedabad, India

12:06–12:30 Bisphenol Analogues and the Microbiota-Gut-Brain Axis: Rethinking Safer Alternatives

Bisphenol-A (BPA), a high production volume plasticizer, and a known endocrine disruptor, was on the radar of regulatory and food safety agencies owing to its negative health impacts. Hence, hundreds of its structural analogues such as BPS, BPF, BPAF, BPB, etc., have been developed as BPA's replacements. However, emerging evidence questions their biological safety.

Our lab is currently focusing on the neurotoxicological aspect and the behavioural effect mediation by targeting the microbiota-gut-brain axis upon BPA and its more prevalent structural analogues/replacement exposures. This presentation delves into the complex interplay between BPA and its alternatives, gut microbiota, and brain functions. Here, I shall be discussing two recent studies concluded by our group in this domain. Experimental techniques such as neurobehavioral assessments for cognition, anxiety, and depression-like behaviour using a standard test battery, biochemical and molecular estimations for inflammatory cytokines, neurotransmitters, and oxido-nitrosative stress markers, gene expression analysis using qRT-PCR, histological investigations, gut permeability assays, and 16S-rRNA metagenomics sequencing for the gut microbial abundance and functional analysis for these bacterial ecological signatures were done.

We identified that bisphenol(s) exposure impaired learning and induced anxiety and depression-like behaviours. Behavioural despairs also show a sexually dimorphic response, particularly in male mice. These exposures lead to a heightened pro-inflammatory response and systemic endotoxemia, altered monoamine neurotransmitter levels/turnovers, and hippocampal

neuronal degeneration and inflammatory responses in the brain. They also increased gut permeability and altered microbial diversity. A mechanistic understanding of these effects was acquired using various gut microbiota manipulation strategies, such as antibiotics-induced microbial depletion and faecal microbial transplants (FMT). Results underscore the pivotal role of the microbiota-gut-brain axis in mediating these toxic effects. The presentation will discuss the broader implications of these findings for public health, emphasizing the need for more stringent regulatory measures and a deeper understanding of the potential risks posed by BPA alternatives.

YIC2 ISN-APSN Young Investigators Colloquium Session 2

10:30–12:30 | Seminar Room 2, 3rd Floor

Chair: *Christina Perry*

Yun Zhu

The Chinese University of Hong Kong

10:30–10:54 Appetite Gating Through Region-Specific Neural Activity Balance in the Extended Amygdala

Understanding the neural mechanisms that govern food intake is essential for addressing obesity and other feeding-related disorders. The extended amygdala is a key hub for integrating motivational and affective signals that influence feeding behavior. Within this network, the anterior bed nucleus of the stria terminalis is emerging as an important regulator, yet the neural mechanisms through which it controls food intake remain largely elusive. Here, we examined how neural activity balance within this region shapes feeding behavior in rats. We found that local manipulation of opioid signaling in this extended amygdala nucleus robustly increased food consumption, with a marked preference for high-fat food, indicating that this region can strongly bias appetite even in the absence of metabolic need. To define the underlying cellular mechanisms, we performed whole-cell patch-clamp recordings and found that this feeding-promoting manipulation strongly suppressed neuronal activity through a potassium channel-dependent postsynaptic mechanism. Importantly, the magnitude of this suppression differed across subregions, revealing substantial local heterogeneity in intrinsic responsiveness. At the synaptic level, we observed a coordinated but nonuniform reorganization of circuit input: excitatory drive was consistently reduced across subregions, whereas inhibitory transmission was selectively diminished in only a subset of subregions. This patterned redistribution of excitation and inhibition suggests that feeding does not arise from a uniform circuit-wide effect, but rather from a subregion-specific shift in the balance of local neural activity. Together, these findings identify the anterior bed nucleus of the stria terminalis as a site where appetite can be gated through coordinated changes in intrinsic excitability and synaptic input. More broadly, they support a model in which neural activity balance within the extended amygdala serves as a dynamic mechanism for promoting food intake and hedonic feeding, while also highlighting a potential target for interventions in disordered eating.

Shenghui Wu

The Hong Kong University of Science and Technology

10:54–11:18 Towards transregional neural prostheses: Re-establishing neural functional connectivity with generative spike prediction models

Damage to communication pathways within the interconnected nervous system often results in severe functional impairments, such as memory disorders in Alzheimer's disease and motor dysfunction after spinal cord and brain injuries. Recent advances in high-density neural interfaces and computational algorithms have opened new possibilities for transregional neural prostheses, which bypass damaged circuits by synthetically creating an artificial information pathway. These systems typically record upstream neural signals and deliver biomimetic electrical stimulation to induce desired behavioral functions. Unlike conventional brain–machine interfaces that replace lost functions with external devices, these approaches utilize the remaining intact neural pathways to naturally generate behavior. However, functional downstream activity cannot be recorded when neurological disorders exist. The key challenge remains in generating biomimetic neural activities that can re-establish neural functional connectivity.

In this talk, Dr. Wu will present a unified computational framework for transregional prostheses, focusing on the recent development of reinforcement learning (RL)-based generative models for neural spike trains. These models precisely relay information from upstream to downstream brain regions on a real-time, single-trial basis by directly maximizing behavior-level rewards. Results demonstrate that the RL-based generative models produce movement-modulated spike patterns akin to downstream recordings from healthy subjects, providing a biomimetic spike encoding framework and outperforming existing methods in different behavioral tasks and neural pathways. By incorporating low-dimensional neural manifold constraints, our approach further induces realistic neural correlations, highlighting its potential for neural prostheses in restoring transregional communication with biomimetic cortical stimulation. Dr. Wu will also discuss future directions for transregional neural prostheses from perspectives of clinical considerations, neuroscience research, and neural engineering innovations.

Chun Hui (Johnny) Park
Department of Health / Impact Institute
Deakin University, Victoria, Australia

11:18–11:42 Repurposing a hypertension medication to treat unipolar and bipolar depression: The Candesartan Adjunctive Depression trials

Approximately 30% of patients taking antidepressants experience treatment-resistance, necessitating novel, safe, and sustainable treatments for unipolar/bipolar depression. Two independent studies nominated angiotensin agents: a genome-wide-associated-data study identified an angiotensin II type 1 receptor (AT1R) antagonist to target AGTR1 (a bipolar disorder candidate gene) and an in vitro gene expression study using human neurons revealed an angiotensin-converting-enzyme inhibitor matched closely with the current bipolar disorder medications in regulating bipolar disorder-related gene expressions.

Candesartan, an AT1R antagonist, crosses the blood-brain barrier to exert neuroprotective effects in the hypothalamic paraventricular nucleus, subfornical organ, prefrontal cortex, hippocampus, and amygdala, as demonstrated in a rat model. AT1Rs are densely expressed in microglia, where blockade downregulates neuroinflammation and oxidative/nitrosative stress via reducing pro-inflammatory cytokine release (e.g., TNF-α, IL-6, and IL-1β). Further, candesartan-induced astrocytic modulation increases the microglial anti-inflammatory marker IL-10 and decreases pro-inflammatory inducible nitric oxide synthase, as demonstrated in vitro. Furthermore, candesartan inhibited NADPH oxidase-mediated ROS, MAPK, and NFκB signalling, and promoted hippocampal neurogenesis in vivo. Additionally, candesartan was more effective in reversing alterations in oxidative and inflammatory stress (i.e., glutathione, TNF-α, and BDNF levels) in the hippocampus and cerebellar vermis than lithium, potentially by improving mitochondrial biogenesis and insulin sensitivity through peroxisome-proliferator-activated receptor gamma (PPAR-ɣ) agonism.

In humans, 12-week candesartan treatment significantly reduced oxidative stress markers including C-reactive protein, 8-epi-prostaglandin F2α, and 8-hydroxydeoxyguanosine compared to patients taking non-angiotensin hypertensive medication. A meta-analysis and Danish population study also supported that AT1R blocker use was associated with improved quality of life and decreased mood disorder diagnoses. Backed by converging evidence, CADET trials investigate the efficacy of adjunctive candesartan in treating unipolar/bipolar depression through 16-week, phase 2/3, double-blinded, randomized, and placebo-controlled clinical trials, with five recruitment sites in Victoria and Queensland, Australia. Successful repurposing will yield an affordable, accessible, tolerable, and mechanistically distinct antidepressant.

Peeraporn Varinthra
Institute of Medical Sciences
Tzu Chi University, Hualien, Taiwan

11:42–12:06 Herbal Modulation of Actin Remodeling Rescues Synaptic Plasticity and Memory in REM Sleep–Deprived Mice

Rapid eye movement (REM)-sleep deprivation (REM-SD) profoundly disrupts synaptic plasticity, destabilizes dendritic spine architecture, alters GABAergic signaling, and accelerates memory decline. Despite growing recognition of sleep loss as a major risk factor for cognitive dysfunction, effective interventions that protect synaptic structure and memory during REM-SD remain limited. Protein kinase C (PKC)–dependent phosphorylation plays a critical role in maintaining synaptic strength and cognitive performance and is also essential for regulating GABAB receptor trafficking and surface stability. Disruption of this signaling axis may therefore represent a key mechanism linking REM-SD to synaptic dysfunction and memory impairment.

This study aims to investigate whether herbal fractions derived from TCU411, an indigenous herbal medicine, could modulate actin remodeling and preserve synaptic plasticity and memory in a mouse model of REM-SD. Behavioral analyses demonstrated that TCU411 treatment significantly alleviated working memory deficits induced by REM-SD, accompanied by a reduction in pathological overexpression of the GABAB receptor subunit 1 (GABABR1) and the restoration of postsynaptic density protein-95 (PSD95) synaptic integrity in the hippocampus. Further fractionation yielded two bioactive fractions, F1 and F2, that effectively rescued impairments in cognitive flexibility, suggesting the presence of potent neurorestorative compounds. Proteomic profiling revealed that treatment with the TCU411-F2 fraction upregulated key synaptic plasticity–related proteins, including CaMKII, PKC-α, and PKC-ɣ, while suppressing cofilin expression. Consistently, western blot analyses confirmed that the TCU411-F2 fraction enhances PKC-α and PKC-ɣ expression and reactivates actin cytoskeleton remodeling pathways involving PAK1, LIMK1, and phosphorylated cofilin. Together, these findings highlight actin

cytoskeleton regulation as a critical mechanistic link between sleep loss and memory impairment and support the therapeutic potential of TCU411 herbal fractions for sleep-related cognitive dysfunction.

Mohammed R Shaker
College of Health & Life Sciences; Neurological Disorders Research Center
Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Qatar Foundation, Doha

12:06–12:30 Patient Derived Brain Organoids Link Preserved Genomic Background to Network Dysfunction in ASD

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental condition with complex genetic architecture, where connecting patient-specific genetic background to brain-relevant molecular mechanisms remains a major challenge. While blood-based genomics can reveal candidate variants, interpretation is often limited without a human neural model system that captures cell-type-specific and developmental phenotypes. Patient-derived induced pluripotent stem cells (iPSCs) and brain organoids provide an experimentally tractable platform to bridge this gap by enabling multi-modal interrogation of disease-associated pathways in a human context.

Here, we investigated a severe ASD case identified in Qatar and leveraged a family-based control framework to define genetic background and map it to downstream molecular and functional consequences in iPSC-derived brain organoids. Whole-genome sequencing of granulocytes from the ASD patient and related controls and generated iPSCs revealed ~90% similarity between granulocyte and iPSC genomes, supporting that reprogramming preserved the patient's genetic background. We then generated brain organoids and performed proteomics profiling to identify dysregulated molecular programs. Integrated omics analysis demonstrated that a subset of highly significant differentially expressed proteins that overlapped with the shared genomic background were associated with Ras signaling pathways. Immunohistochemistry validation supported the proteomics predictions, revealing astroglial proliferation and altered differentiation programs in patient-derived organoids compared with controls. Functional maturation assessed by multi-electrode array recordings at day 45 and day 90 demonstrated an early hyperactive phenotype at day 45 that transitioned to reduced activity by day 90, indicating evolving network dysfunction over developmental time. Collectively, these data establish a patient-specific multi-omics organoid pipeline that links preserved blood to iPSC genomic architecture to organoid proteomic signatures and neurophysiological phenotypes, implicating Ras signaling associated astroglial dysregulation as a candidate contributor to severe ASD pathology.

SS5 Women in Neuroscience Forum

10:30–12:30 | LT 1

Chair: *Ying-Shing Chan; Cora Lai*

Session overview

The Women in Neuroscience Forum celebrates scientific contributions while creating space for candid discussion of career development, leadership, mentorship, and sustainable participation in research. The session combines short research-focused perspectives with a broader exchange on opportunities and challenges across different career stages. It aims to foster connection, visibility, mutual support, and practical insight for building inclusive neuroscience communities.

Participants

Dorothy Tse • *Xiaohong Xu* • *Ha Thi Thanh Huong*

OT2 Open Theatre on Neurotechnology

13:30–14:15 | LT 1

Focusing on high-density SiNAPS probe, 3D atlas multiphoton microscopy, and an advanced virtual-reality platform.

S09 The geometry of neural dynamics: data driven models, network mechanism and brain-inspired AI

14:30–16:30 | LT 3–4

Chair: *Hu Yu*

Session overview

This symposium investigates the geometry of neural dynamics through data-driven models, network mechanisms, and brain-inspired artificial intelligence. It considers how population activity, representational structure, and large-scale connectivity give rise to flexible computation and behaviour. The session highlights reciprocal exchange between neuroscience and AI, using each field to develop more informative theories and models of intelligent systems.

Gerald Pao

Okinawa Institute of Science and Technology, Japan

14:30–15:00 Manifolds for explainable Data Driven Science

Quantitative science has been dominated by physics that tries to determine the relationships of natural variables in the form of equations. For these to have close form analytical solutions mostly requires the relationships among variables to be linear, decomposable and noise hopefully Gaussian. For highly nonlinear highly nonlinear data distributions, the Weierstrass approximation theorem proves that for any on zero error there is an infinity of polynomials that can approximate any data distribution, making the task of finding the correct differential equations a daunting task. However in the last decade it has become apparent that Deep Learning is able to give surprisingly good mappings for these types of nonlinear problems better than traditional physics type approaches, hence proving the existence of such solutions. However the drawback of deep learning mediated fitting is that these are black box solutions lacking explainability. To solve this type of problems in an explainable manner we offer a framework called empirical dynamic modeling EDM to generate embeddings of time series on low dimensional manifolds.These embeddings allow prediction of complex systems, inference of cause and effect relationships to hundreds of thousands of variables that scales linearly with combinatorial complexity, dimensionality, simulate complex systems, guarantee explainability and offer experimentally testability of inferred relationships allowing falsifiability of the obtained data driven hypotheses. We present a new algorithm Manifold dimensional expansion,

based on ideas from the generalized Takens theorem that generically allows the decoding of behavior from brain activity from many types of data generally at 70% accuracy or better. We show a handful of use cases as examples that include brains of animals and humans where we generate realistic behavioral outputs of simulated animal and human behavior from neural activity mappings equivalent to a single behavior brain download.

Camilo Libedinsky

National University of Singapore

15:00–15:30 Inferring Latent Behavioral Strategy from the Representational Geometry of Prefrontal Cortex Activity

Behavioral tasks can be solved employing various strategies. Sometimes, different strategies result in the same observable behavior, making them latent. In this talk I will discuss how we inferred the latent behavioral strategy used by two male monkeys in a working memory updating task by comparing the representational geometry of two prefrontal regions - the lateral prefrontal cortex (LPFC) and the prearcuate cortex (PAC) - with that of recurrent neural network (RNN) models trained to solve the task using different strategies. We found that neural activity patterns in both LPFC and PAC align with only one of the proposed strategies, suggesting that monkeys employ this latent strategy to perform the task. These findings open avenues for investigating the processes that lead to strategy learning and the decision-making mechanisms that determine which strategies are chosen when multiple options are available.

Haiyan Wu

University of Macau, Macao SAR

15:30–16:00 Dynamic integration of dissociable value codes for reward and information in the human prefrontal cortex

Balancing the exploitation of known rewards with exploration for new information is a core challenge in decision neuroscience. While the prefrontal cortex is critical for this process, how its subregions dynamically cooperate to mediate this balance remains unclear. Here, we recorded intracranial stereoelectroencephalography (SEEG) from 17 human

participants performing a gambling task that orthogonalized expected reward and information gain. Using reinforcement learning-based computational modeling, we confirmed that participants assigned intrinsic value to information. Time-frequency analyses identified functionally dissociable value representations: while ventromedial prefrontal cortex (vmPFC) activity encoded the integrated value of the current option, anterior cingulate cortex (ACC) activity tracked reward and information value in a distinct manner. Network dynamics analysis revealed that undirected Theta synchronization (PLV) supported reward integration, whereas directed information flow (PSI) showed that the vmPFC initiates exploration by driving the ACC. Furthermore, Phase-Amplitude Coupling (PAC) identified specific gating mechanisms: a bottom-up striatal-cortical coupling encoded absolute motivational gain, while a top-down ACC Beta-Gamma coupling facilitated deliberation during high-conflict exploration. Crucially, state-space analysis of neural population dynamics confirmed a computational double dissociation: the vmPFC functioned as a value integrator where

representations sharp ened over time, while the ACC functioned as an information differentiator, with its neural state velocity precisely tracking the theoretical rate of information gain. Collectively, these results map a hierarchical architecture where exploration is initiated by value regions, gated by oscillatory control, and realized through a dynamic interplay between the integral of value and the derivative of information.

Yujie Wu
Hong Kong Polytechnic University

16:00–16:30 **From Neural Plasticity to Intelligent Systems: Brain-Inspired Pathways Toward Efficient AI**

The brain and current AI systems exhibit fundamentally different computational and learning characteristics. To design more efficient AI, a promising direction is to understand and harness the brain's underlying mechanisms. In this talk, I will first discuss how to model a fast-learning rule recently uncovered in the brain. I will then illustrate how to leverage and integrate these brain-inspired learning principles to facilitate the development of efficient AI systems.

S10 Molecular mechanisms of neurodegenerative diseases: from protein aggregation to altered chromatin architecture

14:30–16:30 | LT 2

Chair: *Kensuke Ikenaka*

Session overview

This symposium examines molecular mechanisms of neurodegenerative disease, from pathogenic protein assemblies to altered chromatin architecture and cellular vulnerability. It integrates approaches from protein biophysics, neurochemistry, synaptic biology, and genomics to understand how diverse molecular disruptions converge on neuronal dysfunction. The session emphasizes how mechanistic integration can guide biomarker development and disease-modifying strategies.

Kensuke Ikenaka
The University of Osaka, Japan

14:30–15:00 **Reverse Translational Insights into the Mechanisms of Synucleinopathies**

The pathological hallmark of Parkinson's disease (PD) is the accumulation of aggregated alpha-synuclein (aSyn). Although the aggregation process of aSyn has been extensively characterized using in vitro systems as well as cellular and animal models, the molecular mechanisms that drive aSyn aggregation in the human brain remain largely unresolved. Moreover, a fundamental mystery persists as to how aggregation of the same aSyn protein can give rise to distinct neurodegenerative disorders, including PD and multiple system atrophy (MSA). To address these questions, our team has pursued a patientoriented, reverse translational approach, directly interrogating post-mortem human brain tissue using a suite of advanced neurochemical and biophysical techniques. These include Fourier-transform infrared (FT-IR) spectroscopy to define secondary structure signatures, HANABI—a high-throughput amyloid fibril amplification system—to probe disease-specific seeding properties, and mass spectrometry imaging to visualize molecular environments associated with pathogenic aggregates. Through these approaches, we have identified molecular triggers that promote aSyn aggregation in the human brain and have begun to elucidate how distinct biochemical and lipid contexts give rise to divergent pathogenic cascades from a common protein substrate. Building on these insights, I will also present our ongoing efforts to develop therapeutic strategies that selectively target disease-specific aSyn conformations. By bridging patient-derived biochemical signatures with mechanistic neurochemistry, this work underscores the power of reverse translational research to redefine our understanding of synucleinopathies and to guide the development of rational, mechanism-based therapies. We believe that this presentation will stimulate active discussion within the neurochemistry community and inspire new approaches to unraveling disease mechanisms directly from the human brain.

Maiko Uemura
Osaka Metropolitan University, Japan

15:00–15:30 **Neurovascular Modulation of Tau Pathology under Chronic Cerebral Hypoperfusion**

Tau pathology is a central hallmark of Alzheimer's disease (AD), and its accumulation and propagation are influenced by neuronal activity. Vascular dysfunction, particularly chronic cerebral hypoperfusion (CCH), is one of the most prevalent co-pathologies in AD, yet how altered cerebral blood flow and neurovascular function modulate tau pathology remains poorly understood. We investigated whether CCH modifies tau accumulation and propagation through changes in cerebral perfusion and neuronal activity. AD-derived tau extracted from human AD brains was stereotaxically injected into the brains of 3-month-old male C57BL/6 mice. CCH was induced by bilateral common carotid artery stenosis (BCAS). Tau pathology was evaluated at 3, 6, and 12 months post-injection (mpi) using immunohistochemistry (n = 4–6 mice per group; BCAS or sham). Longitudinal assessments of cerebral blood flow, neuronal activity, and vascular responses were performed using arterial spin labeling MRI and in vivo two-photon microscopy. At 3 mpi, CCH suppressed tau accumulation in the vicinity of the injection site. In contrast, at 12 mpi, BCAS promoted local tau accumulation while attenuating contralateral and long-range intracerebral propagation. Functional imaging revealed a biphasic response to CCH: an early phase characterized by enhanced stimulusevoked neuronal activity accompanied by vasodilation, followed by a later phase marked by reduced neuronal responsiveness and altered vascular dynamics. CCH modulates tau pathology in a time-dependent and region-specific manner, enhancing local accumulation while restricting long-range propagation. These findings suggest that alterations in cerebral blood flow, neurovascular responses, and neuronal activity act as key modulators of tau pathology, highlighting the critical role of vascular and functional brain states in shaping tau progression in AD.

Kwok On Lai
City University of Hong Kong

15:30–16:00 ALS-related FUS mutation causes synaptic changes on human stem cell derived cortical neurons in both in vitro astrocyte-neuron co-culture and after in vivo xenotransplantation

Fused in Sarcoma (FUS) gene mutation is one of the leading genetic causes of amyotrophic lateral sclerosis (ALS). This gene encodes a multi-functional DNA/RNA-binding protein. In post-mortem brain samples as well as human induced pluripotent stem cell (hiPSCs)-derived neurons, many of the ALSrelated FUS mutant proteins form cytoplasmic aggregates or inclusions which are believed to cause the neuronal damage. Majority of the human FUS-ALS studies involve differentiation of the hiPSCs into spinal motoneurons. Given the non-motor deficits observed in transgenic mouse models of FUS-ALS, it is imperative to determine how ALS-FUS mutations also affect hiPSC-derived neurons in the brain. Here we employ CRISPR/Cas9 to knock-in two individual missense mutations (R521C and F525L) into the nuclear localization signal at the C-terminus of the FUS protein. The hiPSCs were differentiated into cortical neurons and co-cultured with rat astrocytes for 6 weeks. Compared to wild-type neurons in which FUS was restricted in the nucleus, cortical neurons carrying the clinically severe P525L-FUS mutation exhibited diffuse cytoplasmic localization. Despite lacking FUS aggregate, the P525L-FUS neurons showed significantly fewer dendrite arborizations and PSD-95 puncta than the wild-type FUS neurons. Substantial changes in the expression of mRNAs that encode a large repertoire of synaptic proteins were also identified in the FUS mutant neurons via RNAseq. To study the effects of the FUS mutations in vivo, GFP-expressing neural stem cells were transplanted into the prefrontal cortex and dorsal hippocampus of NOD/SCID mice. Dendritic spines were observed in the grafted hiPSC-derived cortical neurons 4 months after transplantation, and the P525L-FUS mutant neurons possessed significantly fewer dendritic spines than control neurons. Our study provides new insights into human ALS-FUS pathology by showing that the FUS P525L missense mutation can lead to synaptic phenotypes independently without cytoplasmic FUS aggregation.

Marina Kennerson
University of Sydney, Australia

16:00–16:30 Illuminating the "dark genome" - frontiers beyond the exome to genetically solve undiagnosed neurological disease

More than 130 genes are known to cause hereditary neuropathies (HN), the most common peripheral nerve disorders seen in neuromuscular clinics. Yet despite major gene-discovery success over the past 15 years, around 40% of affected families still lack a molecular diagnosis, even in the current era of advanced genomic resources and high-throughput sequencing. HN genetics is undergoing a major transition, moving beyond traditional gene panels and exome sequencing to integrated whole-genome, long-read, repeat-expansion, and transcriptome-led discovery frameworks, particularly for unsolved axonal forms of HN. This shift is revealing the non-coding or "dark genome" as a far more complex genetic architecture, in which structural variants, tandem repeats, regulatory disruption, and isoform-specific effects account for a growing proportion of "missing" diagnoses. Together, these advances create an exciting platform to develop and apply cutting-edge genomic technologies to resolve long-standing diagnostic challenges and translate novel discoveries into precision medicine. This presentation will highlight our work investigating structural variation (SV) as a cause of hereditary neuropathies. SVs, genomic rearrangements typically >50 bp are increasingly recognised as important contributors to Mendelian disease yet remain under-detected by conventional testing. Our team has identified complex SVs underlying two inherited peripheral neuropathies: X-linked Charcot-Marie-Tooth neuropathy (CMTX3) and distal hereditary motor neuropathy (DHMN1). Using patient-derived iPSC motor neurons, we showed that a 78 kb insertion in CMTX3 dysregulates a key neuronal developmental transcription factor, while a 1.35 Mb insertion in DHMN1 generates a novel UBE3C intergenic fusion transcript. To define the mechanistic consequences of these rearrangements, we have developed an integrated pipeline that combines tissue-relevant transcriptomics with 3D genome-informed multi-omics analyses, providing a scalable framework to investigate the challenging "dark genome" for resolving other genetically unsolved Mendelian neurodegenerative disorders.

S11 From tag to trace: how synapse store lasting memories

14:30–16:30 | Seminar Room 1, 3rd Floor

Chair: *Sajikumar Sreedharan*

Session overview

This symposium explores how synapses encode, stabilize, and retrieve enduring memories. It brings together molecular and circuit perspectives on synaptic tagging, plasticity-related signalling, and the persistence of information across time. The session considers how transient activity is converted into durable neural change and how disruptions of these processes may contribute to cognitive and psychiatric disorders.

Yong-Seok Lee

Seoul National University, Republic of Korea

14:30–15:00 **Circuit mechanism of social memory consolidation in mice**

Episodic memories are initially encoded in the hippocampus and subsequently undergo systems consolidation into the neocortex. The nature of memory stored in the hippocampus and neocortex also differs, with the cortex shown to encode memories in more generalized forms. Although several brain regions are known to encode social information, the specific cortical regions and circuits involved in the consolidation of social memory and the nature of the information encoded in the cortex remain unclear. Using in vivo Ca2+ imaging and optogenetic manipulations, we found that infralimbic (IL) neurons projecting to the nucleus accumbens shell (IL→NAcSh) neurons store consolidated social memory. Inactivating IL→NAcSh neurons that responded to a familiar conspecific impaired the recognition of other familiar mice including littermates, demonstrating that these neuronal activities support social familiarity. Furthermore, inactivating hippocampal ventral CA1 neurons projecting to the IL disrupted the consolidation of memory for newly familiarized mice while sparing the recognition of littermates. These findings demonstrate the critical role of hippocampal-cortical interactions in the consolidation of social memory.

Sheeja Navakkode

National University of Singapore

15:00–15:30 **Alpha-Ketoglutarate Rescues Synaptic Plasticity and Associativity in an Animal Model of Alzheimer's Disease**

Alzheimer's disease (AD) is characterized by progressive cognitive decline driven in part by early synaptic dysfunction. Alpha-ketoglutarate (AKG), a key tricarboxylic acid (TCA) cycle metabolite, extends lifespan and healthspan in multiple animal models, yet its role in AD-related synaptic deficits remains poorly understood. Here, we show that calcium alpha-ketoglutarate (CaAKG) restores hippocampal synaptic function in APP/PS1 mice. Treatment with AKG or CaAKG rescued long-term potentiation (LTP) at CA1 synapses, with a more pronounced effect in female AD mice. This rescue occurred via NMDA receptor-independent mechanisms involving L-type calcium channels and calcium-permeable AMPA receptors and was accompanied by increased LC3-II expression, indicating enhanced autophagy. Importantly, CaAKG also facilitated synaptic tagging and capture, implicating restoration of associative memory mechanisms. Together, these findings highlight CaAKG as a metabolic modulator that promotes synaptic resilience by restoring plasticity and associativity in Alzheimer's disease.

Dorothy Tse

Edge Hill University, United Kingdom

15:30–16:00 **From prior knowledge to novelty: How experience shapes memory formation**

Memory is shaped by a dynamic interplay between prior knowledge and novelty. Schemas, which represent organised prior knowledge, provide a framework that facilitates the rapid acquisition and integration of new information, whereas novel experiences can trigger powerful mechanisms that enhance long-term memory formation.

The talk will begin by examining how novelty influences memory using animal models. Environmental novelty, experienced either before or after memory encoding, enhances long-term memory retention. Optogenetic activation of the locus coeruleus mimics this enhancement and reveals that novelty strengthens memory consolidation through dopaminergic signalling within the hippocampus. The talk will then examine how prior knowledge influences learning. Studies in animal models demonstrate that schema-consistent information can be rapidly incorporated into existing knowledge structures through coordinated interactions between the hippocampus and medial prefrontal cortex. Finally, findings from a

translational spatial shopping mall paradigm will illustrate how schema-based learning can be investigated in humans and how prior knowledge supports new learning in younger and older adults, providing new insights into cognitive ageing.

Together, these findings support a gradient theory of schema and novelty, proposing that experiences exist along a continuum from highly familiar to entirely novel. Rather than acting as independent processes, prior knowledge and novelty interact to shape how new experiences are encoded and integrated into existing knowledge. This framework provides new insights into the neural mechanisms underlying learning and memory and has important implications for understanding memory across the lifespan.

Sajikumar Sreedharan
National University of Singapore

16:00–16:30 **Hippocampal CA2-CA1 Interactions in Metaplastic Control of Memory Formation**

The hippocampus is a core brain structure for spatial and episodic memory, functions classically attributed to CA1 pyramidal neurons. In contrast, hippocampal area CA2 has been primarily associated with social memory processing. Although CA2 forms direct anatomical connections with CA1, the functional significance of this pathway for memory consolidation has remained largely unexplored. Here, we investigated whether CA2–CA1 interactions provide a circuit mechanism that integrates social experience with episodic memory through metaplastic processes. Using a combination of behaving mouse models and in vitro electrophysiology, we selectively activated CA2 neurons either by exposure to novel social stimuli or by targeted electrical stimulation prior to inhibitory avoidance learning or induction of activity-dependent synaptic plasticity in CA1. We demonstrate that social novelty robustly enhances the consolidation of CA1-dependent memory. This facilitation was abolished by selective chemogenetic silencing of CA2 neurons projecting to CA1, indicating a critical and causal role for direct CA2–CA1 connectivity.

At both synaptic and behavioral levels, CA2-mediated priming was time-dependent and associated with increased expression of the plasticity-related protein protein kinase M zeta (PKMζ). Importantly, prior activation of CA2 lowered the threshold for long-term potentiation in CA1 by engaging synaptic tagging and capture mechanisms, thereby promoting associativity and converting otherwise transient synaptic changes into persistent plasticity and long-term memory.

S12 Behavioral and cognitive flexibility in health and disease: Neural circuit mechanisms and beyond

14:30–16:30 | LT 1

Chair: *Ya Ke*

Session overview

This symposium examines behavioural and cognitive flexibility in health and disease. It considers how neural circuits enable the brain to update learned associations, adapt to changing environments, and preserve stable performance when appropriate. By integrating work on memory, decision-making, inhibitory control, and psychiatric vulnerability, the session highlights mechanisms that govern the balance between flexibility and stability.

Seung-Hee Lee

Center for Synaptic Brain Dysfunctions
Korea Advanced Institute of Science and Technology (Kaist) / Institute for Basic Science (Ibs), Republic of Korea

14:30–15:00 Parallel Circuits in the Posterior Parietal Cortex Resolve the Stability-flexibility Dilemma for Rapid Behavioral Adaptation

Rapid behavioral adaptation requires the brain to solve a fundamental computational dilemma: flexibly updating learned rules while maintaining stable motor performance. This flexibility-stability trade-off is central to cognitive function, artificial intelligence, and psychiatric disorders, yet the circuit architecture implementing this balance has remained elusive. Here, we identify the parallel circuits in the posterior parietal cortex (PPC) that coordinate this critical balance. Using a within-session auditory reversal paradigm in mice, we demonstrate that the PPC orchestrates adaptive learning through two parallel, anatomically distinct pathways projecting to the auditory cortex (AC) and inferior colliculus (IC). Circuit-specific manipulations reveal a functional double dissociation: the PPC-to-AC circuit facilitates flexible rule updating by encoding dynamic stimulus-outcome contingencies and demixing task variables during transitions, whereas the PPC-to-IC circuit preserves stable action execution across changing rules. Crucially, we found that PPC activity is transiently necessary during the transition phase but becomes redundant once performance stabilizes, marking it as a dedicated controller for non-steady-state behavior. Using a feedforward network model, we further demonstrated that this structural segregation is a computational necessity. Merging these signals into a single top-down control results in a significant delay in reversal learning. This parallel architecture solves the classic explore-exploit dilemma by physically segregating adaptive and stable computations into distinct circuits. Our findings provide a mechanistic framework for how the cortex enables rapid adaptation without sacrificing stability.

Masaki Isoda

Department of System Neuroscience; Center for Brain Research
National Institute for Physiological Sciences, Japan

15:00–15:30 Social Reward Monitoring and Valuation in the Macaque Cortico-subcortical Networks

Why do people care not only about their own rewards but also those of others? One plausible reason is that, in the absence of objective measures, individuals evaluate their own possessions through comparison with others. Such social comparison provides a psychological mechanism for self-evaluating one's attributes. Another reason is that competition for limited resources – such as food, territory, and mates – is often inevitable. This social competition is fundamental to natural selection and profoundly affects cognition and emotion. But which brain regions monitor these rewards? And how does the prospect of another's gain affect neural activity in an observer's brain? To address these questions, we devised a social Pavlovian conditioning procedure in which two monkeys, facing each other, were rewarded with different probabilities under conditions mimicking social competition. We found that neurons in the medial prefrontal cortex (MPFC) represent agent-specific reward information, while dopamine neurons in the midbrain represent subjective value by integrating information about others' rewards. Furthermore, neurons in the lateral hypothalamus (LH) represent a mixture of these signals. Notably, functional disconnection between the MPFC and LH rendered animals significantly less susceptible to the prospect of others' rewards, while leaving the response to their own rewards intact. Our findings suggest that cortico-subcortical circuits play a critical role in subjective reward valuation within social contexts, potentially underlying complex social emotions such as envy.

Xiaoyang Zhang
School of Life Sciences
Nanjing University, China

15:30–16:00 **Revisiting the Cerebellum in Behavioral Inflexibility in Autism: Insights from Circuit and Neuroimmune Mechanisms**

Traditionally viewed as a motor structure, the cerebellum is now recognized for its role in higher-order functions, including the behavioral inflexibility characteristic of autism spectrum disorders (ASD). This report investigates the underlying cerebellar circuit and neuroimmune mechanisms. We examine two major pathways converging on Purkinje cells (PCs) in the social cognition-linked Crus I subregion. First, the cerebellar oxytocin circuit: although PCs in Crus I express oxytocin receptors, neither electrophysiological rescue in a maternal immune activation (MIA) model of autism nor the induction of ASD-like behaviors upon receptor blockade was observed, indicating a limited role in core pathophysiology. In sharp contrast, a key neuroimmune pathway was identified: microglia-derived interleukin-17A (IL-17A) critically regulates social behavior by modulating PC excitability and inhibitory synaptic transmission. Disruption of this IL-17A signaling recapitulates core ASD-like deficits, while its restoration rescues both PC function and behavioral symptoms. Collectively, these findings delineate distinct cerebellar contributions to ASD, downplaying the role of local oxytocin signaling while highlighting microglia-PC communication via IL-17A as a fundamental regulator and a promising therapeutic target for behavioral inflexibility in autism.

Hiroshi Makino
Department of Physiology
Keio University School of Medicine, Japan

16:00–16:30 **Learning in intelligent systems**

Recent years have witnessed a renewed convergence between artificial intelligence (AI) and neuroscience. AI has offered new theoretical frameworks for understanding how the brain solves complex computational problems, while neuroscience has inspired novel algorithms and architectures that allow machines to emulate biological cognitive abilities. Despite this growing synergy, direct comparisons between artificial and biological intelligent systems remain limited. We address this gap by examining behavior and neural representations across multiple domains of intelligence in both systems. By deriving theoretical predictions from AI models and empirically testing them in mice, we demonstrate that the brain employs representations strikingly similar to those observed in artificial systems. Specifically, we identify parallel mechanisms in the compositional representation of subtasks and shared value representations during cooperation. These findings highlight fundamental similarities between biological and artificial intelligence and emphasize the importance of comparative approaches for uncovering the general principles of cognition.

OS3 Oral presentation session 3

14:30–16:30 | Seminar Room 2, 3rd Floor

Han Kyoung Choe

14:30–14:50 Master clock-thalamic-prefrontal circuit controls circadian social priority

Social behaviors arise from complex brain operations that adapt to intricate targets and varying states. Achieving a singular social goal requires an extensive social brain network, of which computation is malleable and subject to modulation by diverse internal factors. However, how the brain leverages its internal state to navigate competing social goals is elusive. Here we show that the priority between competing instincts—social novelty versus sexual preference—exhibits a distinct circadian pattern. This is controlled by a two-component circuit linking the master clock in the suprachiasmatic nucleus (SCN) to the medial prefrontal cortex (mPFC), a key brain region in the social brain network. Specifically, SCNVIP neurons project to Vipr2-expressing neurons within the thalamic nucleus reuniens (RE), which in turn projects to the mPFC to mediate this behavior. The function of Vipr2 in the RE is critical for shaping the circadian pattern of both appetitive and consummatory social behaviors. This allows higher social functions to be engaged in a timely manner, appropriately aligning prioritized social behaviors with the body's clock-regulated reproductive system. Overall, this SCN-RE-mPFC circuit provides a neural principle through which the master clock coordinates the prefrontal cortex to resolve a conflict of motivated behaviors by referencing an internal state. This work was supported by the following grant: RS-2020-NR049577, RS-2024-00439579.

Jan Schnupp

Gerald Choa Neuroscience Institute, Chinese University of Hong Kong, Sha Tin, Hong Kong SAR
Department of Otorhinolaryngology, Head and Neck Surgery, Chinese University of Hong Kong, Sha Tin, Hong Kong SAR
School of Biomedical Sciences, Chinese University of Hong Kong, Sha Tin, Hong Kong SAR
Neurobiological Research Laboratory, Section for Experimental and Clinical Otology, Department of Otorhinolaryngology, Faculty of Medicine, Medical Center – University of Freiburg, Killianstr. 5, Freiburg, Germany, 79106
Bernstein Center Freiburg and Faculty of Biology, University of Freiburg, Freiburg, Germany

14:50–15:10 Rethinking Cochlear Implants: The Need for Precise Temporal Coding in Prostehtic Hearing

Cochlear implants (CIs) are remarkable prosthetic devices which have allowed over one million severely deaf individuals to regain sufficient auditory perception to have conversations on the phone, but they are not without their shortcomings. For example, patients often experience difficulties in utilizing temporal cues for spatial hearing or pitch perception. Investigating the causes of this poor temporal processing in patients is challenging due to the confounding influence of their clinical needs on experimental design. We have therefore conducted a series of studies on neonatally deafened rats, examining both their behavioral and their physiological sensitivity to interaural time differences (ITDs) as a sound localization cue. Notably, our CI rats achieved almost ten times better outcomes compared to typical human patients. Importantly, our research emphasizes the importance of delivering ITDs in pulse timing rather than through stimulus envelopes for effective ITD detection. We also observed that sub-optimal pulse timing can conflict with the processing of other spatial cues, such as interaural level differences (ILDs). We argue that prolonged exposure to random or misleading pulse timing from clinical processors may cause maladaptive suppression of innate sensitivity to precise temporal cues. This is likely to affect not just binaural hearing, but also the ability to use temporal fine structure cues for pitch perception or auditory scene analysis. We therefore predict that implementing improved CI processing strategies that effectively deliver precise temporal information in pulse timing could lead to significantly enhanced patient outcomes.

Shengqi Zhang

Southeast University, China

15:10–15:30 Preliminary Analysis of Hindlimb Coordination using Footprint Based DeepLabCut and Transfomer model In SCI Rodent

Background: in the study of animal behavior, especially gait analysis, expensive equipment and complicated software are required for analysis, which limits popularity of this analysis. Goal: To develop a cost-efficient software DeepLabCut Analysis (DCLA) with a certain degree of accuracy on rodent animal gait analysis Method: The footprints of normal rats and mice walking on the treadmill were videoed by a high-speed camera, which were then input into DeepLabCutTM (DLC) to build a standardized model of footprints trajectories. Subsequently, we conducted Basso-Beattie-Bresnahan (BBB) and Basso Mouse Scale (BMS) locomotor functional evaluation on rats and mice with moderate 10th thoracic contusive spinal cord injury (T10-cSCI) respectively. Those rats with BBB score between 10-21 and mice with BMS score between 5-9 were videoed for their footprints during walking on the treadmill. By inputting the processed videos of injured animals into the

standardized model, we obtained H5 files with coordinates data for further analysis. Finally, we analyzed the distance between footprints and angles between trajectories using DLCA software and transfomer model. Results: There was significantly difference in the coefficient of variation (CV) of distance between left and right hindlimb footprints comparing SCI rats and sham rats. There was significantly difference in the CV of stride length between left forelimb and hindlimb when comparing SCI rats and sham rats. There was also significant difference in the CV of length between the footprints of diagonal forelimb and hindlimb when comparing SCI rat and the sham rat. To predict the missing or occluded hind paw trajectories from the observable front paw and body movements, a Transformer-based sequence-to-sequence model was developed. Conclusion: DCLA provided another dimension of evaluation on hindlimb coordination after rodent SCI which can be used as a cost-efficient and accurate and objective supplemental method for classic BBB and BMS method evaluating limb coordination.

Xiaowei Zhu

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Department of Genetics, Stanford University, Palo Alto, CA, USA

15:30–15:50 Deep Learning-Based Detection of Somatic LINE1 Insertions Reveals Disease-Specific Disruptions in Neurodevelopmental Disorders

Somatic retrotransposition of LINE1 mobile elements during brain development is hypothesized to contribute to neurodevelopmental disorders (NDDs). However, detecting these somatic mobile element insertions (MEIs) is challenging due to their low frequency (~1% of cells).

Here, we developed RetroNet, an algorithm that encodes pairs of sequencing reads into images and uses the state-of-the-art deep learning approach to identify somatic MEIs with as few as two reads. We applied RetroNet to deep-coverage whole-genome sequencing data from 204 postmortem brains across Autism Spectrum Disorder (ASD, N=60), Schizophrenia (SZ, N=66), Tourette Syndrome (TS, N=19), and controls (N=59). While the average number of somatic LINE1 insertions (~3.09 per brain) did not differ significantly between cases and controls, the functional impact of these insertions was disease-specific. Somatic LINE1 insertions were significantly enriched in known disease-related genes in ASD brains compared to controls (28.3% vs. 11.3%, P=0.031). Furthermore, affected genes were enriched in the small GTPase-binding pathway for SZ (adjusted P=0.0045) and GABA-A receptor activity for TS (adjusted P=0.014).

To investigate these functional impacts, we validated two somatic LINE1 insertions within the introns of GABRB3 and CFAP47 in a TS patient. These mutations were present across multiple brain regions and cell types at frequencies ranging from 0.14% to 2.38%, pointing to an origin in early neuroepithelial cells. Because the GABRB3 insertion likely reduces the expression of the GABA-A receptor beta-3 subunit, we modeled this effect using local GABA-A receptor inhibition in the mouse striatum. This intervention induced isolated, dysrhythmic muscle twitches accompanied by time-locked cortical spikes, closely mimicking TS phenotypes. Overall, our findings suggest that early somatic loss-of-function mutations caused by MEIs can significantly contribute to the etiology of complex neurological disorders.

Funding: This work was supported by Hong Kong RGS Early Career Scheme 21104822, and Hong Kong RGS General Research Funds 11105123 and 11105125.

Nik Nasihah Nik Ramli

Management and Science University, Malaysia

15:50–16:10 Integrating Environmental Enrichment and Vitamin K2: A Preventive Strategy for Stress-Induced Depression

Background: Depression is a growing global health burden, requiring multidisciplinary approaches that strengthen existing treatments while incorporating preventive strategies. Environmental enrichment (EE), encompassing physical, cognitive, sensory and social stimulation, is well known to enhance neuroplasticity and stress resilience. In parallel, vitamin K2 (menaquinone-7; MK-7) has emerged as a modulator of brain health by regulating osteocalcin (OCN), a bone-derived hormone implicated in cognition. This study investigated whether combined EE and MK-7 preconditioning confers synergistic protection against chronic social defeat stress (CSDS). Methods: Male C57BL/6N mice received MK-7 (100 μg), EE, or their combination for four weeks prior to a 10-day CSDS protocol. Depressive-like behaviours were assessed using the

forced swim test (FST) and tail suspension test (TST), while cognitive performance was evaluated using the novel object recognition (NOR) and Y-maze tests. Brain and serum levels of undercarboxylated OCN (uOCN), brain-derived neurotrophic factor (BDNF), and neuroplasticity markers (MAP2, GAP-43) were quantified. Results: EE or MK-7 alone produced limited behavioural effects. In contrast, combined preconditioning significantly reduced immobility in FST and TST ($p < 0.001$), comparable to fluoxetine. Cognitive deficits were fully reversed in NOR and Y-maze ($p < 0.001$), whereas monotherapies improved only short-term recognition memory. Brain uOCN levels were significantly elevated ($p = 0.006$) without changes in serum levels. BDNF, MAP2, and GAP-43 were significantly upregulated, indicating enhanced neuroplasticity. Conclusion: Combined EE and MK-7 preconditioning exert synergistic antidepressant and procognitive effects, supporting integrative environmental and nutritional strategies as a promising preventive approach for depression.

Kavita Babu
Indian Institute of Science (IISc), Bangalore, India

16:10–16:30 **Eavesdropping on Worm Conversations: Investigating the Transfer of Memory from One Worm to Another**

Native preferences in organisms can be modified through learning. Caenorhabditis elegans has proven to be an important model system to study this behavioural plasticity. In this study, we have studied long-term associative memory (LTAM) in C. elegans by training worms using two cues– a native chemoattractant and heat as the repulsive cue. This training method results in LTAM formation, observed in the form of loss of attraction to the chemoattractant lasting for upto 24 hours. We show that during training with heat and isoamyl alcohol (IAA), C. elegans release factors onto the plate that act as signalling cues for maintaining LTAM. Hence, removal of worms from these plates causes them to lose this memory despite undergoing aversive training. These molecules can in turn be taken up by naïve and memory-defective mutant worms, that have not undergone training, inducing aversive learning in these animals. We further show that the memory is specific to the cue used for training C. elegans. In order to investigate the underlying molecular mechanism of this phenomenon, we studied LTAM formation in multiple mutants and found that extracellular vesicles (EVs) sent out by the IL2 neurons in C. elegans during training are required for this process. Finally, we show that a single molecule that is released through EVs allows animals to mimic LTAM specifically to IAA when added to the plate. Here, we propose a mechanism by which C. elegans upon aversive training, release factors onto the plate through EVs, which can further be taken up by naïve worms (or memory-defective mutants and C. briggsae) and induce aversive learning in those animals without any prior training. Our work shows that memory can be transferred from a trained animal to an untrained worm, paving for a new avenue of communication and signaling in C. elegans.

GL2 Time and Punishment: Dynamic Encoding of Emotional Memory

16:50–17:50 | LT 3–4

Chair: *Ya Ke*

Special Guest Speaker

16:50–17:50 **Time and Punishment: Dynamic Encoding of Emotional Memory**

Abstract not provided in the current source material.

Wednesday, 26 August 2026

S13 Uncovering novel molecular mechanisms in brain diseases

09:00–11:00 | LT 1

Chair: *Min Zhuo*

Session overview

This symposium highlights emerging molecular mechanisms that contribute to brain disease. It brings together studies spanning cellular signalling, genetic variation, protein quality control, and disease-relevant models to identify new points of vulnerability and intervention. The session emphasizes how mechanistic discovery can create a stronger foundation for biomarker development, therapeutic targeting, and precision approaches to neurological disorders.

Magdalena Koziol

Chinese Institute for Brain Research, China

09:00–09:30 Decoding Novel Regulatory Mechanisms in the Brain: A Spatial Map of RNA Modifications Revealed by DREAMS

The epitranscriptome, comprising dynamic RNA modifications, is a crucial layer of gene regulation implicated in brain function and disease. However, a lack of tools to spatially map these modifications in complex tissues such as the brain has been a major bottleneck, obscuring novel regulatory mechanisms and potential therapeutic targets. We introduce DNA RNA Elements Areal Mass Spectrometry (DREAMS), a transformative spatial metabolomics platform that simultaneously images numerous DNA and RNA modifications in intact tissue sections. Applying DREAMS to the mouse brain, we generated the first comprehensive spatial atlas of nucleic acid modifications, revealing distinct, region-specific epitranscriptomic landscapes. Crucially, this spatial resolution enabled a paradigm-shifting discovery: we identified the DNA demethylase TET1 as a novel and direct regulator of a pivotal RNA modification, a function previously unknown for this enzyme. We validated this cross-modulatory activity in vitro and in vivo, establishing TET enzymes as master regulators of interconnected nucleic acid networks. This work provides a powerful new methodological framework. By making invisible regulatory layers visible, DREAMS is poised to illuminate novel molecular mechanisms underlying brain physiology and the etiology of complex neurological diseases.

Meewhi Kim

Pavlov Institute of Physiology Russian Academy of Sciences, Russia

09:30–10:00 Potential direct role of synuclein in dopamine transport - implications for Parkinson's disease pathogeneses

Parkinson disease (PD) is a progressive neurodegenerative disorder that is caused by dysfunction and death of dopaminergic neurons. Mutations in the gene encoding α-synuclein (ASYN) have been linked with familial PD (FPD). In the present report we propose a novel hypothesis that ASYN functions as DA+/H+ exchanger that can facilitate transport of dopamine across synaptic vesicle (SV) membrane by taking advantage of proton gradient between SV lumen and cytoplasm. Our results suggest that familial PD mutations interfere with different steps of the DA+/H+ exchange cycle. We also predicted that similar impairment in ASYN DA +/H+ exchange function also occurs as a result on neuronal aging due to changes in SV lipid composition and size anddissipation of SV pH gradient. Proposed novel functional role of ASYN provides novel insights into its biological role and its role in PD pathogenesis.

Ilya Bezprozvanny

Pavlov Institute of Physiology Russian Academy of Sciences, Russia

10:00–10:30 Targeting neuronal calcium signaling to treat Alzheimer's disease

Alzheimer's disease (AD) and other neurodegenerative disorders are a major health and economic problems. The main emphasis on treating these disorders has been based on the idea of targeting the amyloid pathway, but these efforts have not yielded effective disease-modifying therapies. Here I will discuss the importance of neuronal calcium dysregulation in AD. I will focus on connection between neuronal calcium signaling and dysregulation of autophagic pathway in AD neurons. The main problem in translation of "calcium hypothesis of AD" to the clinic has been concern about potential side effects of calcium channel blockers and inhibitors of calcium signaling enzymes in non-neuronal tissues. I will discuss use of recently developed positive allosteric modulators (PAMs) of sarco-endoplasmic reticulum calcium (SERCA) pump as potential

approach to solve this problem and to normalize neuronal calcium signaling in AD neurons. SERCA PAMs offer promising therapeutic leads for developing disease-modifying therapy for AD.

Min Zhuo
Fujian Medical University, China

10:30–11:00 **Cortical mechanisms for chronic pain and anxiety**

The anterior cingulate cortex (ACC) and insular cortex (IC) are two important cortical area for the coding of pain perception and pain-related emotional responses. Cumulative evidence using integrative experimental approaches have shown that excitatory synapses within these areas are highly plastic, and undergo potentiation and excitation after peripheral injuries. In this talk, I will discuss evidence from rodent studies that ACC/IC activation contributes to chronic pain states and describe several forms of synaptic plasticity that may underlie this effect. In particular, one form of long-term potentiation (LTP), which is triggered by the activation of NMDA receptors and expressed by an increase in AMPA-receptor function, sustains the affective component of the pain state. Another form of LTP, which is triggered by the activation of kainite-receptors and expressed by an increase in glutamate release, may contribute to pain-related anxiety. At network level, I will present recent studies and preliminary results of synaptic modulation/plasticity between ACC-ACC; ACC-retrosplenial cortex (RSC) and thalamus-ACC in freely moving animals. Finally, I will discuss recent translational progress made in leading novel AC1 inhibitor for the treatment of different types of chronic pain, anxiety and depression.

SS6 Bridging Basic & Clinical Neuroscience Session 2

09:00–11:00 | LT 2

Chair: *William Leung*

Session overview

This translational session brings together clinical questions, experimental models, and precision technologies across cerebrovascular disease, epilepsy, and neuro-oncology. It considers how risk prediction, quantitative behavioural analysis, genomic profiling, and liquid-biopsy approaches can reveal actionable mechanisms and improve patient stratification. The session highlights the value of linking biological discovery with clinically relevant measurement and intervention.

William Leung

Department of Medicine, Queen Mary Hospital, The University of Hong Kong

09:00–09:30 Developing Risk Prediction Models for Cerebrovascular-related Epilepsies

Stroke is the most common cause of adult-onset epilepsy. Early identification of stroke patients at high risk of post-stroke epilepsy (PSE) may allow interventions to halt the post-ischemic epileptogenic cascade. With increased accessibility of neuroimaging and stroke reperfusion therapies in recent years, existing risk scores (e.g. SeLECT, SeLECT2·0) based on older stroke cohorts may not be applicable in modern stroke management.

In this talk, we will share our recent publication in Neurology regarding the development of the new IsCHEMiA score in an international multi-centre collaborative effort across USA, Japan, and Hong Kong SAR, China. The IsCHEMiA score is composed of clinical and neuroimaging variables that are readily obtainable as part of routine stroke management. Important neuroimaging parameters known to be associated with PSE, including infarct size and hemorrhagic transformation, were newly included in our prediction model. The IsCHEMiA score outperformed existing scores including SeLECT and SeLECT2·0 in the prediction of epilepsy after ischemic stroke. It also serves as a foundation for designing future clinical trials on anti-epileptogenic therapies in acute ischemic stroke.

We will also share our ongoing work in further optimizing the IsCHEMiA score using multimodal signal analysis, and our preliminary findings for epilepsies related to intracranial hemorrhage, subarachnoid hemorrhage, and cerebral amyloid angiopathy.

Geoffrey Lau

City University of Hong Kong

09:30–10:00 Automated behavior classification of julius seizure mutants in Drosophila

Epilepsy affects over 50 million people worldwide. Comparing to electrophysiology, seizure behavior study is still preliminary. Bang-sensitive (BS) Drosophila mutants display seizure behaviors in response to mechanical disturbances. We previously identified mutations in the julius seizure (jus) gene (formerly CG14509) as a key driver of BS seizures. Creating a series of jus allelic combinations allow for control and comparison of seizure behaviors. Here, we integrate this unique genetic model with advanced computational analysis, establishing a deep-learning-based pipeline to enable the classification of nuanced seizure stages. Our classifier achieved 90% accuracy in distinguishing stages with fine-grained differences, enabling refined categorization of tonic seizures, spasms, and clonic subphases. Phenotyping of different mutants revealed that jus lines engage a conserved repertoire of seizure stages: paralysis (P), tonic seizure (T), spasm (S), clonic seizure (C), and recovery (R). Notably, while all jus mutants adhered to the general progression of P→T→S→C→R, each line exhibited distinct patterns in stage duration and transition probabilities. Our work establishes a relationship between specific genetic mutations and complex motor outputs. Our findings not only advance the understanding of seizure dynamics in Drosophila but also provide a framework for unbiased seizure behavior assessment, reinforcing the potential of Drosophila as a model for studying the mechanisms of epilepsy and developing anti-epileptic drugs.

Funding acknowledgement: This work was supported by the Hong Kong Research Grants Council (RGC/GRF 11104521 to C.G.L.), internal funds from City University of Hong Kong (9610354 and 9380104 to C.G.L.), and the Jockey Club College of Veterinary Medicine and Life Sciences of City University of Hong Kong / Cornell University Graduate Program Fund.

Aya El Helali
Department of Clinical Oncology, School of Medicine, Lfs Faculty of Medicine, Univertsity of Hong Kong

10:00–10:30 Novel Genomic Landscapes in Glioblastoma: Implications for Precision Neuro-Oncology

Glioblastoma (GBM) remains the most lethal primary brain tumour in adults, with a median overall survival of approximately 10-15 months despite maximal surgical resection, radiotherapy, and temozolomide chemotherapy. A central obstacle to therapeutic progress is the profound intratumoral heterogeneity that drives treatment resistance, recurrence, and immune evasion. Conventional short-read sequencing approaches have provided important insights into the mutational landscape of GBM but fail to capture the full complexity of transcriptomic and structural genomic alterations that underpin tumour biology.

In this talk, I will discuss our group's efforts to characterize glioblastoma heterogeneity at unprecedented resolution using advanced genomic technologies, including single-cell long-read sequencing. By profiling over 210,000 individual cells from 27 IDH-wildtype GBM tumours, we constructed the most comprehensive isoform-resolution atlas of glioblastoma to date, encompassing both tumour cells and the surrounding immune and stromal microenvironment. This approach revealed thousands of previously unannotated RNA isoforms, including tumour-specific transcripts absent from normal brain tissue, which represent potential targets for precision therapeutics and personalized neoantigen-based immunotherapy.

I will also discuss the clinical translation of these discoveries through our institutional molecular tumour board framework, and the broader implications of emerging genomic features, including extrachromosomal DNA (ecDNA) amplification and DNA damage repair deficiencies, for treatment stratification and novel therapeutic strategies in recurrent disease. Finally, I will outline how integrating multi-omic data into clinical decision-making can bridge the gap between basic genomic discovery and improved patient outcomes in neuro-oncology.

Youngjin Lee
City University of Hong Kong

10:30–11:00 Liquid Biopsy for Glioblastoma Immune Evasion by Plasmonic Biosensing of Exosomal PD-L1 or PD-1 from Tumor Cells and Their Associated Microglia

Glioblastoma (GBM) is an aggressive brain tumor with challenges in early diagnosis and effective treatment, partly due to the blood-brain barrier (BBB). A hallmark of GBM is its reliance on glycolytic reprogramming for its survival and growth, consequently producing vast amount of lactate. Elevated lactates enhance programmed death ligand 1 (PD-L1) expression and exosome secretion in GBM cells (GMs). These exosomes, enriched with PD-L1, can cross the BBB and enter systemic circulation. Exosomal PD-L1 interacts with programmed cell death protein 1 (PD-1) on invaded T cells in GBM, suppressing their immune activity. Despite its significance, limited research has been conducted on surface PD-L1 or PD-1 levels in exosomes derived from GMs and GBM-associated microglia/macrophages (GAMs) as potential peripheral biomarkers for GBM diagnosis, prognosis, and immunotherapy response. Particularly, their sensitive detection with high-performing optical biosensors remains largely underexplored.

In this study, we found that both PD-L1 and PD-1 levels were notably elevated in GMs, GAMs, and their secreted exosomes, particularly under lactate-enriched conditions, underscoring their role as biomarkers for GBM malignancy. To facilitate the sensitive detection of these surface biomarkers on exosomes, we developed a localized surface plasmon resonance (LSPR) biosensor using Au-Pt bimetallic nanoislands (BNIs) sensor chips. This new biosensor demonstrated good performance in quantifying heightened PD-L1 levels on exosomes derived from lactate-treated GMs. Furthermore, it accurately identified increased PD-L1 or PD-1 levels in enriched GMs- and GAMs- derived exosomes by immunocapture, as well as in total exosomes from the blood of GBM mouse models and human patients. In conclusion, these findings highlight the potential of the Au-Pt BNIs LSPR biosensor as a minimally invasive, label-free diagnostic tool. Its ability to rapidly and sensitively measure exosomal PD-L1 and PD-1 levels in blood introduces a promising liquid biopsy approach for monitoring GBM-associated immune evasion and evaluating therapeutic responses in real-time.

Funding: This work was supported by City University of Hong Kong (grant nos. 11104420, 11105223, and 2025SMA097), General Research Fund (GRF)-Hong Kong Research Grants Council (grant nos. 11103918 and 11104421), and Tung Biomedical Sciences Centre ASDC_Sub (grant no. 9609311) awarded to Y.L. at City University of Hong Kong.

YIC3 ISN-APSN Young Investigators Colloquium Session 3

09:00–11:00 | Seminar Room 2, 3rd Floor

Chair: *Victor Anggono*

Karthik Dhananjayan
Amrita Vishwa Vidyapeetham University, India

09:00–09:24 A Sulfonic Acid Analogue for Parkinsons Disease – Preclinical Evidence and Translational Potential

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor behavioral deficits. The present study systematically evaluated the effects of a sulfonic acid analogue (SAA) against behavioral dysfunction in N2 Caenorhabditis elegans (C. elegans) and C57BL/6 mice following rotenone exposure. In C. elegans, rotenone exposure markedly impaired basal slowing behaviour, a dopaminergic-dependent response, reducing the basal slowing index from 0.373 ± 0.003 to 0.052 ± 0.002 in controls; The SAA treatment (100μM) significantly restored this response to 0.332 ± 0.002, $p<0.05$. Ethanol-directed chemotaxis was similarly altered, with the chemotaxis index shifting from −0.20 ± 0.05 to +0.30 ± 0.05 following rotenone exposure in controls, indicating disrupted sensory neuronal integration; SAA normalized it to −0.10 ± 0.05. Locomotor function (LF) assessed by thrashing was reduced under rotenone treatment (42.18 ± 0.27 vs 73.81 ± 0.70 thrashes/min), whereas SAA improved LF activity to 57.62 ± 0.48 thrashes/min. Pharyngeal pumping, reflecting neuromuscular and metabolic integrity, declined from 241.65 ± 1.98 pumps/min to 37.82 ± 0.59 in controls following rotenone exposure; and was partially restored to 80.14 ± 0.71 pumps/min with SAA treatment. In mice, SAA enhanced the motor coordination, and locomotion in rotenone-induced behavioural abnormalities. In addition, SAA effectively modulated the levels of BDNF, and anti-oxidant gene expression in brains of mice challenged with Rotenone. We identified that SAA effectively attenuated these functional disturbances across multiple behavioral domains, supporting its modulatory potential in rotenone-induced models of Parkinson's disease. Furthermore, the studies are underway to identify the mechanistic pathways underlying this modulation against rotenone-induced abnormalities.

Shubham Dwivedi
Department of Pharmaceutical Sciences, School of Health Sciences and Technology
UPES, Dehradun, India

09:24–09:48 Identification and Evaluation of Natural mGluR5 Modulators from a Traditional Chinese Medicine Library using Zebrafish Larvae Model of Autism

Metabotropic glutamate receptor 5 (mGluR5) is a key regulator of synaptic plasticity and neurodevelopment and has been intensely implicated in the pathogenesis of autism spectrum disorder (ASD). The activation of mGluR5 by L-glutamate regulates intracellular signaling pathways, which are essential for neuronal function, and its dysfunction leads to the development of ASD-related behavioral and molecular dysfunctions. Negative allosteric modulators (NAMs) of mGluR5 have emerged as promising therapeutic agents, but their synthetic counterparts have largely failed in clinical development due to toxicity and poor efficacy. Hence, there is a need to identify safe and efficacious natural mGluR5 modulators.

In the current study, a thorough in silico screening of a Traditional Chinese Medicine (TCM) library was conducted using E-pharmacophore modeling, ligand-based pharmacophore screening, molecular docking, ADME/T prediction, and molecular dynamics (MD) simulations to identify potential mGluR5 NAMs. Fifty-two top-ranked compounds were identified and were further assessed for optimal pharmacokinetic properties and robust protein-ligand interactions. The selected candidates were further assessed for embryonic toxicity and therapeutic efficacy in a valproic acid (75 μM, 4–120 hpf)-induced zebrafish larvae model of autism. Four lead compounds (MG5_TCM01, MG5_TCM02, MG5_TCM03, and MG5_TCM04) showed strong rescue of autism-like symptoms, such as thigmotaxis, circling, and attention deficits, in a dose-dependent manner. In addition, the treatment normalized the expression of essential genes in the mGluR5 pathway linked to ASD. MG5_TCM03 showed the most potent therapeutic potential. In summary, the present study reveals new natural mGluR5 modulators with high therapeutic potential for ASD. However, further screening on other preclinical models along with in-depth mechanistic studies is ongoing and is warranted for confirmation.

Hoyong Park
Department of Biological Sciences (Neurophysiology Laboratory)
Konkuk University, Republic of Korea

09:48–10:12 Stress disrupts neuromodulatory control of synaptic transmission

The lateral habenula (LHb) is a key regulator of aversive processing and is strongly implicated in depressive disorders. LHb hyperactivity and enhanced excitatory synaptic transmission are consistently observed in rodent models of depression. Notably, LHb synaptic efficacy is not static but exhibits intrinsic temporal variation, including time-dependent modulation of presynaptic release probability. This suggests that LHb activity is dynamically tuned across physiological states, potentially through multiple neurochemical systems.

Here, we examined how stress disrupts this temporal synaptic regulation and focused on two major neuromodulatory pathways: glucocorticoid receptor (GR) signaling and mu-opioid receptor (mOR) signaling. We found that acute stress exposure, as well as treatment with corticosterone (CORT), abolishes temporal variation in presynaptic release probability and induces persistent presynaptic potentiation in the LHb, indicating that GR activation can override endogenous temporal regulation and promote maladaptive strengthening of excitatory inputs. In parallel, mOR activation in naïve animals suppresses synaptic transmission and reduces LHb neuronal firing, consistent with an endogenous inhibitory brake. However, following stress exposure, mOR-mediated synaptic suppression is markedly attenuated, and behavioral protection is observed only when mOR signaling is engaged prior to stress. These findings suggest that stress not only enhances presynaptic excitatory efficacy but also impairs opioid-dependent inhibitory modulation that normally constrains LHb activity. Together, these results support a model in which stress drives depression-like LHb hyperactivity through collapse of temporal synaptic regulation and dysfunction of neuromodulatory inhibitory control. This framework highlights GR and mOR signaling as key determinants of LHb synaptic state transitions and identifies potential neurochemical targets for preventing maladaptive circuit activation following stress.

Waralee Ruankham
Faculty of Medical Technology
Mahidol University, Salaya, Nakhon Pathom, Thailand

10:12–10:36 Unraveling network pharmacology and molecular simulation of thiazole sulfonamides against Parkinson's disease

Parkinson's disease (PD) remains the second most prevalent neurodegenerative disorder. Current treatments are limited in halting disease progression, necessitating the discovery of novel neuroprotective strategies. To evaluate clinical viability and avoid the common pitfalls of late-phase drug failure, extensive in silico profiling of novel thiazole sulfonamides was conducted using ADMET (i.e., absorption, distribution, metabolism, excretion, and toxicity) prediction, multidisciplinary network pharmacology, and molecular simulation. Pharmacokinetic analysis using SwissADME, pkCSM, and ProTox-II confirmed that these hybrids met drug-like criteria, including Lipinski, Ghose, Veber, Egan, and Muegge. Particularly, the candidates exhibited moderate penetration across the gastrointestinal tract, central nervous system, and blood-brain barrier, with no predicted risks of carcinogenicity, immunotoxicity, or mutagenicity.

Integrating multilayer computational networks between the hybrids and PD by Comparative Toxicogenomics Database (CTD) and Protein-Protein Interaction (PPI) data, a network analysis of 280 overlapping targets revealed 122 core proteins, notably protein kinase A (PRKACA), nuclear factor-kappa B1 (NFKB1), glycogen synthase kinase-3 beta (GSK3B), and sirtuin 1 (SIRT1), as key regulators of inflammation, cell survival, and mitochondrial disruption in neurodegeneration. The molecular docking simulations demonstrated that these compounds occupied the same binding pocket as the known SIRT1 activator, namely resveratrol, with stronger binding affinities. Moreover, in vitro assessment using human SH-SY5Y neuronal cells challenged with 6-hydroxydopamine demonstrated that the compounds significantly mitigated intracellular oxidative stress, reduced lactate dehydrogenase leakage, and restored mitochondrial membrane potential, influencing key SIRT1 downstream cascades-related cellular longevity and neuroinflammation essential for PD treatment. Collectively, these findings highlight the potential of these thiazole sulfonamides as promising SIRT1 activator candidates for further in vivo and clinical validation in PD therapy.

Norsyifa Harun
Centre for Drug Research
Universiti Sains Malaysia, Penang, Malaysia

10:36–11:00 Preclinical Assessment of Dependence Liability and Withdrawal Effects of Mitragynine, the Principal Alkaloid of Kratom (Mitragyna speciosa)

Kratom (Mitragyna speciosa Korth), an indigenous Southeast Asian plant increasingly used locally and globally, has been proposed as a potential treatment for opioid use disorder. However, evidence on the dependence liability of its primary psychoactive alkaloid, mitragynine (MG), remains limited. This study aimed to evaluate the physiological and psychological dependence potential of MG using operant conditioning models in rats.

To assess physiological withdrawal signs, the study employed an operant conditioning approach known as scheduled-controlled behaviour. Rats were first trained under a fixed-ratio 10 (FR-10) schedule of reinforcement. Subsequently, they received twice-daily administrations of MG or morphine for 14 consecutive days to assess the development of physiological dependence. Withdrawal was examined following drug cessation and antagonist-precipitated withdrawal. Unlike morphine, MG-treated rats showed no suppression of lever-pressing responses following cessation of MG treatment. However, withdrawal signs were observed in MG-treated rats when precipitated by naloxone, and these were comparable to those seen in morphine-dependent rats. The potential therapeutic effects of MG were further evaluated in morphine-dependent rats using the same behavioural paradigm. Higher doses of MG (10 and 30 mg/kg) attenuated naloxone-precipitated morphine withdrawal, whereas lower doses of buprenorphine (0.3 and 1.0 mg/kg) produced similar effects.

To assess psychological dependence, particularly anxiety-like withdrawal symptoms, a pentylenetetrazol (PTZ) discrimination assay was employed. Rats were trained under a tandem FR-10/VI-15 schedule to discriminate PTZ (16 mg/kg) from vehicle. Following chronic drug treatment and naloxone-precipitated withdrawal, the PTZ generalization effect was assessed at several withdrawal time points. Naloxone failed to elicit PTZ-like responding in MG-treated rats, whereas morphine-treated rats exhibited clear anxiogenic-like withdrawal effects.

Overall, these findings suggest that MG does not produce significant physiological or psychological dependence, yet effectively alleviates morphine withdrawal symptoms, supporting its potential as a novel pharmacotherapeutic agent for opioid use disorder.

YIC4 ISN-APSN Young Investigators Colloquium Session 4

09:00–11:00 | Seminar Room 3, 3rd Floor

Chair: *Yoshifumi Abe*

Abu Md Mamum Tarif
Shimane University, Japan

09:00–09:24 LINC Complex Dysfunction Disrupts Synaptic Myonuclei and Drives NMJ Decline in Age-Related Sarcopenia

Age-related sarcopenia is often accompanied by breakdown of the neuromuscular junction (NMJ), but how changes inside muscle nuclei contribute to this process is still not well understood. Here, using senescence-accelerated prone mice (SAMP8) with age-matched resistant controls (SAMR1), together with a natural aging cohort (young, 24 months, and 30 months), we show that nuclear envelope disruption occurs specifically in myonuclei located near the NMJ and is closely linked to NMJ damage during aging. SAMP8 mice developed clear sarcopenia-like features, including lower body weight, reduced hindlimb muscle mass, and weaker performance in grip strength and treadmill tests. Muscle staining and morphometric analyses revealed aging-related remodeling, including reduced oxidative staining in plantaris, a shift toward smaller myofibers with higher fiber density, and selective changes in fiber-type composition consistent with altered contractile identity. At the NMJ, SAMP8 muscles showed structural deterioration, with reduced presynaptic terminal area, marked fragmentation of postsynaptic acetylcholine receptors, and decreased alignment between pre- and postsynaptic structures. Strikingly, quantitative confocal analysis demonstrated that NMJ-associated (synaptic) myonuclei show selective loss of enrichment of LINC complex–related molecules, while extra-synaptic nuclei were largely preserved. (To protect potential patent applications for planned rescue experiments, the specific target molecule name is intentionally not disclosed here and is described in general terms). Co-expression patterns further suggested a mild but consistent weakening of the coupling among LINC complex–related molecules within the synaptic nuclear region. Importantly, we observed similar synaptic-nuclear changes in naturally aged mice (24 and 30 months) compared with young animals, supporting that this is a common feature of muscle aging. Together, these results suggest that NMJ deterioration in sarcopenia is linked to a local failure of the synaptic myonuclear LINC–lamina system, highlighting synapse-specific nuclear envelope vulnerability as an important step in age-related muscle decline.

Neha
Faculty of Applied & Basic Sciences, Sgt University, India

09:24–09:48 Systems Biology Insights into Brain Ageing: Computational Evaluation of Skiammianine Using Network Pharmacology and Molecular Dynamics

Brain ageing is a multifaceted biological process driven by cumulative molecular and cellular alterations, including neuroinflammation, oxidative stress, synaptic dysfunction, and impaired cellular homeostasis, which collectively contribute to cognitive decline and increased vulnerability to neurodegenerative disorders. Owing to its complex etiology, effective therapeutic intervention for brain ageing requires multi-target modulation rather than single-target strategies. In this context, Skimmianine, a plant-derived alkaloid, represents a promising bioactive compound with potential neuroprotective properties, although its mechanistic role in brain ageing remains poorly understood. In the present study, a systems biology-based computational approach was employed to elucidate the molecular mechanisms underlying skimmianine-mediated modulation of brain ageing. Putative molecular targets of skimmianine were identified using established in silico target prediction tools, while brain ageing–associated genes were curated from publicly available databases. A compound–target–pathway interaction network was constructed and analyzed to identify key hub proteins and enriched biological pathways relevant to neuronal survival, synaptic plasticity, neuroinflammatory regulation, oxidative stress response, and mitochondrial function. Molecular docking studies were subsequently performed to evaluate the binding affinity and interaction patterns of skimmianine with prioritized hub targets. To further assess the stability and dynamic behavior of the ligand–protein complexes, molecular dynamics simulations were conducted under physiological conditions. The integrative analysis revealed that skimmianine exhibits stable interactions with multiple proteins implicated in brain ageing–related signaling pathways, supporting its potential role as a multi-target modulator. Overall, this study provides a comprehensive computational framework elucidating the systems-level mechanisms of skimmianine in brain ageing. The findings offer valuable insights into its neuroprotective potential and lay a foundation for future experimental validation and therapeutic exploration aimed at promoting healthy brain ageing.

RaiArp Sukrit Promtang
Pathumthani University, Thailand

09:48–10:12 Antihypertensive Reserpine Drug Induces Toxicity and Disrupts Dopamine-Dependent Neurobehavioral Function in Caenorhabditis elegans

Reserpine is an antihypertensive drug known to deplete monoamine neurotransmitters, including dopamine, serotonin, norepinephrine, and epinephrine, via irreversible inhibition of vesicular monoamine transporters (VMAT/cat-1). Therefore, it has been widely used to model dopaminergic (DAergic) dysfunction. However, the extent to which reserpine induces neurotoxicity and functional impairment remains incompletely understood. In this study, we investigated the effects of reserpine on oxidative stress, neuronal integrity, dopamine-dependent neurobehavioral outcomes, lifespan regulation via DAF-16 transcription factor, and the underlying molecular mechanisms using the Caenorhabditis elegans (C. elegans) model. Exposure to 190 μM reserpine significantly increased reactive oxygen species (ROS) and lipid peroxidation (malondialdehyde, MDA), while reducing glutathione (GSH) levels, indicating pronounced oxidative stress. Despite the absence of degeneration of DAergic neurons in the BY250 strain (dat-1p::gfp), reserpine markedly impaired dopamine-dependent behaviors, including food detection and food-dependent locomotion. These findings indicate that reserpine primarily induces functional deficits in DAergic neurotransmission rather than structural neuronal loss. Notably, reserpine toxicity promoted nuclear accumulation of DAF-16 and extended lifespan. Transcriptomic analysis further revealed that reserpine predominantly affected metabolic pathways, characterized by upregulation of acdh-1 (mitochondrial stress marker) and cyc-2.2 (cytochrome c 2.2), along with downregulation of gst-3/5/30 (glutathione S-transferases) and sir-2.3 (NAD^+-dependent mitochondrial sirtuin). Collectively, our results show that reserpine mediates toxicity and dopamine-associated neurobehavioral dysfunction primarily through oxidative stress. Moreover, this toxicity appears to involve metabolic signaling and DAF-16-dependent regulation associated with mild mitochondrial stress and sirtuin modulation, contributing to lifespan and metabolic adaptation. This study highlights the utility of C. elegans as a sensitive model for dissecting early functional alterations and fundamental mechanisms underlying reserpine-mediated neurodegenerative processes.

Kate Inyoung Oh
School of Clinical Medicine / School of Biomedical Sciences, Lks Faculty of Medicine
The University of Hong Kong

10:12–10:36 Investigating the metabolic changes on neuroimmune responses triggered by the first or second systemic inflammation and the potential therapeutic interventions in the murine models

Immune crosstalk between body and brain is increasingly being recognized. Sterile and non-sterile inflammation activates immune cells in the body, leading to systemic inflammation. Systemic inflammation can further induce neuroimmune responses via various mediators.

This study investigated whether systemic inflammation could induce neuroimmune responses in young adult mice and whether these neuroimmune responses persist after the systemic inflammation has been resolved. Sterile inflammation was induced by a laparotomy performed under sevoflurane. Non-sterile inflammation was induced by bacterial endotoxin challenges. A second episode of systemic inflammation was induced 28 days after the first to assess the differential neuroimmune responses between the first and second challenges. The neuroimmune responses were evaluated by investigating the activation of microglia.

Microglia activation in the hippocampus persisted until at least day 14 when systemic inflammation had subsided. The hippocampus displayed enhanced glycolysis and an attenuated TCA cycle after the first or second challenges. Afterwards, it was hypothesized that the metabolic changes in persistent neuroimmune responses might be implicated in mitochondrial damage. To verify this hypothesis, a recombinant adeno-associated virus was designed and injected into the lateral ventricle of the mice to detect mitochondrial damage (mitophagy) in microglia. The mitochondrial and DNA damage were detected in the hippocampus, indicating that the metabolic changes were associated with mitochondrial damage and dysfunction.

To further investigate the effects of metabolic alteration in microglia, other recombinant adeno-associated viruses were designed to downregulate glycolytic enzymes, phosphofructokinases 1/2, respectively, in microglia. Consequently, it significantly reduced mitochondrial and DNA damage in the hippocampus after systemic challenges. In addition, the intensity of homeostatic microglia significantly increased.

This study advanced our understanding of the metabolic changes and nuclear damage in the neuroimmune responses followed by mitochondrial damage. Taken together, downregulation of enhanced glycolysis in microglia could be a potent therapeutic strategy to prevent neuronal damage after systemic inflammation.

Bryan Ng
Institute for Human Development and Potential & Adjunct Scientist, Imcb
*Agency for Science, Technology and Research (A*STAR), Singapore*

10:36–11:00 **Integrating accelerated ageing in human glial cells**

Ageing is the strongest risk factor for dementia and the underlying neurodegenerative disease (NDD) pathologies leading to increasing NDD prevalence due to a globally ageing population. Animal models have been widely used for NDD studies, although they do not naturally develop neurodegenerative pathologies linked to human NDD and differ inherently in their biology from humans. Human induced pluripotent stem cells (iPSCs) thus emerge as a unique experimental model that captures the genetic background of any donor while retaining the capabilities to self-renew and differentiate into any cell type in vitro.

Yet, the lack of ageing-driven phenotypes in iPSC-derived cells presents a direct contradiction to recapitulating cellular ageing in studying age-related NDD. In this study, we address this limitation by integrating accelerated ageing in human iPSC-derived microglia and astrocytes. We hypothesise that accelerated ageing in vitro exacerbates cellular pathologies of patient-derived glial cells, leading to more accurate disease modelling and providing opportunities to target ageing as a viable strategy to mitigate NDD pathogenesis.

We employed an inducible CRISPR-Cas9-mediated interference (CRISPRi) method against individual targets which have been implicated in regulating ageing in vivo. These edited iPSCs are differentiated into glial cells for ageing-related phenotype measurements and assays measuring functional decline. We showed that two weeks of CRISPRi against individual targets resulted in the upregulation of cellular senescence and impaired functional outcomes.

We will next test whether the removal of the CRISPRi mechanism can reverse the ageing phenotypes, as well as integrating this system into an Asian Alzheimer's disease patient-derived iPSC line to study the effects of accelerated ageing on cellular pathologies. With an optimised and novel genetic strategy that can be applied at scale to any human iPSC line, we aim to integrate accelerated ageing for more accurate NDD modelling that can be harnessed for downstream studies.

S14 Synaptic strengthening in memory consolidation

11:30–13:00 | Seminar Room 1, 3rd Floor

Chair: *Supin Chompoopong*

Session overview

This symposium examines synaptic strengthening as a central process in memory consolidation. It considers how activity-dependent plasticity, receptor regulation, intracellular signalling, and circuit reorganization cooperate to stabilize information over time. By connecting molecular mechanisms with systems-level memory function, the session offers insight into how durable learning is formed and how its disruption may contribute to disease.

Supin Chompoopong
Department of Anatomy, Faculty of Medicine Siriraj Hospital
Mahidol University, Bangkok, Thailand

11:30–12:00 Microglial modulation in cognitive impairment

Microglia, the resident immune cells of the central nervous system, playing a key role in mediating inflammatory responses that lead to cognitive dysfunction. Microglial modulation focuses on shift microglia from a pro-inflammatory to an anti-inflammatory phenotype, reducing neuroinflammation, synaptic loss, neuronal death and enhancing phagocytic clearance of pathological proteins (amyloid-β) directly mitigating cognitive decline. Targeting pathways like TREM2 and inhibiting microglia-mediated synaptic loss has shown efficacy in reducing neuronal injury in neurodegenerative conditions, Alzheimer's disease (AD), and stroke. Phenotype modulation of microglia promotes anti-inflammatory polarization to release neurotrophic factors and decreases pro-inflammatory cytokines.

Recent research highlights several approaches to modulate microglial activity and restore cognitive function. Strategies aim to transition microglia from a neurotoxic state to a neuroprotective state by controlling the balance between inflammation and tissue repair. Targeting specific signaling pathways including TREM2 and PI3K Pathways. TREM2, this receptor is a key regulator of microglial survival and phagocytosis, modulating its activity is a major target for preventing AD progression. Blocking microglial PI3K signaling has been shown to reverse cognitive features of neurodegenerative diseases in rodent models. In addition, during sleep, microglia increase the expression of GABAA receptors in layer 1 synapses (not observed in layer 5 synapses), a modulation that depends on P2RX7, TNF-α, and Ca2+/calmodulin-dependent protein kinase II (CaMKII) and is required for proper memory consolidation. Our study with preclinical interventions aimed at modulating microglial function, including depletion strategies, polarization toward anti-inflammatory phenotypes, and inhibition of inflammatory pathways like NF-κB and NLRP3 have shown efficacy in reducing neuroinflammation and preserving cognitive function in animal models.

Peeraporn Varinthra
Institute of Medical Sciences
Tzu Chi University, Hualien, Taiwan

12:00–12:30 Herbal Modulation of Synaptic Plasticity and Memory in REM Sleep– Deprived Mice and Alzheimer's Mouse Model

Rapid eye movement sleep deprivation (REM-SD) profoundly disrupts synaptic plasticity, destabilizes dendritic spine architecture, alters GABAergic signaling, and accelerates memory decline. Despite growing recognition of sleep loss as a major risk factor for cognitive dysfunction, effective interventions that protect synaptic structure and memory during REM-SD remain limited. Protein kinase C (PKC)-dependent phosphorylation, a critical role in maintaining synaptic strength and cognitive performance is also essential for regulating GABAB receptor trafficking and surface stability. Disruption of this signaling pathway may be a key mechanism linking REM-SD to synaptic dysfunction and memory impairment.

The herbal fractions derived from TCU411, an indigenous herbal medicine has been demonstrated the modulation of actin remodeling and the preservation synaptic plasticity and memory in a mouse model of REM-SD. Behavioral analyses demonstrated that TCU411 treatment significantly alleviated working memory deficits induced by REM-SD, accompanied by a reduction in pathological overexpression of the GABAB receptor subunit 1 (GABAB R1) and the restoration of postsynaptic density protein-95 (PSD95) synaptic integrity in the hippocampus. Further fractionation yielded two bioactive fractions, F1 and F2, that effectively rescued impairments in cognitive flexibility, suggesting the presence of potent neurorestorative compounds. Proteomic profiling revealed that treatment with the TCU411-F2 fraction upregulated key synaptic plasticity-related proteins, including CaMKII, PKC-α, and PKC-γ, while suppressing cofilin expression. Consistently, western blot

analyses confirmed that the TCU411-F2 fraction enhances PKC-α and PKC-γ expression and reactivates actin cytoskeleton remodeling pathways involving PAK1, LIMK1, and phosphorylated cofilin. Together, these findings highlight actin cytoskeleton regulation as a critical mechanistic link between sleep loss and memory impairment and support the therapeutic potential of TCU411 herbal fractions for sleep-related cognitive dysfunction.

Sukonthar Ngmpramuan
Research Center for Neuroscience, Institute of Molecular Biosciences
Mahidol University, Nakhon Pathom, Thailand

12:30–13:00 **Disruption of synaptic strengthening leads to cognitive impairment in transgenic mouse model**

Despite the central role of memory consolidation, the vulnerability of synaptic strengthening under pathological conditions remains incompletely understood. Transgenic mouse models of cognitive impairment provide valuable insights into how disruptions of synaptic strengthening lead to memory failure. In disease-related transgenic models, including β-thalassemia mice, hippocampus-dependent learning and memory are markedly impaired, reflecting a failure to sustain synaptic strengthening rather than nonspecific sensory or motor dysfunction. Cognitive impairment is closely associated with selective vulnerability of hippocampal neurons, particularly within the CA3 region, a critical hub for recurrent excitation and pattern completion. Integrity of CA3 circuitry is essential for maintaining LTP and stabilizing memory engrams; disruption at this level therefore represents a key point at which synaptic strengthening and memory consolidation break down.

Beyond intrinsic neuronal alterations, systemic factors further compromise synaptic plasticity. Cognitive impairment in β-thalassaemia mice was also significantly correlated with several intrinsic β-thalassaemic factors including iron overload, anaemia, damaged red blood cells, phosphatidylserine-exposed RBC large and medium extracellular vesicles. The iron overload, the chronic metabolic and vascular stressors could disrupt the neurovascular environment, impair blood-brain barrier integrity, and promote neuroinflammation, indirectly undermining the synaptic conditions required for LTP maintenance and long-term memory stabilization. Together, evidence from transgenic mouse models underscores synaptic strengthening as the central mechanism underlying memory consolidation and highlights how genetic, metabolic, and vascular insults converge to impair this process, providing a framework for identifying therapeutic strategies to preserve synaptic plasticity and long-term memory.

S15 Metabolic and signaling dysregulation in pathogenesis: molecular mechanisms and pharmacological interventions

11:30–13:00 | LT 1

Chair: *Zhuo Huang*

Session overview

This symposium explores metabolic and signalling dysregulation in disease pathogenesis. It considers how altered cellular energy balance, inflammatory pathways, stress responses, and pharmacological modulation shape neural vulnerability and progression. The session highlights the value of integrating molecular mechanisms with therapeutic development to identify tractable targets for prevention and treatment.

Zhuo Huang
School of Pharmaceutical Sciences
Idg/McGovern Institute for Brain Research, Peking University, Beijing, China

11:30–11:50 Transcriptional and Post-translational Regulation of Nav1.2 Channels: Novel Mechanisms Linking Neuronal Plasticity to Epileptogenesis and Pharmacological Intervention

Dysregulation of neuronal excitability and plasticity is a hallmark of epilepsy. The voltage-gated sodium channel Nav1.2, encoded by SCN2A, is a critical regulator of this process. This presentation summarizes our recent work uncovering two novel, complementary regulatory axes controlling Nav1.2, linking fundamental molecular mechanisms to potential pharmacological intervention.

First, we identify the transcription factor DEC2 as an activity-induced repressor of SCN2A. Following seizures, DEC2 is upregulated and binds to the Scn2a promoter, suppressing its expression. Knocking down DEC2 increases neuronal intrinsic excitability, synaptic drive, and seizure susceptibility, while its overexpression has protective effects. Furthermore, we demonstrate that the anticonvulsant cannabidiol (CBD) exerts part of its effect by enhancing this DEC2-SCN2A transcriptional axis.

Second, we discover a post-translational pathway mediated by the ubiquitin ligase adaptor PTPRN. Neuronal activity elevates PTPRN, which recruits the E3 ligase NEDD4L to Nav1.2, promoting its ubiquitination and clathrin-dependent endocytosis. This reduces surface channel density and neuronal excitability. Accordingly, PTPRN knockout increases seizure susceptibility, while its overexpression is protective.

In conclusion, we delineate a multi-layered regulatory network for Nav1.2, encompassing transcriptional repression (DEC2-SCN2A) and post-translational turnover (PTPRN-NEDD4L). These pathways represent critical homeostatic responses to hyperexcitability and provide novel therapeutic targets for modulating neuronal signaling in epilepsy and related disorders.

Chao Yan
State Key Laboratory of Pharmaceutical Biotechnology & School of Life Sciences
Artificial Intelligence Biomedical Technology Research Institute, Nanjing University, Nanjing, China

11:50–12:10 Targeting Neuron–Glia Interactions: From Mechanistic Insights to Next-Generation Therapeutics

Neuron–glia interactions are dynamic metabolic and signaling interfaces that shape synaptic stability and disease progression. We aim to identify actionable molecular checkpoints within these intercellular networks.

We first defined lipid-accumulated reactive astrocytes (LARA), a pathogenic astrocytic state characterized by excessive lipid deposition and metabolic rewiring. LARA exhibit impaired homeostatic support and heightened inflammatory signaling, highlighting lipid metabolism as a central regulator of astrocyte dysfunction.

We further uncovered that microglia directly sense inhibitory neurotransmission via functional GABA receptors. This signaling axis selectively promotes pruning of inhibitory synapses, revealing a mechanism by which microglia reshape excitation–inhibition balance.

Most recently, we identified a distinct SCD1^{+} microglial subpopulation marked by elevated stearoyl-CoA desaturase 1. These microglia produce the glycerophospholipid lysophosphatidylcholine (LPC), which activates the lipid receptor LPAR2 on excitatory synapses, driving synaptic overexcitation and circuit instability. Genetic or pharmacological inhibition of SCD1 or LPAR2 suppresses this maladaptive neuron–glia signaling cascade and restores network balance in preclinical models.

Together, our findings position lipid metabolism and neurotransmitter sensing as convergent, druggable nodes in neuron–glia crosstalk, providing a mechanistic and translational framework for next-generation therapeutics targeting circuit dysfunction.

Xin-an Liu
The Brain Cognition and Brain Disease Institute (Bcbdi)
Shenzhen Institutes of Advanced Technology (SIAT), China
Chinese Academy of Sciences (Cas), China

12:10–12:30 Microbiota–Neuroepithelial Signalling in Pediatric Epilepsy: From Mechanisms to Microbiota-Based Therapy

Drug-resistant epilepsy remains a major challenge in pediatric neurology, affecting approximately one-third of children with epilepsy despite substantial advances in antiseizure therapies. Emerging evidence suggests that the gut microbiota is an important regulator of brain function; however, the mechanisms by which intestinal microbes influence seizure susceptibility have remained largely elusive.

In this lecture, I will present our recent work uncovering a previously unrecognized microbiota–neuroepithelial signalling pathway underlying microbiota–brain communication in epilepsy. Using complementary clinical, multi-omics, and mechanistic approaches, we demonstrated that Bacteroides fragilis suppresses seizure activity by engaging intestinal neuroepithelial cells, vagal cholinergic signalling, and downstream neural circuits, providing mechanistic evidence that microbiota-derived signals can directly modulate brain excitability and seizure susceptibility. These findings establish a mechanistic foundation for microbiota-based therapeutic strategies in epilepsy.

Building upon this work, we are further investigating the microbiota-associated heterogeneity of pediatric epilepsy and exploring artificial intelligence-enabled multimodal models for patient stratification, early risk prediction, and precision microbiota-based intervention. Together, these efforts aim to translate mechanistic discoveries into personalized diagnostic and therapeutic strategies, advancing precision medicine for children with epilepsy.

Yu Fu
*Institute of Molecular and Cell Biology (Imcb), Agency for Science, Technology and Research (A*Star), Singapore*

12:30–13:00 The role of gut-brain communication in feeding regulation

Coordinated actions of central and peripheral neurons safeguard physiological functions. For feeding regulation, how the central nervous system hypothalamic neurons integrate peripheral inputs to coordinate feeding behaviour is still unclear. Previous research has provided controversial results about the role of vagal pathway in energy homeostasis regulation, and it's still unclear what components of feeding regulation is more regulated by vagal inputs.

In current research, we revealed functional specifications of hypothalamic feeding regulation neurons in homeostatic and maladaptive feeding paradigms, and examined the function of vagal inputs in different forms of feeding behaviour. It appears that vagal inputs are largely dispensable for homeostatic feeding regulation, but plays a critical role in maladaptive feeding driven by palatable food. Our research started to provide a conceptual framework for better understanding feeding regulation neural networks.

SS7 Publishing Forum

11:30–13:00 | LT 2

Chair: *Wing Ho Yung; Ying-Shing Chan*

Session overview

This Publishing Forum introduces a range of neuroscience-related journals and the communities they serve, helping researchers understand differences in editorial scope, readership, article formats, and review expectations. Editors and journal representatives will discuss how authors can select appropriate venues, communicate findings effectively, and navigate peer review and research integrity. The session also examines how artificial intelligence is reshaping manuscript preparation, literature discovery, editorial assessment, and scholarly dissemination, with emphasis on responsible and transparent use.

Participants

Ying-Shing Chan • *Tasia Asakawa* • *Jason Bie* • *Hong Jin*

OS4 Oral presentation session 4

11:30–13:00 | Seminar Room 2, 3rd Floor

Chen Xi

Department of Biomedical Sciences, City University of Hong Kong, Kowloon Tong, Hong Kong SAR, P.R. China
Department of Neuroscience, City University of Hong Kong, Kowloon Tong, Hong Kong SAR, P.R. China
Key Laboratory of Mental Health of the Ministry of Education, Guangdong-Hong Kong-Macao Greater Bay Area Center for Brain Science and Brain-Inspired Intelligence, Guangdong-Hong Kong Joint Laboratory for Psychiatric Disorders, Guangdong Province Key Laboratory of Psychiatric Disorders, Guangdong Basic Research Center of Excellence for Integrated Traditional and Western Medicine for Qingzhi Diseases, and School of Basic Medical Sciences, Southern Medical University, Guangzhou, China

11:30–11:53 A thalamocortical circuit with central lateral nucleus and anterior cingulate cortex optimizes flight behavior via subcortical areas

Innate defensive behavior is vital for animal survival and must be actively regulated to elicit appropriate responses. This study identifies a pathway from the central lateral thalamic nucleus (CL) to the posterior anterior cingulate cortex (pACC) that optimizes sound-induced flight behavior. We demonstrate, using anatomical tracing and physiological recordings, that both pACC-projecting CL neurons and their target pACC neurons encode key variables of this behavior, such as sound intensity and flight speed. Functional manipulations reveal that the CL-pACC pathway functions as a 'brake' on flight: activation suppresses it, while silencing facilitates it. Mechanistically, CL projections primarily drive layer 5 pACC neurons, which activate GABAergic neurons in the zona incerta (ZI), inhibiting the superior colliculus (SC) in its deep layers. Additionally, this pathway boosts visual responses in SC's superficial layers, likely improving navigated flight. By regulating subcortical areas and enhancing visual responses, the CL-pACC pathway prevents overreaction and supports adaptive flight, thereby increasing survival.

Joydeep Bhattacharya

Academy of Music, School of Creative Arts, Hong Kong Baptist University, Hong Kong
Penn Center for Neuroaesthetics, University of Pennsylvania, Philadelphia, USA
Thrust of Computational Media and Arts, Hong Kong University of Science and Technology (Guangzhou), Guangzhou, China

11:53–12:16 Between Object and Observer: A Multilevel Account of Aesthetic Judgment

Aesthetic judgments are simultaneously idiosyncratic and lawful: shaped by who you are, yet reliably influenced by properties of the artwork itself. Drawing on a series of behavioural and EEG studies examining responses to poetry and visual art, we propose a multilevel framework in which aesthetic evaluation emerges from dynamic interactions across three levels: stimulus features (originality, imagery, and statistical image properties), observer characteristics (personality and related individual differences), and neural processing (distributed, partially dissociable EEG signatures identified using machine-learning approaches). Across studies, stimulus-level properties reliably influenced aesthetic responses, but these effects were systematically moderated by individual differences, helping explain substantial variability across observers. EEG data further revealed that distinct evaluative dimensions engage partially dissociable neural processes organised around a shared evaluative axis, with anticipatory neural states contributing to subsequent aesthetic judgments prior to stimulus onset. The framework treats aesthetic judgment not as a fixed property of either object or observer, but as an emergent outcome of interactions among perceptual, affective, cognitive, and individual-difference factors. By reconciling stimulus-centred and observer-centred accounts, it offers a principled explanation for why aesthetic experiences are simultaneously shared and deeply personal. Beyond synthesis, the framework generates testable predictions about when stimulus and observer factors should interact, providing a foundation for cross-domain generalisation in empirical aesthetics.

Kwun Nok Mimi Man

Max Planck Florida Institute for Neuroscience, United States
Harvard University, United States
McGill University, Canada

12:16–12:38 A Novel Red Sensor for Measurements of Both Phasic and Tonic Dopamine Release In Vivo

Dopaminergic neurons exhibit two firing modes, phasic and tonic. While phasic firing is known to encode reward- and goal-directed behavior, the function of tonic firing remains far less understood. Tonic dopamine (DA) levels have been proposed to encode task-relevant states such as motivation and reward availability, but their precise function has been difficult to pinpoint, owing to a lack of technology for measuring DA over the longer timescales of minutes to hours. We engineered FLIM-dLight, a novel red DA sensor for fluorescence lifetime imaging (FLIM) that enables quantitative measurements of dopamine. FLIM-dLight is bright, has high affinity for DA (EC_{50} in neurons = 17 nM), and shows a large lifetime increase of ~850 ps at saturating DA. Using FLIM fiber photometry, FLIM-dLight reported phasic DA time-locked to food pellet

consumption. Under two-photon imaging, we obtained a DA dose-response curve and determined baseline and evoked DA concentrations during electrical stimulation of striatal brain slices. Cocaine significantly increased both baseline and evoked DA concentrations in slices, consistent with well-established fast-scan cyclic voltammetry recordings but not resolvable by intensity-based optical sensors. We also found regional differences in DA levels between the lateral and medial dorsal striatum. Using two-photon imaging of the dorsolateral striatum through GRIN lenses, we observed a significant decrease in sensor lifetime in 6-OHDA-lesioned Parkinson's disease (PD) model mice, indicating reduced tonic DA. Finally, FLIM-dLight revealed that the PD medication levodopa rescues striatal DA levels in 6-OHDA mice dose-dependently, with the decay of the DA response likewise depending on levodopa dose. Together, these data establish FLIM-dLight as a tool for measuring and tracking absolute DA concentrations across short and long timescales, enabling comparison of tonic DA across animal models and revealing spatial differences and dose-dependent DA dynamics. (Funding: NIH, USA: U19 NS123719, R61 AG094651, R01 MH110504)

Hyokeun Park

Division of Life Science and 2Department of Physics
Hong Kong University of Science and Technology, Hong Kong SAR

12:38–13:00 **Exocytosis and dynamics of inhibitory synaptic vesicles**

The balance between excitation and inhibition also plays an important role in processing cognitive tasks, including learning and memory. Neurons can excite or inhibit other neurons by releasing excitatory or inhibitory neurotransmitters. Less research has focused on inhibitory synapses, despite recent studies that showed the importance of these synapses. Recently, specific proteins have been identified in inhibitory synapses, suggesting the presence of unique release machinery. Nevertheless, the dynamic properties of inhibitory vesicles that underlies their release of neurotransmitters remain poorly understood. Here, we investigated the exocytosis and dynamics of individual inhibitory synaptic vesicles using a real-time three-dimensional (3D) microscope with nanometer-resolution tracking in live neurons. We found the unique exocytosis and dynamics of inhibitory synaptic vesicles during electrical stimulation compared with excitatory vesicles. Moreover, we observed the distinct spatial distribution and dynamics of spontaneously recycled inhibitory synaptic vesicles. These exocytosis and dynamics of inhibitory synaptic vesicles facilitate efficient inhibitory synaptic transmission in the brain.

This work was supported by the Research Grants Council of Hong Kong (Grants 16102322 and N_HKUST648/24)

PL5 Deciphering the Biochemistry of Long-term Memory

14:00–15:00 | LT 3–4

Chair: *Woong Sun*

Haruhiko Bito

Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, Japan

14:00–15:00 Deciphering the Biochemistry of Long-term Memory

Two separable yet interactive cellular activity features have been associated with neuronal populations implicated in memory formation. The first feature concerns the induction of synaptic plasticity at synapses that receive characteristic stimuli to trigger postsynaptic NMDA receptor signaling during such cognitive events. The second relates to activity-dependent gene expression via a synapse-to-nucleus signaling mediated mainly by a transcription factor CREB. Synaptic inputs locally trigger neuroplastic signaling at the stimulated synapses while also turning on activity-dependent mechanisms linking synapses and the nucleus, which control long-term memory and late-phase long-term plasticity. Single synapse LTP recording of glutamate receptor lateral diffusion showed that trafficking of Arc to weak synapses, through an inverse synaptic tagging mechanism during the late phase of long-term plasticity, underlies late-phase heterosynaptic depression. Thus, Arc is a critical mechanistic component that facilitates long-term maintenance of strong-to-weak contrast of synaptic weights on a stimulated dendrite. These findings pave the way toward a better understanding of the neuropathological significance of disrupting learning-associated transcriptional signaling in disorders such as schizophrenia, autism, and intellectual disability.

Biography

Haruhiko Bito is a Professor and Chair of Neurochemistry at the University of Tokyo. He graduated from the University of Tokyo with an M.D. and a Ph.D. in Biochemistry in 1993. After postdoctoral training at Stanford University as an HFSP Fellow in Richard W. Tsien laboratory, he started his own laboratory in Pharmacology at Kyoto University in 1997 before moving to head the Department of Neurochemistry at the University of Tokyo in 2003. Dr. Bito has deciphered novel functions of many members of the CaMK family, and elucidated the bidirectional neuronal signaling between the synapses and the nucleus, essential for late-phase plasticity and long-term memory. Dr. Bito has also designed powerful molecular tools (E-SARE synthetic activity-dependent enhancer and next-generation Ca2+ indicators XCaMPs) that help capture and measure neuronal ensemble activity critical for cognition.

He received the Young Investigator Awards from the Japanese Societies for Pharmacology (2003) and Biochemistry (2004), the Tsukahara Award from the Japan Neuroscience Society (2011), AND Investigator Award (Molecular Brain, 2015), and the Setsuro Ebashi Award from the Japanese Pharmacological Society (2020).

He has served on multiple international committees, including FENS Program Committee (2016-2018) and SfN Program Committee (2018-2024). He was the Program Chair of the Annual Meeting 2023 of the Society for Neuroscience. He was also the Founding Chair of the China-Japan-Korea International Neuroscience Meeting series which has kicked off in 2021.

S16 Revisiting classical monoamine neurochemistry with next-generation monitoring technologies

15:00–17:00 | LT 1

Chair: *ChiHye Chung*

Session overview

This symposium revisits classical monoamine neurochemistry through next-generation monitoring technologies. It considers how genetically encoded sensors, advanced imaging, high-speed measurement, and in vivo recording are redefining the spatial and temporal organization of dopamine, serotonin, and related signalling systems. The session links these methodological advances to a more precise understanding of behaviour, cognition, and neuropsychiatric disease.

Jun Julius Zhu
Wenzhou Medical University, China

15:00–15:30 **Nanoscopic Visualization of Neuromodulatory Transmission**

Transmitters such as monoamines and neuropeptides, orchestrates diverse physiological actions. However, our limited understanding of neuromodulation, stemming from the limitations of current analysis methods, hampers our grasp of emotions, behaviors, and neurological and psychiatric disorders like Alzheimer's disease, addiction, depression, metabolic and social behavior disorders. Our recent advancements in electronic, mechanical, optical, and algorithmic innovations have enabled the pioneering nanoscopic visualization of neuromodulatory transmission (Lin et al., 2021; Zhu et al., 2024). I will discuss the biophysical principles underlying this visualization breakthrough. Subsequently, I will introduce our genetically encoded sensorbased imaging and analysis method (GESAIP) that enables for characterization of transmission modes and quantal analysis of the synaptic properties of neuromodulatory signaling in rat, mouse, and human ex vivo tissues (Jing et al., 2018; Borden et al., 2020; Zhang et al., 2025). Lastly, I will present our development of a next-generation miniscope designed to extend these quantitative analytical capabilities to intact healthy and diseased brains across diverse behavioral states (Kazemipour et al., 2019; Borden et al., 2020; Zhu et al., 2024).

Jihye Seong
Seoul National University, Republic of Korea

15:30–16:00 **Decoding Dopamine and Serotonin Receptor Crosstalk Using Genetically Encoded Biosensors**

Dopamine and serotonin are among the most studied neuromodulators in the brain, yet many aspects of their receptor-level signaling remain poorly understood. In this talk, I present genetically encoded fluorescent biosensors that enable direct, real-time monitoring of monoamine receptor activity, offering a fresh perspective on classical neurochemistry. First, I introduce multicolor fluorescent biosensors for dopamine receptor subtypes DRD1 and DRD2, called R-DRD1 and G-DRD2. These sensors provide sensitive, subtypeselective visualization of dopamine transmission. Notably, these biosensors were applied to illuminate functional crosstalk between DRD1–DRD2 heterodimers, which was previously inaccessible with conventional methods. Heteromerization is a mechanism through which receptor complexes acquire signaling properties fundamentally distinct from their monomeric counterparts. We also applied this approach to identify functional crosstalk between the serotonin 2A receptor (5HT2A) and DRD2 within a heteromeric complex. Using cp-FP-based sensors PsychLight2 and G-DRD2, we directly monitored the individual activities of 5HT2A and DRD2, revealing differential crosstalk between these receptors. Together, these results demonstrate how next-generation biosensors can reframe our understanding of monoamine signaling, uncovering receptor interactions with direct relevance to psychiatric disease and therapeutic development.

ChiHye Chung
Konkuk University, Republic of Korea

16:00–16:30 **Competitive Interactions Shape Social Hierarchy via Prefrontal Dopamine Release**

Social hierarchies emerge through repeated competitive interactions, yet the neurochemical mechanisms underlying their formation and stabilization remain unclear. Using the tube test paradigm in mice, we show that social ranks are initially unstable but become stabilized through repeated competitive encounters. Rankings derived from the tube test display significant correlations after stabilization, highlighting the instructive role of competition in hierarchy formation. Given that the medial prefrontal cortex (mPFC) regulates competitive behavior and that dopamine receptor–expressing neurons exhibit rank-dependent properties, we hypothesized that competition-driven hierarchy formation is mediated by dopamine

dynamics in the mPFC. Pharmacological blockade of D1- or D2-type dopamine receptors in the mPFC during competition disrupted rank stabilization. Moreover, fiber photometry using a genetically encoded dopamine sensor revealed distinct temporal dopamine dynamics between winners and losers during competitive encounters. Dopamine release patterns varied according to competitive outcome, suggesting differentiated dopaminergic signaling that encodes social status information. These findings indicate that competition-induced dopamine release in the mPFC serves as a key mechanism underlying the formation and stabilization of social hierarchies, linking monoaminergic dynamics to emergent social structure.

Satoshi Kida
The University of Tokyo, Japan

16:30–17:00 **Hippocampal clock regulates memory retrieval via Dopamine-PKA signaling pathway**

Cognitive performance in people varies according to time-of-day, with memory retrieval declining in the late afternoon-early evening. However, functional roles of local brain circadian clocks in memory performance remains unclear. Here we show that hippocampal clock regulates time-of-day retrieval profile. Impaired hippocampal circadian clock disrupted retrieval of hippocampal memories at Zeitgeber Time 8-12. This altered retrieval profile was associated with downregulation of hippocampal Dopamine-cAMP signaling in dnBMAL1 mice. These changes included decreases in Dopamine Receptors (D1-R and D5-R) and GluA1-S845 phosphorylation by PKA. Consistently, pharmacological activation of cAMP-signals or D1/5Rs rescued impaired retrieval efficiency in dnBMAL1 mice. Importantly, GluA1 S845A knock-in mice showed similar retrieval deficits with dnBMAL1 mice. Our findings suggest mechanisms underlying regulation of retrieval efficiency by hippocampal clock through D1/5R-cAMP-PKA-mediated GluA1 phosphorylation.

S17 Bridging genetic diversity to clinical innovation in Parkinson's disease: Asia-Pacific perspectives

15:00–17:00 | LT 2

Chair: *Wael Mohamed*

Session overview

This symposium examines how genetic diversity can be translated into clinical innovation in Parkinson's disease across Asia-Pacific populations. It considers population genomics, disease modelling, biomarker discovery, and therapeutic development as complementary routes toward earlier diagnosis and more individualized care. The session emphasizes regional collaboration, inclusive data resources, and the connection between mechanistic neuroscience and real-world clinical impact.

Wael Mohamed

International Islamic University Malaysia, Malaysia

15:00–15:30 AfrAbia-PD-Genomic Consortium: Seeing the Unseen

Genomic research in Parkinson's Disease (PD) has historically skewed heavily toward populations of European ancestry, leaving a critical gap in our understanding of the disease's global genetic architecture. The AfrAbia-PD-Genomic Consortium (AA-PD-GC) was established to address this disparity by bridging collaborative research across under-represented populations in Africa and the Arabian Peninsula. It is funded by GP2 and MJF.

This talk explores the consortium's mission to "see the unseen"—uncovering unique genetic variants, novel risk loci, and ancestral modifiers that have remained hidden in traditional datasets. By leveraging cross-border partnerships, advanced genomic sequencing, and localized clinical insights, the initiative aims to map the distinct genetic landscape of PD within these diverse cohorts. Ultimately, these findings are vital for dismantling global health inequities and paving the way toward truly inclusive, global precision medicine for neurodegenerative disorders.

Yamashita Toshihide

Department of Molecular Neuroscience
Graduate School of Medicine, Osaka University, Osaka, Japan

15:30–16:00 Repulsive Guidance Molecule-a as a Therapeutic Target Linking Neurodegeneration and Neuroinflammation in Parkinson's Disease

Repulsive guidance molecule-a (RGMa) is a glycosylphosphatidylinositol-anchored protein expressed in glial and immune cells and is a well-established inhibitor of axonal growth in the adult central nervous system (CNS). Neutralization of RGMa using monoclonal antibodies promotes neural rewiring and functional recovery after spinal cord injury, findings that have led to ongoing international clinical trials of the humanized anti-RGMa antibody, unasnemab. Beyond axon guidance, accumulating evidence indicates that RGMa plays a critical role in neuroimmune regulation. RGMa expressed in dendritic cells enhances T-cell activation and exacerbates autoimmune neuroinflammation, while anti-RGMa antibody treatment suppresses neutrophil infiltration and inflammatory chemokine expression in neuromyelitis optica. These multimodal actions suggest that RGMa links neural degeneration with immune dysregulation.

We recently identified a previously unrecognized role of RGMa in Parkinson's disease (PD) pathophysiology. RGMa regulates blood-brain barrier integrity and neuronal survival in the CNS. Systemic administration of anti-RGMa antibodies significantly reduced the loss of tyrosine hydroxylase-positive dopaminergic neurons and attenuated microglial/macrophage accumulation in the substantia nigra in a mouse model of PD. Conversely, selective overexpression of RGMa in dopaminergic neurons induced progressive neuronal degeneration, neuroinflammation, and motor impairment. Mechanistically, increased RGMa expression promoted pro-inflammatory cytokine production in microglia, suggesting a feed-forward loop between neuronal RGMa signaling and innate immune activation. These findings position RGMa as a key molecular mediator linking neurodegeneration, neuroinflammation, and barrier dysfunction in PD. Targeting RGMa therefore represents a promising disease-modifying strategy that bridges mechanistic discovery and clinical innovation. Ongoing and planned clinical studies of anti-RGMa antibodies highlight their translational potential for PD and other neurodegenerative and neuroimmune disorders.

Yih-Ru Wu
College of Medicine, Chang Gung University; Department of Neurology, Taiwan
Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan

16:00–16:30 Population Genomics in Parkinson's Disease: Insights from Asia-Pacific Cohorts

Parkinson's disease (PD) is a complex neurodegenerative disorder driven by the interplay of genetic susceptibility, environmental exposure, and population-specific factors. While most large-scale genomic discoveries have originated from European-ancestry cohorts, the Asia-Pacific region represents one of the most genetically diverse and rapidly aging populations globally, yet remains substantially underrepresented in PD genomics research. This talk explores how population genomics approaches applied to Asia-Pacific cohorts are reshaping our understanding of PD biology, risk architecture, and translational opportunities.

Drawing on multi-ancestry genome-wide association studies, whole-genome sequencing initiatives, and regional biobanks, we highlight key discoveries of ancestry-specific risk variants, novel loci, and allelic heterogeneity in established PD genes such as LRRK2, GBA1, SNCA, and PRKN. The integration of diverse populations enhances fine-mapping resolution, improves polygenic risk prediction across ancestries, and uncovers gene-environment interactions relevant to regional exposures, lifestyle, and demographic transitions. We also discuss the role of founder effects, rare variant enrichment, and population structure in shaping disease susceptibility across East Asia, South Asia, Southeast Asia, Oceania, and Pacific Island populations.

Beyond discovery science, the talk emphasizes the clinical and public health implications of inclusive genomics: equitable risk stratification, culturally informed genetic counseling, biomarker development, and the potential for precision medicine approaches tailored to diverse populations. Challenges related to data harmonization, ethical governance, capacity building, and sustainable international collaboration are addressed, alongside emerging solutions leveraging cloud-based analytics, federated data sharing, and regional research networks.

By advancing population-driven genomic insights from the Asia-Pacific region, this work aims to close ancestry gaps in PD research, strengthen global discovery power, and accelerate the translation of genomic knowledge into improved diagnosis, prevention, and personalized care for patients worldwide.

Kaavya Marasimhalu
Department of Neurology
National Neuroscience Institute (Sgh Campus), Singapore

16:30–17:00 Clinical genetic testing in PD and neurodegenerative diseases: challenges and future directions

Parkinson's Disease (PD), and neurodegenerative diseases (NDD) as a whole are complex disorders with both genetic and environmental causes. Despite advances in improving knowledge about the genetic underpinnings of PD and NDD, clinical use of genetics in PD and NDD is low. Patients are either not referred for clinical genetic testing, or if referred, often decline due to social and financial concerns.

In this talk, we will explore the barriers towards clinical genetic testing in PD and other NDD. We will also explore the lack of clear consensus guidelines about clinical genetic testing. Regulatory aspects of genetic counselling and their implication on expanding clinical genetic testing will also be discussed.

S18 Physical exercise and brain health: mechanisms, interventions, and translational perspectives

15:00–17:00 | Seminar Room 3, 3rd Floor

Chair: *Sonata Yau*

Session overview

This symposium examines physical exercise as a modulator of brain health across the lifespan. It considers how activity influences neural plasticity, cognition, neuroprotection, and vulnerability to neurodegenerative and psychiatric disorders, drawing on both experimental and clinical perspectives. The session highlights the mechanisms, intervention strategies, and translational questions that will shape exercise-based approaches to brain health.

Wei Pang Teo
Motor Behaviour Laboratory
National Institute of Education, Nanyang Technological University, Singapore

15:00–15:30 From Daily Behavior to Neural Degeneration: Compositional Time-Use as a Mechanistic Risk Factor for Dementia

The transition from healthy aging to dementia involves progressive disruption of neural structure, connectivity, and plasticity. Identifying behavioural factors that contribute to neural resilience or vulnerability is critical for early intervention. Daily time-use represents a fundamental, yet underutilized, dimension of behavioural exposure. Because time allocation across sleep, sedentary behaviour, and active states is constrained within a fixed 24-hour period, these behaviours form a compositional system. Compositional data analysis enables rigorous quantification of relative behavioural allocation and its association with neural outcomes.

This talk will synthesize evidence linking compositional time-use to neural markers of dementia risk, including hippocampal atrophy, white matter microstructural degradation, and altered functional connectivity. Compositions characterized by reduced sleep integrity, elevated sedentary allocation, and limited engagement in physically or cognitively stimulating activities are associated with neural signatures consistent with reduced plasticity and increased neurodegenerative vulnerability.

These associations are supported by convergent mechanistic pathways. Sleep plays a critical role in glymphatic clearance of neurotoxic proteins and synaptic homeostasis. Physical activity promotes neurogenesis, neurotrophic signaling, and vascular health. Cognitive engagement strengthens synaptic networks and supports functional reserve. Conversely, prolonged sedentary states may contribute to metabolic dysregulation and reduced neural stimulation. Importantly, these mechanisms operate interactively within the compositional structure of daily time allocation.

I will propose that compositional time-use represents a mechanistically meaningful behavioural exposure that shapes neural integrity over extended time scales. By framing dementia risk in terms of the relative balance of daily behaviours, compositional approaches provide a biologically grounded framework for early detection and intervention.

Liye Zou
Body-Brain-Mind Laboratory
School of Psychology, Wuhan Sport University, China

15:30–16:00 Sitting, Switching, and Brain Health: A Mechanistic Path from Sedentary Behavior to Strategic Exercise

Sedentary behavior is increasingly viewed as a distinct brain-health exposure, not simply "low physical activity," with associations that can vary across the lifespan and depend on how sedentary time is accumulated and measured (Zou et al., 2024). To increase mechanistic precision, our work advances a neurobiological taxonomy that differentiates cognitively active versus cognitively passive sedentary behaviors, as well as key moderators (for example, age and life context) that may shape brain-health links (Zhang et al., 2025).

Building on this framework, we test a practical countermeasure: brief exercise breaks before and during prolonged sitting (Yu et al., 2025; Zhang et al., 2025). In a randomized crossover study in a simulated classroom setting, interrupting sitting with short bouts of cycling improved executive function and was accompanied by microvascular changes (retinal vessel diameters) and altered cortical activation and connectivity, consistent with coupled vascular–network mechanisms (Yu et al., 2025).

Finally, we connect these mechanistic findings to learning by integrating embodied cognition with cognitive load theory (Zou et al., 2025), and by proposing a dual-process account in which physical activity supports academic performance through both domain-general and domain-specific executive functions (Zhang et al., 2025), including field evidence that brief pre-class exercise can selectively enhance mathematics-specific inhibitory control (Zhang et al., 2026).

Li Zhang
Ghm Institute of Cns Regeneration
Jinan University, Guangzhou, China

16:00–16:30 **Exercise, neuroprotection and mental health**

Exercise training is one of the popular non-drug approaches to improve cognitive or mental disorders. However, the understanding of the complete mechanism of exercise training, especially for the peripheral-central axis in modulating synaptic function, is far from complete. Our group has previously provided in vivo evidence showing the improvement of cortical synaptogenesis and synaptic activity by treadmill training using the mouse model (Sci Adv 2019, Mol Psychiatry 2021). Recently, we have focused on circulating molecules and illustrated their roles in modulating synaptic functions. These peripheral factors can help to alleviate neuroinflammation (Cell Rep 2023), as well as directly affecting synaptic functions via RNA methylation (Adv Sci 2022) or protein lactylation (Cell Metab 2024), contributing to the improvement of cortical and subcortical neural circuits (Nat Commun 2025) for improving mental functions. Our work provides more evidence for understanding the body-brain axis during exercise intervention of brain diseases.

Teresa Liu-Ambrose
Department of Physical Therapy, University of British Columbia, Canada

16:30–17:00 **Exercise to promote cognitive health in at-risk older adults**

The importance of physical activity in promoting brain health and in reducing dementia risk. However, whether exercise interventions should be recommended for the management of individuals with at risk for dementia, such as those with mild cognitive impairment or a history of stroke, is not clear. In this presentation, we will review and summarize evidence to date and discuss future research to advance our understanding of the role of exercise in promoting brain health in at risk adults.

S19 Large-scale network organization underlying brain function – from effective connectivity to dynamics modeling

15:00–17:00 | Seminar Room 1, 3rd Floor

Chair: *Changsong Zhou*

Session overview

This symposium investigates large-scale network organization underlying brain function, from effective connectivity to dynamic modelling. It considers how structural connections, distributed neural activity, and information flow support cognition, behaviour, and individual differences. The session highlights interdisciplinary approaches that combine data analysis, network theory, and computational modelling to explain how complex brain dynamics emerge.

Quanying Liu

South University of Science and Technology, China

15:00–15:30 Artificial intelligence as a surrogate brain: bridging neural dynamical models and data

The brain is a dynamic system, characterized by intricate spatiotemporal dynamics that underpin cognitive functions and behaviors. In this talk, I will first introduce to build an artificial intelligence (AI) to predict the future brain dynamics from the past data. The trained AI model serves as a surrogate brain. By conducting virtual perturbation experiments on this surrogate brain, we can obtain a whole-brain effective connectome. This effective connectome reflects the intensity, directionality, and excitatory-inhibitory characteristics of the brain's information flow, capturing the causal relationships between different brain regions. Furthermore, I will introduce an AI surrogate brain-guided optimal control framework for controlling biological neural dynamics. We have validated this framework through experiments on in vitro neurons, which suggest that the closed-loop electrical stimulation designed with our framework can effectively achieve the control goals. Our framework paves new ways for the personalized treatment of brain diseases, the enhancement of brain functions, and the regulation of behavior.

Daqin Guo

University of Electronic Science and Technology of China

15:30–16:00 Decomposing Functional Connectivity into Tract-Explainable and Tract-Underexplained Components: Insights into Human Brain Functional Organization

Structural connectivity inferred from diffusion MRI constrains large-scale functional connectivity but does not fully account for its empirical patterns, indicating contributions from non-tract factors. In this talk, I will introduce a model-based framework that distinguishes two complementary components of functional synchrony: tract-explainable synchrony and tract-underexplained synchrony. Across two independent cohorts, we find that both components are highly reproducible yet exhibit distinct biological and network characteristics. Tract-explainable synchrony closely align with white matter architecture and supported globally efficient integration, whereas tract-underexplained synchrony is associated with multi-scale cortical similarity features, including microstructure, receptor, and gene-expression patterns, and exhibited higher modularity. The relative expression of these two components varies systematically along the sensorimotor-to-association cortical hierarchy, with tract-underexplained synchrony showing greater individual variability and stronger behavioral relevance. Together, our findings suggest that human functional connectivity arises from the interplay between an anatomy-anchored integrative scaffold and a complementary non-tract-mediated coordination layer.

Xiaoyu Chen

Shanghai Jiaotong University, China

16:00–16:30 Emergence of Cortical Hierarchy in Harmonizing Functional and Effective Connectome with Large-scale Biophysical Modelling

Incorporation of cortical hierarchy improves fitting of functional connectome (FC) from structural connectome (SC) using reduced Wong-Wang model. However, its necessity remains unknown due to difficulty in model training as well as limited data modality. Here, we developed a connectome-based back-propagation training procedure that enables nodal parameters to be trained independently across cortical nodes, thereby exploring nodal heterogeneity with full degrees of freedom. We then introduced effective connectome (EC) from direct electrical stimulation dataset F-TRACT, and adopted a two-step training pipeline that integrates information from both EC and FC. In the well-trained model, hierarchical specialization anatomically emerges that recurrent strength and intrinsic noise level both increase along the hierarchical axis from sensory-

motor to association areas. Moreover, we found an empirical divergence that node strength of EC is positively correlated with hierarchy, whereas node strength of FC shows negative correlation. With demonstrated impact of heterogeneity of node dynamics as to modeled node strength, we finally illustrated a unique relationship between hierarchy, connectomes and model parameters. Our cross-modality work highlights the underlying organization of brain-wide dynamics, by paving the way for deep learning enforced biophysical modeling.

Changsong Zhou
Hong Kong Baptist University

16:30–17:00 Stiff network modeling reveals behavior-sensitive dimensions of large-scale brain network underlying individual differences

Individual differences in cognitive performance coexist with a largely conserved macroscale organization of brain networks, posing a central challenge for brain–behavior research: how can network-level variation give rise to meaningful behavioral diversity without disrupting global architecture? Here we introduce Stiff Network Modeling (SNM), a sensitivity-based framework that represents large-scale brain networks using regional excitability and interregional coupling, organized by behavioral impact rather than variance. Using working memory task fMRI data from over one thousand individuals, we show that behavioral sensitivity is concentrated in a small portion of coordinated, stiff parameter combinations that form network-level patterns (eigennetworks), whereas most inter-individual variation occurs along sloppy directions with little influence on behavior. By optimally combining these behavior-sensitive eigennetworks, SNM yields a compact, behavior-aligned task-processing network and a scalar measure that predicts working memory performance and generalizes across resampling. Sensitivity-based sparsification shows that behavioral leverage concentrates on a small, interpretable subset of regions and connections, providing greater stability and predictive power than variance-based connectome models. The same sensitivity-defined network links functional dynamics with structural connectivity, cortical microstructure, and transcriptomic gradients, including PANX1 expression. Together, these findings show that individual cognitive differences preferentially align with low-variance but high-impact coordinated structural and functional network patterns, resolving the dissociation between neural variability and behavioral relevance in brain–behavior studies.

PART II

Poster Abstracts

Complete poster directories and 170 full abstracts

Poster directory

Browse every poster by presentation date. Full titles are retained for reference.

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Computational and Theoretical Neuroscience · Han Cui

24-P022 Data Compression Through the Lens of Synaptic Competition: A Bio-Inspired Approach
Computational and Theoretical Neuroscience · Mingzhe Zhang

24-P023 Representational drift under spontaneous activity - self-organized criticality enhances representational reliability
Computational and Theoretical Neuroscience · Zhuda Yang

24-P024 Informative Value of Baseline Regional Brain Volumetry for Cognitive Outcomes Following Donepezil Treatment in Alzheimer's Disease
Disorders of the Nervous System · Heo Jae Hyeok

24-P025 Blood-Based Biomarkers for Alzheimer's Disease in Down Syndrome: A Systematic Review of Plasma p-tau217 and Neurofilament Light
Disorders of the Nervous System · Sai Han Htun

24-P026 A Non-Human Primate Model of Parkinson's Disease Exhibiting Slowly Progressive Motor Symptoms Following Nigral Injection of α-Synuclein Preformed Fibrils
Disorders of the Nervous System · Naohiro Fujita

24-P027 Therapeutic Efficacy of 4-Hydroxyisoleucine In Experimental Rat Model Of Demyelination: Neuroprotection Through IGF-1 and GLP-1 Level Restoration
Disorders of the Nervous System · Zuber Khan

24-P028 Single-Nucleus Transcriptomic Analysis Reveals Impaired Dentate Gyrus Granule Neuron Maturation in the MECP2- Deficient Marmoset Hippocampus
Disorders of the Nervous System · Ching Chi Jimmy He

24-P029 The Role of Parvalbumin Interneurons in Hippocampal Alzheimer's Pathology and Potential Treatment for Alzheimer's Disease
Disorders of the Nervous System · Wenyuan XIE

24-P030 Perirhinal Amyloid Pathology Disrupts Hippocampal Cognitive Maps in Alzheimer's Disease
Disorders of the Nervous System · My Linh Truong

24-P031 A novel CDD mouse model carrying a nonsense mutation R550X
Disorders of the Nervous System · Xiaoman Yang

24-P032 TPC2 Inhibition Rescues Microglial ER-phagy to Suppress STING-Driven Neuroinflammation and Cognitive Decline in Alzheimer's Disease
Disorders of the Nervous System · Xiaoming Cui

24-P033 Cationic Polystyrene Nanoplastics Exacerbate Alzheimer's Disease Pathological by Impairing the Microglial Autophagy- Lysosome Pathway and Triggering Neuroinflammation
Disorders of the Nervous System · Jie Xiao

24-P034 Nell-1 is a Synaptic Organizer Promoting Hippocampal Synaptogenesis
Disorders of the Nervous System · Yangbo Zhou

24-P035 Dysregulation of Senescence-associated genes orchestrates immune microenvironment in Parkinson's disease
Disorders of the Nervous System · Yi Li

24-P036 Sub-chronic MK801 in Adolescent Mice Induces Shifts of Schizophrenia-like Positive to Negative Symptoms and Persistent Sleep Oscillatory Dysregulation
Disorders of the Nervous System · Lok In Lauren Wong

24-P037 Topical Hydrogel Delivery of Small Molecules Promotes Retinal Ganglion Cell Survival and Optic Nerve Regeneration: A Drug Repurposing Strategy for Glaucoma
Disorders of the Nervous System · Linjing Mi

24-P038 State-dependent plasticity of the olfactory cortex regulates novel food learning
Internal States and Homeostasis · Esther Fung Yin Ngo

24-P039 Optimizing the Speech Processing of Cochlear Implants with Artificial Neural Networks
Neurotransmission and Neuroplasticity · Xiaohan Bao

24-P040 mGluR5-Mediated Astrocytic Calcium Signaling Regulates EAAT2 Expression and Novel Object Recognition Memory
Neurotransmission and Neuroplasticity · Yue Huang

24-P041 The Effects of α-Synuclein Mutation on Synaptic Transmission
Neurotransmission and Neuroplasticity · Hoi Dik Au-Yeung

24-P042 Disrupting laboratory fear memory reconsolidation with individualized, neuroimaging guided, PTSD-protective circuit TMS: A pre-clinical experiment in healthy participants
Disorders of the Nervous System · Zhiqi Zhang

24-P043 Astrocyte-Specific Double Stranded RNA–ADAR1 Signalling Links Innate Immunity to Complement Activation in Parkinson's Disease
Cell Biology of Neurons and Glia · Yang Liu

24-P044 Reduced lysosomal proteolytic activity promotes intracellular protein aggregation and disrupts neuronal maturation
Cell Biology of Neurons and Glia · Yuuki Fujiwara

24-P045 R-spondin 3 orchestrates oligodendrocyte lineage progression through an LGR4–FGFR3 receptor complex to drive white matter development and repair
Cell Biology of Neurons and Glia · Xiaohaua Jiang

24-P046 YY1-Wnt10b-Fzd4 Axis Regulates Purkinje Cell Development and Its Dysfunction Leads to Cerebellar Ataxia
Cell Biology of Neurons and Glia · Ying Lam Lui

24-P047 Targeted delivery of Spike replicon RNAs via VRPs to microglia and its impact on neuroinflammation
Cell Biology of Neurons and Glia · Man Kit Tong

24-P048 Burden of Idiopathic Developmental Intellectual Disability Attributable to Lead Exposure in Northeast Asia, 1990–2023: A Systematic Analysis for the Global Burden of Disease Study 2023.
Cognition and Behavior · Ramadhan Mlekwa

24-P049 Burden of Idiopathic Developmental Intellectual Disability Attributable to Lead Exposure in Northeast Asia, 1990–2023: A Systematic Analysis for the Global Burden of Disease Study 2023.
Cognition and Behavior · Baraka Wanjara

24-P050 Unique dynamics and distinct pools of spontaneously recycled inhibitory synaptic vesicles revealed by real-time three- dimensional single-vesicle tracking
Neurotransmission and Neuroplasticity · Chungwon Park

24-P051 A Novel Sequential Dexterous Forelimb Task Reveals Learning-Dependent Refinement of Motor Cortical Population s
Sensory and Motor Systems · Yinan Zheng

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24-P003 *24 Aug 2026*

N-Ethylmaleimide Sensitive Factor Deletion in Dopamine 2 Receptor Cells Induces Neuronal and Dopamine Loss

Min-Jue Xie ***(Presenter)***[1,2,3], *Koshi Murata*[2,4], *Hiroshi Kuniishi*[1,2,3], *Yugo Fukazawa*[2,4], *Hideo Matsuzaki*[1,2,3]

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Abstract

N-ethylmaleimide-sensitive factor (NSF) is essential for membrane fusion processes that regulate neurotransmitter release and membrane protein trafficking. Although NSF has been reported to bind dopamine 2 receptor (D2R), and its dysfunction has been linked to neuropsychiatric disorders, the precise role of NSF in D2R-expressing neurons remains unclear. To address this question, we generated D2R-specific NSF conditional knockout (NSF-cKO) mice and analyzed their neuropathological and behavioral phenotypes. Targeted deletion of NSF in D2R-expressing cells resulted in a marked reduction of D2R-positive neurons, increased apoptosis in the striatum during postnatal development, and reduced striatal volume. In NSF-cKO mice, dopamine levels in the striatum were significantly decreased, whereas noradrenaline levels were increased. Serotonin levels did not show significant changes. Moreover, we found a reduction in tyrosine hydroxylase (TH)-positive neurons in the substantia nigra pars compacta, along with decreased expression of dopamine transporter (DAT) and TH in the striatum, indicating impaired dopaminergic transmission. Behaviorally, NSF-cKO mice exhibited attention-deficit/hyperactivity disorder (ADHD)-like phenotypes, including hyperactivity and impulsivity. Notably, combined treatment with methylphenidate and a D2R agonist significantly ameliorated these behavioral abnormalities. These findings suggest that NSF plays a neuroprotective role in D2R-expressing neurons during postnatal development and that loss of NSF leads to dopaminergic dysfunction in the striatum, thereby contributing to ADHD-like behavioral phenotypes.

24-P004 *24 Aug 2026*

Temporal divergence of BDNF- and NT3-driven transcriptional programs defines a PLCγ-dependent gene module for presynaptic, axonal, and vesicular trafficking machinery in cortical neurons

Saki Akigawa ***(Presenter)***[1], *Shingo Suzuki*[1], *Nazurah Abdul Aziz Amal*[2], *Hikari Ohtabi*[1], *Ken-ichi Ohta*[1], *Takanori Miki*[1]

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Abstract

Brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3) are co-expressed throughout the mammalian brain and transduce signals through structurally related Trk receptors, yet whether they orchestrate distinct or redundant transcriptional programs in cortical neurons remains unresolved. Resolving this question is critical for delineating the non-overlapping physiological roles of each neurotrophin and for understanding how Trk-coupled signaling shapes circuit-level gene expression.

To address this, we performed time-resolved RNA sequencing on primary cultured cortical neurons stimulated with BDNF or NT3, and systematically compared shared and ligand-specific differentially expressed genes (DEGs) at 1, 3, and 6 hours post-stimulation.

At 1 hour, the two neurotrophins elicited highly concordant responses, with the majority of upregulated genes shared between conditions, indicative of a common early transcriptional program. This convergence, however, proved transient. From 3 hours onward, BDNF progressively recruited a substantially larger cohort of ligand-specific DEGs than NT3, and downregulated genes diverged more sharply between the two conditions than upregulated genes at every time point. Strikingly, transcripts that remained persistently upregulated exclusively under BDNF were enriched for presynaptic structural organization, axonal transport, and intracellular vesicular trafficking, implicating BDNF in a coordinated, sustained program that couples presynaptic remodeling with the axonal and vesicular machinery required to supply and maintain it.

24-P005 *24 Aug 2026*

Slitrk paralogs configure excitatory synaptic specificity via different extracellular and intracellular mechanisms

Byeongchan Kim ***(Presenter)***[1], *Dongwook Kim*[1,2], *Jinhu Kim*[1,2], *Jiwon Um*[1,2], *Jaewon Ko*[1,2]

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Abstract

Synapses are basic elementary units of neural information transfer that connect neurons into specifically wired neural circuits. During development, synapses undergo seemingly distinct stages of biological processes that are shaped by diverse actions of synaptic cell-adhesion molecules (CAMs), which are involved in dictating synapse assembly, specification of synaptic properties, synaptic plasticity, and even synapse elimination. Among these, vertebrate neural circuit properties are shaped by synaptic cell adhesion molecules (CAMs). CAMs often have multiple paralogs but the possible redundancy of such paralogs remains underexplored. Using circuit-specific conditional knockout (cKO) mice deficient for Slitrk1 and Slitrk2, we show that these paralogs lack specific laminar expression in mature hippocampal neurons but divergently guide the specificity of neural circuits in distinct hippocampal subfields. Slitrk1 and Slitrk2 regulate distinct facets of excitatory synaptic properties in a microcircuit-dependent manner through binding to LAR-RPTPs, and additionally in the case of Slitrk2, through binding to PDZ domain-containing proteins and TrkB. Analyses of Slitrk2 V89M knock-in mice revealed that this schizophrenia-associated substitution acts uniquely as a loss-of-function mutation in some microcircuits to impair excitatory synaptic transmission, asynchronous release, and spatial reference memory. These findings demonstrate that even structurally and biochemically similar synaptic CAMs can play completely distinct roles in specifying neural circuit architecture.

24-P006 *24 Aug 2026*

Rab23 deletion affects lipid homeostasis and cognitive function

Yunhong Du ***(Presenter)***[1], *Catherine Hong Huan HOR*[1]

Presenter: *Yunhong Du*

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Abstract

RAB23 is a small GTPase known to regulate vesicle trafficking, and the mutation of RAB23 is a pathogenic factor of Carpenter Syndrome (CS) in humans, with common symptoms including polysyndactyly, obesity, and intellectual disability. However, the mechanism of the RAB23 defect causing intellectual disability remains unknown. There are previous findings show that knockdown of other Rabs, including Rab5, Rab7, and Rab18 lead to abnormal lipid droplet (LD) formation, and neurodegeneration diseases are consistently accompanied by increased lipid accumulation within the CNS. Here, we ask whether RAB23 can affect the lipid accumulation in the CNS. Firstly, we performed Open Field Test (OFT) and Y-Maze test on Nestin-cre:Rab23f/f mice and found that Rab23 Nestin-conditional knockout (Nes-CKO) mice show decreased spatial recognition ability. The Immunohistochemistry staining also revealed increased lipid accumulation in Rab23 Nes-CKO mice liver, implies Rab23 mutation disrupted the lipid homeostasis. Then, we cultured Rab23 knockout (KO) Mouse Embryo Fibroblast (MEF) E13.5 from Actin-cre:Rab23f/f mice embryos, and found that the Rab23 KO MEF will accumulate more LD. To investigate the potential underlying mechanism, we performed data mining in RAB23 interactors, and found Caveolin-1 (CAV1), the structural protein of caveolae and a regulator of cellular cholesterol homeostasis, emerges as a candidate regulator at the intersection of the lipid accumulation process. The mislocalization of CAV1 is known to cooperate with LD accumulation; we hence examine the cellular localization of CAV1. The results show that CAV1 mislocalizes in Rab23 KO MEFs, suggesting Rab23 may regulate lipid homeostasis through CAV1 localization. Based on these findings, we speculate that Rab23 KO will cause LD accumulation in mice brain, and thus induce neuroinflammation and exacerbate neurodegeneration. In future work, we will further investigate the role of RAB23 in CAV1 intracellular trafficking and determine the mechanistic function of RAB23 in CAV1 localization.

24-P007 *24 Aug 2026*

TNRC6A, a Core Component of P-Bodies, Mediates Aging-Related Dendritic Spine Alterations and Spatial Memory Decline via miRNA-Mediated Synaptic Genes

*Xinrong Li **(Presenter)**[1,2,3], Cai Ying[3], Yang Xiaoman[3], Xu Haoyu[3], Zhu Yao[3], Yuan Shiyang[3], Tin Chung[1], Chen Shih-Chi[2,4], Chan Wai Yan Kannie[1,2], Ip Pak Kan Jacque[3,5]*

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Abstract

Age-related spatial memory decline is closely linked to hippocampal CA1 dysfunction, but the molecular mechanisms underlying this vulnerability remain poorly understood. TNRC6A (Trinucleotide Repeat Containing Adaptor 6A) is a key component of P-bodies, which critically facilitate miRNA-mediated gene silencing and promote mRNA decay or translational repression. However, its roles in hippocampal neuronal morphology and age-related neurodegeneration have not been fully elucidated. The present study demonstrates that TNRC6A is essential for maintaining hippocampal neuronal morphology and supporting spatial learning and memory during aging. In aged mice, TNRC6A protein levels specifically decline in the hippocampal cornu ammonis 1 (CA1) region, while mRNA levels remain unchanged, indicating post-translational regulation. Additionally, ubiquitination of TNRC6A is significantly elevated in aged mice. TNRC6A knockdown in mature hippocampal neurons mimics aging-like neurodegeneration phenotypes, including dendritic simplification, loss of mushroom spines, dysregulation of synaptic plasticity-related genes, and impaired spatial learning and memory abilities. Together, these findings identify TNRC6A as a critical regulator of neuronal integrity in the aging hippocampus and reveal how dysregulated RNA-binding protein homeostasis and miRNA function contribute to brain aging. These findings also link P-body biology to neuronal aging mechanisms, supporting TNRC6A modulation as a potential therapeutic strategy for age-related hippocampal neurodegeneration.

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24-P008 *24 Aug 2026*

Lhx1/5-dependent EAAT4 expression contributes to Purkinje cell dendritic development and synaptic microenvironment

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Abstract

The cerebellum plays a crucial role in motor coordination by integrating signals from various brain regions. Purkinje cells, characterized by their extensive dendritic trees, are essential for cerebellar function as they process and integrate large volumes of signals, generating the sole output of the cerebellar cortex. Defects in Purkinje cells are closely associated with spinocerebellar ataxias (SCA), a group of inherited disorders that severely impair motor function.

This study investigates the effects of Lhx1/5 inactivation on Purkinje cell function and neurotransmitter homeostasis. We utilized Pcp2-cre Lhx1/5 double conditional knockout (DKO) mice, which exhibited significant motor deficits and reduced cerebellar size, associated with impaired dendritic growth. Through microarray analysis, we identified EAAT4, a Purkinje cell-specific excitatory amino acid transporter, as a key candidate, with decreased expression in DKO mice. This reduction correlated with defects in Purkinje cell dendritic development and irregular electrophysiological properties. Chromatin immunoprecipitation (ChIP) assays and dual luciferase assays confirmed that Lhx1/5 directly activate the expression of EAAT4.

Additionally, we applied EAAT4 siRNA in cerebellar slice cultures to exclusively knock down EAAT4 expression. This treatment caused significant disruptions in glutamate and GABA homeostasis, likely due to compromised synaptic stability, as evidenced by reduced levels of key synaptic scaffolding proteins such as PSD95, GluD2, and subunits of AMPAR and NMDAR. These molecular changes suggest an imbalance between excitatory and inhibitory signaling, potentially contributing to the dendritic defects and electrophysiological abnormalities observed in Purkinje cells.

In conclusion, this study reveals the transcriptional regulation of EAAT4 by Lhx1/5, highlighting the critical role of EAAT4 in maintaining synaptic microenvironment and promoting Purkinje cell development.

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24-P009 *24 Aug 2026*

Modified NGF-expressing Induced Human Mesenchymal Stem Cells Promote Early Peripheral Nerve Regeneration in Rodents

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Abstract

One of major clinical challenges in the field of peripheral nerve regeneration after injury is limited functional recovery. Although the Nerve growth factor (NGF) has been proposed to promote nerve regeneration, its short half-life and unstable delivery restricted clinical applications. In this study, we proposed a novel therapeutic strategy that combines protein engineering and sustainable cell expression. We directionally induced human pluripotent stem cells (iPSCs) into mesenchymal stem cells (MSCs) and genetically engineered them to constantly secrete long-acting NGF-Fc fusion protein. In vitro experiments confirmed that the conditioned medium of the cells could significantly promote the neurite outgrowth of PC12 cells. In mouse sciatic nerve crush injury model, locally transplantation of NGF-Fc expressing MSCs at the injury site showed significantly improved sciatic nerve function in the early stage of recovery. Our study confirmed that targeted delivery of the long-acting NGF-Fc protein through iPSC-MSC platform can effectively promote nerve regeneration and provided a new strategy with great clinical transformation prospects for peripheral nerve regeneration.

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24-P043 *24 Aug 2026*

Astrocyte-Specific Double Stranded RNA–ADAR1 Signalling Links Innate Immunity to Complement Activation in Parkinson's Disease

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Abstract

Background

Dysregulated innate immune activation is a key feature of Parkinson's disease (PD), but the upstream triggers and cell-type-specific mechanisms remain unclear. Double-stranded RNA (dsRNA) has emerged as a potential driver of innate immune responses. Adenosine deaminase acting on RNA 1 (ADAR1), particularly its interferon-inducible p150 isoform, edits dsRNA to limit aberrant immune activation. Whether this dsRNA–ADAR1 axis contributes to neuroinflammation in PD in a cell-type-specific manner is unknown.

Methods

We performed immunofluorescence on post-mortem cingulate cortex from PD and control cases to assess dsRNA, ADAR1 p150 and pathological α-synuclein. We integrated these findings with single-nucleus RNA sequencing data from three human brain datasets. An eight-module gene scoring framework was applied to assess dsRNA processing, sensing, and downstream innate immune pathways in neurons and astrocytes.

Results: dsRNA and ADAR1 p150 protein preferentially accumulated in astrocytes, and astrocytic ADAR1 p150 levels correlated with their α-synuclein pathology. Transcriptomic analyses showed that neurons were enriched for dsRNA editing and processing machinery, whereas astrocytes scored higher for dsRNA sensing, innate immune responses, and transposable element control. Overall pathway activity did not differ between PD and controls after covariate adjustment. However, network analyses revealed cell-type-specific coupling patterns. Complement activation showed a strong and selective association with dsRNA-related pathways in astrocytes, whereas interferon and NF-κB signalling were shared across cell types. In astrocytes, ADAR1-associated gene programmes were enriched for oxidative phosphorylation and PD-related pathways. Conclusions

These findings identify astrocytes as a central site of relative dsRNA accumulation and ADAR1 p150 induction in the PD cortex. The selective coupling of dsRNA sensing to complement activation in astrocytes highlights a cell-type-specific innate immune pathway with potential relevance for disease progression and therapeutic targeting.

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24-P044 *24 Aug 2026*

Reduced lysosomal proteolytic activity promotes intracellular protein aggregation and disrupts neuronal maturation

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Abstract

Lysosomal proteolysis is essential for the maintenance of intracellular proteostasis, yet its contribution to neuronal development remains incompletely understood. Since neurons are particularly vulnerable to the accumulation of aberrant proteins, disruption of lysosomal degradation may have a significant impact on neurodevelopment. In the present study, we investigated the role of lysosomal proteolytic activity during neuronal maturation using primary cultured neurons. We found that lysosomal proteolytic activity increased during neuronal development. Pharmacological inhibition of lysosomal proteases resulted in marked accumulation of intracellular aggregated proteins, including ubiquitinated proteins. These changes were accompanied by impaired neuronal morphogenesis, characterized by reduced neurite length and complexity, as well as decreased expression of neuronal maturation markers. Proteomic analyses further revealed that the accumulated aggregates were enriched with proteins involved in neuronal development and differentiation. Collectively, our findings demonstrate that sufficient lysosomal proteolytic capacity is required for maintaining proteostasis during neuronal development and suggest that disruption of lysosomal protein degradation contributes to neurodevelopmental abnormalities through the accumulation of aggregated proteins.

24-P045 *24 Aug 2026*

R-spondin 3 orchestrates oligodendrocyte lineage progression through an LGR4–FGFR3 receptor complex to drive white matter development and repair

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Abstract

White matter injury, characterized by oligodendrocyte (OL) loss and remyelination failure, underlies diverse neurological disorders, yet the upstream signals governing OL maturation remain incompletely defined. Here, we identify R-spondin 3 (RSPO3) as a critical regulator of OL lineage progression. Rspo3 expression peaks during postnatal myelination and becomes enriched in mature OLs. Conditional ablation of Rspo3 in $Ng2^{+}$ lineage cells impairs developmental myelination and compromises remyelination following demyelinating injury. Mechanistically, RSPO3 functions independently of canonical Wnt signaling and instead signals through LGR4, which directly interacts with FGFR3 to form a functional receptor complex in differentiating oligodendrocyte progenitor cells (OPCs). RSPO3 enhances FGFR3–FRS2α phosphorylation, leading to coordinated activation of AKT and ERK–CREB signaling, thereby driving pro-differentiation transcriptional programs and

myelin gene expression. Disruption of FGFR3, AKT, or CREB abolishes RSPO3-driven differentiation, establishing this signaling axis as essential. Local and intranasal delivery of recombinant RSPO3 accelerates OL regeneration, enhances remyelination, and improves functional outcomes in both focal demyelination and neonatal hypoxic–ischemic injury models. Importantly, the pro-myelinating role of RSPO3 was recapitulated in a human ESC-derived OL platform, underscoring the translational relevance of this pathway. Collectively, these findings define a previously unrecognized LGR4–FGFR3 signaling mechanism governing stage-specific OL maturation and position RSPO3 as a compelling therapeutic candidate for white matter regeneration.

24-P046 *24 Aug 2026*

YY1-Wnt10b-Fzd4 Axis Regulates Purkinje Cell Development and Its Dysfunction Leads to Cerebellar Ataxia

*Ying Lam Lui **(Presenter)**[1], Thomas Chun Ning Leung[1], Tsz Ho Li[1], Ting Fung Chan[1,2], Kin Ming Kwan[1,2,3,4]*

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Abstract

Postnatal Purkinje cell (PC) development is vital for motor coordination; its disruption causes ataxia. The transcription factor Yin Yang 1 (YY1) is implicated in Gabriele-de Vries syndrome, characterized by ataxic symptoms. Utilizing a PC-specific Yy1 conditional knockout (cKO) mouse model, we establish YY1's indispensable role in PC dendritogenesis and synaptogenesis. Yy1 cKO mice exhibit progressive cerebellar atrophy and severe ataxia, alongside significant deficits in PC dendritic arborization and spine maturation. Mechanistically, we identified Wnt10b as a direct transcriptional target of YY1. The YY1-driven activation of Wnt10b and its receptor Fzd4 forms an autocrine signaling loop critical for PC development. In cerebellar slice cultures, Wnt10b knockdown recapitulates the Yy1 cKO phenotypes, while recombinant Wnt10b partially restores dendrite growth but not PKCγ expression, a crucial downstream effector. This pathway modulates PC structure and function, partly via PKCγ and β-catenin signaling. Our findings elucidate a mechanistic link between YY1 dysfunction and cerebellar ataxia, providing insights into Gabriele-de Vries syndrome and identifying potential therapeutic avenues. The work is supported by the grants from the Research Grant Council of the Hong Kong Special Administration Region (project nos. GRF 14112224, 14114921, CRF C4002-21E and AoE/M-402/25-N) and a Chinese University of Hong Kong Direct Grant for Research.

24-P047 *24 Aug 2026*

Targeted delivery of Spike replicon RNAs via VRPs to microglia and its impact on neuroinflammation

*Man Kit Tong **(Presenter)**[1], Lina Bao[1], Young Jin LEE[1]*

Presenter: *Man Kit Tong*

[1] *City University of Hong Kong, Hong Kong SAR*

Abstract

Venezuelan equine encephalitis virus (VEEV) replicon particles (VRPs) are single-cycle, self-amplifying RNA delivery vehicles capable of high intracellular cargo expression without productive spread. However, achieving targeted genetic delivery to resident CNS microglia across different administration pathways remains a major obstacle. Crucially, the exact mechanisms by which targeted spike protein expression within microglia drives chronic neuroinflammation and subsequent neuronal injury or toxicity remain uncharacterized. Our studies established route-dependent delivery and a pathological model in young adult mice, comparing intracranial (IC), intraperitoneal plus intramuscular (IP+IM), and intranasal (IN) administration of engineered VRPs carrying Spike or mutant Spike replicon RNAs, and examined their effects on microglia-targeted delivery and neuroinflammatory responses in the brain. Intranasal DiR-labelled endothelial cells (EC)-derived exosome biodistribution experiments were utilized for testing secondary exosomes-mediated brain delivery and microglial uptake. Our in vitro and in vivo experimental models demonstrated highly specific and robust Spike protein expression in microglia, with minimal off-target delivery to astrocytes or neurons. Following delivery, we observed a profound shift in the microglial phenotype, characterized by the upregulation of pro-inflammatory cytokines (TNF-α, and IL-6) alongside

extensive reactive gliosis. More importantly, this localized Spike expression triggered chronic neuroinflammation, leading to downstream synaptic loss and localized neuronal apoptosis. These findings establish VRPs as a highly effective tool for microglia-specific delivery of replicon RNA in the brain. Furthermore, this model highlights the direct role of microglial Spike expression in driving neuroinflammatory cascades, providing valuable insights into the mechanisms of SARS-CoV-2-induced neurological complications.

24-EP2 *24 Aug 2026*

Oxidative Stress Promotes Pathological TDP-43 Protein Accumulation via the ERK1/2 Signaling Pathway

Yuge Chang[1] ***(Presenter)***, *Weiwei Cheng*[1]

Presenter: *Yuge Chang*

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Abstract

Oxidative stress is a major risk factor for Alzheimer's disease (AD), but the underlying molecular mechanisms remain elusive. Pathological TAR DNA-binding protein-43 (TDP-43) is a key hallmark of multiple neurodegenerative diseases, including AD, and has been closely linked to oxidative stress. In this study, we demonstrated that oxidative stress induced aberrant activation of ERK1/2, promoted TDP-43 pathology, and caused massive neuronal death. Pharmacological inhibition with U0126 or genetic knockdown of ERK1/2 effectively rescued these phenotypes. These findings were further validated in induced pluripotent stem cells (iPSCs)-derived neurons, where oxidative stress also triggered pronounced cytoplasmic mislocalization of the TDP-43. Mechanistically, we found that oxidative stress significantly increased Hsp70 phosphorylation, which markedly enhanced the binding of Hsp70 to TDP-43 C-terminal fragments (CTFs) and promoted the recruitment of CHIP-a co-chaperone CHIP with E3 ubiquitin ligase activity-to the Hsp70-TDP-43 complex. Consequently, CHIP-mediated K63-linked ubiquitination of TDP-43 CTFs was substantially increased, while K48-linked ubiquitination remained unchanged. This shift in ubiquitination patterns impaired the efficient degradation of TDP-43 through ubiquitin–proteasome pathway, leading to their accumulation in the insoluble protein fraction and subsequent cytotoxicity. Altogether, our work elucidates a novel signaling mechanism that links oxidative stress to TDP-43 pathology, and identify the ERK1/2 pathway as a promising therapeutic target for TDP-43-associated neurodegenerative diseases.

24-EP3 *24 Aug 2026*

Inhibiting Connexin 43 Hemichannel Opening Tempers Irradiation-induced p65 NF-κB And YAP Modulation In Astrocytes And Limits Astrogliosis

Hanane TAHIRI[1], *Nathalie Rouach*[2], *Katja Witschas*[1,3], *Luc Leybaert*[1], *Alain J. Labro*[1]

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Abstract

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Background

While reactive astrogliosis is a neuroprotective response to injury, excessive activation can become pathological, driving gliovascular unit dysfunction and neuroinflammation. Astrocytes maintain brain homeostasis and blood-brain barrier (BBB) integrity via endothelial cross-talk, mediated largely by Connexin 43 (Cx43) gap junctions and hemichannels (HCs). While HCs remain mostly closed under basal conditions, stress-induced opening serves as a pathological pathway. This study investigated how irradiation-induced Cx43HC opening in astrocytes drives acute neuroinflammation and astrogliosis.

Methods

C57BL/6 mice, global Cx30 knock-out mice, or MK4 mice received 20 Gy cranial irradiation. Cx43HC opening was prevented, pharmacologically with TAT-Gap19 (7.5 µmol/kg) or genetically in MK4 mice harboring Cx43 variants with mutated MAPK phosphorylation sites. Inflammatory responses and astrogliosis were analyzed via Western blotting and immunohistochemistry between 0.5-24 h post-irradiation. BBB permeability was assessed using 10 kDa Dextran Texas Red.

Results

Irradiation triggered a biphasic response in astrocytes within 24 h. Initial pro-inflammatory signaling involved NF-κB activation, YAP inactivation, and the induction of a neurotoxic phenotype (production of complement component 3, C3). This coincided with a loss of homeostatic markers, specifically the downregulation of Kir4.1 and Kir6.1, and the upregulation of Cx43. The pro-inflammatory signaling was transient with NF-κB and YAP phosphorylation states and C3 levels returning to baseline by 24 h. At this time, a shift toward a proliferative astrocyte state occurred, marked by nuclear YAP translocation and increased Kir4.1/AQP4 co-localization, accompanied by detectable astrogliosis (marked by GFAP/S100β). Inhibiting Cx43HC opening significantly tempered the pro-inflammatory response and prevented both astrogliosis and BBB alterations. Astrocyte-specific Cx30 deficiency, similarly reduced astrogliosis, though less effectively than reducing Cx43HC opening.

Conclusions

Radiation-induced cellular stress promotes Cx43HC opening, stimulating a transient pro-inflammatory NF-κB/YAP response and the induction of neurotoxic astrocytes, leading to astrogliosis. Consequently, Cx43HC represents a target to modulate excessive astrocyte signaling that drives radiation-induced neurotoxicity.

25-P037 *25 Aug 2026*

LKB1-dependent Dendritic Morphogenesis in Horizontal Cells Regulates Spatial Organization of Photoreceptor Ribbon Synapses

Akari Hagiwara ***(Presenter)***[1,7]*, Yuno Asai*[1]*, Saki Kawamura*[1]*, Yamato Hida*[2]*, Kagayaki Kato*[3,4]*, Toshihisa Ohtsuka*[2]*, Nobuhiko Ohno*[5,6]

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Abstract

The vertebrate retina forms a highly organized laminated structure in which neuronal morphology and synaptic architecture are precisely coordinated to enable visual processing. The serine/threonine kinase LKB1 is a key regulator of intracellular signaling and neuronal morphogenesis. In photoreceptors, LKB1 controls axonal dynamics through downstream AMPK signaling, and its dysfunction induces ectopic ribbon synapse formation. However, the role of LKB1 in horizontal cells (HCs) and its contribution to synaptic organization remain unclear. Here, we generated HC–specific LKB1 conditional knockout mice (LKB1-HC) to investigate how LKB1-dependent HC morphogenesis influences retinal circuit formation. While retinal lamination was preserved in LKB1-HC mice, HCs exhibited reduced neurite branching, accompanied by aberrant ectopic localization of photoreceptor synapses.

To determine whether HC LKB1 affects ribbon synapse architecture at the ultrastructural level, we performed serial-section electron microscopy and three-dimensional reconstruction of cone photoreceptor terminals. Quantitative analyses revealed a slight reduction in cone terminal volume and an increase in ribbon synapse density within terminals in the LKB1-HC mice. However, the nearest distance between ribbon synapses was not significantly different between control and LKB1-HC. To further evaluate spatial distribution, an approximate basal plane of the cone pedicle was defined based on segmentation of the postsynaptic densities (PSDs) of OFF bipolar cells. Using this reference plane, ribbon synapses were positioned significantly closer to the basal surface in LKB1-HC mice. In contrast, ribbon orientation, quantified by applying principal component analysis (PCA) to voxel coordinates, showed little difference between groups. Overall, LKB1-dependent HC morphogenesis contributes to the fine spatial organization of ribbon synapses within photoreceptor terminals.

25-P038 *25 Aug 2026*

Neuroprotective Effects of Clozapine Against Phencyclidine-Induced Cytotoxicity in SH-SY5Y Cells

*Akira Yoshimi **(Presenter)**[1], Nagi Miyata[1], Misaki Kumagae[1], Yuki Saito[1], Masaki Kano[1], Shinji Kitagaki[2], Yukihiro Noda[1]*

Presenter: *Akira Yoshima*

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Abstract

Background

Neurodevelopmental abnormalities are implicated in the pathophysiology of schizophrenia. Clozapine (CLZ), an atypical antipsychotic, has demonstrated neuroprotective and neuroplasticity-enhancing effects and is effective for treatment-resistant psychiatric symptoms. However, its detailed molecular mechanisms remain unclear. Phencyclidine (PCP), which induces schizophrenia-like symptoms, is widely used as a pharmacological model for investigating the pathophysiology of schizophrenia. This study investigated the effects of CLZ on PCP-induced cytotoxicity in the human neuroblastoma cell line SH-SY5Y by assessing cell viability, membrane damage, apoptotic progression, and gene expression related to cell death and survival.

Methods

SH-SY5Y cells were exposed to PCP (25, 50, and 100 μM) and CLZ (10, 25, 50, and 100 μM), either alone or in combination, for 24 hours. Cell viability was assessed using the MTS assay, cytotoxicity using the LDH assay, apoptotic progression was evaluated by flow cytometry, and gene expression was analyzed by real-time PCR.

Results

Exposure to 100 μM PCP significantly decreased cell viability compared to the control group. This reduction was attenuated by pre-exposure to 10 or 25 μM CLZ. In contrast, no significant differences were observed in cytotoxicity or apoptotic progression between PCP-exposed cells and cells pre-exposed to CLZ or exposed to CLZ alone. Exposure to 100 μM PCP significantly increased CASP3 mRNA expression, an executioner of apoptosis, and showed a trend toward an increased BAX/BCL2 ratio. These PCP-induced increases were attenuated by pre-exposure to 25 μM CLZ.

Conclusions

PCP exposure induces cytotoxicity and apoptotic signaling in SH-SY5Y cells, with reduced cell viability and increased CASP3 expression and BAX/BCL2 ratio. CLZ pre-exposure mitigates these effects, suggesting a preventive neuroprotective role against PCP-induced cellular damage.

Acknowledgements

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25-P039 *25 Aug 2026*

Standardized Extract of Centella asiatica (SECA) Attenuates Nitric Oxide Production and NF-κB Activation in Lipopolysaccharide-Induced Microglial Cells: In Vitro and In Silico Evidence

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Abstract

Alzheimer's Disease (AD) is associated with chronic neuroinflammation, in which hyperactivated microglia release pro-inflammatory mediators, including nitric oxide (NO). Activation of the Toll-like receptor 4/myeloid differentiation factor-2 (TLR4/MD-2) complex by lipopolysaccharide (LPS) triggers downstream inflammatory signaling pathways, particularly nuclear factor-kappa B (NF-κB), leading to microglial activation and inflammatory mediators production. Centella asiatica, traditionally used as a neuroprotective herb, contains four major triterpenes - asiatic acid, asiaticoside, madecassic acid, and madecassoside. While standardized extract of Centella asiatica (SECA) exhibits anti-inflammatory activity, the contributions of its individual triterpenes and their potential interactions with TLR4/NF-κB pathway remain unclear. Ultra-performance liquid chromatography (UPLC) was performed to identify and quantify triterpenes in SECA. The anti-neuroinflammatory effects of SECA and its triterpenes were evaluated using Griess assay by measuring NO production in LPS-induced BV2

microglial cells. The expression of phosphorylated NF-κB (p-NF-κB) and total NF-κB were evaluated by Western blot analysis. Molecular docking using AutoDock was performed to predict potential interactions of the triterpenes in SECA with the TLR4/MD-2 complex (PDB: 3VQ2). SECA contained highest concentration of asiaticoside (34.9%) followed by madecassoside (34.8%), madecassic acid (18.4%) and asiatic acid (12.0%). SECA and its triterpenes significantly reduced NO production at highest concentrations (100 μg/mL and 100 μM), with SECA showing the strongest inhibitory activity, suggesting synergistic effects. SECA attenuated NF-κB activation by reducing p-NF-κB expression while maintaining total NF-κB levels. Molecular docking demonstrated favorable binding affinities between triterpenes with TLR4/MD-2 (−7.8 to −9.6 kcal/mol), with asiaticoside exhibit the strongest binding strength. These findings suggest that SECA may attenuate microglial inflammatory response through modulation of TLR4/NF-κB signaling pathway. Together, the in vitro and in silico results strengthen the rationale for SECA as a promising natural therapeutic candidate to modulate neuroinflammation in AD.

25-P040 *25 Aug 2026*

Mitochondrial OXPHOS Imbalance and Impaired Mitophagy in Fragile X Syndrome

*Byung Geun Ha **(Presenter)**[1], Jung-Yoon Heo[1], Yu-Jin Jang[1], Sung-Jin Jeong[1]*

Presenter: *Byung Geun Ha*

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Abstract

Fragile X Syndrome (FXS) is characterized by metabolic dysregulation and impaired neural proteostasis, though the precise mechanisms linking mitochondrial dysfunction to proteotoxic accumulation remain elusive. This study delineates a pathogenic basis of FXS by integrating proteomic profiling of cortical tissue and neuron-derived extracellular vesicles (EVs) from FXS mouse model, Fmr1-/y (Fragile X Messenger Ribonucleoprotein 1 knockout). A proteomic analysis of the Fmr1-/y cortex revealed a stoichiometric imbalance within the mitochondrial oxidative phosphorylation (OXPHOS) system and Fmr1-/y neurons-derived EVs exhibited a severe deficiency in mitochondrial OXPHOS proteins. We examined whether the imbalance of the mitochondrial OXPHOS system affects the mitochondrial function in neurons. A functional assay was performed in primary neurons derived from Fmr1-/y cortex, revealing a chronic mitochondrial hyperpolarization. In addition to functional deficit, an aberrant, collapsed distribution of vimentin intermediate filaments and a significant downregulation of key mitophagy-related proteins were observed in neurons of Fmr1-/y mice.

In summary, we hypothesize that metabolic-driven mitochondrial dysregulation serves as a core driver of cortical proteotoxic accumulation, leading to failure loading of the mitochondrial protein into EVs in Fmr1-/y neurons, which is associated to mitochondrial dysfunction. This study provides insight into the repositioning of FXS fundamentally as a neurodevelopmental disorder of mitochondrial quality control.

This research was funded by KBRI basic research programs (26-BR-02-01, 26-BR-05-04), and the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (RS-2025-02315195 & RS-2025-25422000).

25-P041 *25 Aug 2026*

Cytoplasmic FUS triggers dendritic and synaptic deficits in hiPSC-derived cortical neurons which is uncoupled from aggregation: from cell culture to xenotransplantation

*Tian Wang **(Presenter)**[1], Angelo D. Flores[1], Quanwei Lyu[1], Alex Yat-Ping Tsui[2], Ying Cai[3], Zhinan Lin[1], Yijun Xu[1], Chi Him Eddie Ma[1], Xiaowei Zhu[1], Jacque Pak Kan Ip[3], Daisy Kwok-Yan Shum[2], Ying-Shing Chan[2], Kwok-On Lai[1]*

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Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are incurable and fatal neurodegenerative diseases. Mis-localization of the DNA/RNA-binding protein fused in sarcoma (FUS) in the cytoplasm and its aggregation into cytoplasmic inclusions are implicated in neuronal degeneration in some of the ALS and FTLD patients. However, cytoplasmic mis-localization of FUS—caused by mutations that disrupt the nuclear localization signal (NLS)—leads to defective synaptic development and function in rodent brain neurons independently of FUS aggregation. Whether similar deficits arise in human neurons independently of FUS aggregate formation remains unexplored. Furthermore, although

stressful life experiences are an environmental risk factor for neurodegenerative diseases including FTLD, their effects on human neurons at the cellular level remain challenging to study. Using CRISPR/Cas9-mediated genome editing, we generated human induced pluripotent stem cell (hiPSC) clones carrying ALS-associated mutations in the NLS of FUS, along with a C-terminal V5-tag. After differenting the hiPSC clones into synapse-forming cortical neurons in vitro, we found although cultured hiPSC-derived neurons carrying the FUS-P525L mutation only exhibit diffuse cytoplasmic FUS without detectable aggregation, they display reduced dendritic arborizations and PSD-95 density. Through transplantation of hiPSC-derived neural progenitors into the prefrontal cortex and hippocampus of NOD/SCID mice, P525L-FUS mutant neurons transplanted into the hippocampus showed significant dendritic spine loss specifically after the host mice were subjected to chronic restraint stress. This occurred despite no increase in cytoplasmic FUS aggregation or stress granule formation in the mutant grafted neurons following chronic stress. We demonstrate, for the first time, the interplay between genetic deficits and stressful experiences in aggravating the disease phenotype of human brain neurons.

This study is supported in part by the Research Grant Council of Hong Kong [General Research Fund (GRF) 11101624 and 11102422; Collaborative Research Fund (CRF) C1024-22G] and the US National Academy of Medicine (Healthy Longevity Catalyst Award HLCA/M-106/25

25-P042 *25 Aug 2026*

The Role of BMP signaling in Maintaining Choroid plexus Epithelial Cell Identity

*Ho Hin Cheung **(Presenter)**[1], Chun Ning Leung[1], Kin Ming Kwan[1,2,3,4]*

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Abstract

Choroid plexus (ChP) is a specialized epithelial tissue that produces cerebrospinal fluid and forms the blood-CSF barrier. BMP signaling is known to regulate polarity and integrity in diverse epithelial tissues. However, its role in maintaining epithelial identity in choroid plexus has not been investigated.

In this study, we developed a ChP-specific gene deletion model by performing intracerebroventricular (ICV) injection of TAT-Cre recombinase into neonatal (P0–P1) mice. Successful ventricular distribution was confirmed by injection of 0.1% trypan blue, which rapidly flowed through all ventricles. Validation using Rosa26-YFP reporter mice demonstrated bright and highly specific YFP expression restricted to the choroid plexus epithelium, with minimal recombination detected in other brain regions.

TAT-Cre was then injected into Smad1/5 floxed (Smad1/5 fl/fl) neonatal mice to induce conditional knockout. Western blot analysis at 36 hours post-injection showed significant downregulation of both Smad1 and Smad5 protein levels in the choroid plexus. This was further confirmed by semi-quantitative RT-PCR, which showed reduced Smad1 and Smad5 mRNA expressions. Notably, loss of Smad1/5 also led to a significant reduction in Syndecan-1 (Sdc1) expression at both protein and mRNA levels.

These preliminary findings suggest that BMP signaling via Smad1/5 may play a role in maintaining choroid plexus epithelial identity after birth, at least partly through regulation of Syndecan-1. Future studies will investigate whether Smad1/5 deletion affects blood-CSF barrier integrity by assessing leakage across the choroid plexus, changes in tight junction proteins, and alterations in cell adhesion properties, particularly Syndecan-1-mediated interactions with the extracellular matrix. This work lays the foundation for understanding the postnatal functions of BMP signaling in choroid plexus epithelial maintenance and barrier function

The work was supported by the grants from the Research Grant Council of the Hong Kong Special Administration Region (project nos. GRF 14112224, 14114921, CRF C4002-21E and AoE/M-05/12) and a Chinese University of Hong Kong Direct Grant for Research

25-P058 *25 Aug 2026*

SENP8 Regulates the Deneddylation Process Critical for Neuronal Development

Seungha Lee ***(Presenter)***[1], *Young Ho Suh*[2]

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Abstract

Neddylation is a cellular process in which the neural precursor cell expressed, developmentally down-regulated 8 (NEDD8) is conjugated to the lysine residue of target proteins via serial enzymatic cascades. Recently, it has been demonstrated that neddylation is required for synaptic clustering of metabotropic glutamate receptor 7 (mGlu7) and postsynaptic density protein 95 (PSD-95), and the inhibition of neddylation impairs neurite outgrowth and excitatory synaptic maturation. In this study, we hypothesized that deneddylating enzymes can regulate neuronal development by counteracting the process of neddylation. We find that the SUMO peptidase family member, NEDD8 specific (SENP8) acts as a key neuronal deneddylase targeting the global neuronal substrates in primary rat cultured neurons. We demonstrate that SENP8 expression levels are developmentally regulated, peaking around the first postnatal week and gradually diminishing in mature brain and neurons. We find that SENP8 negatively regulates neurite outgrowth through multiple pathways, including actin dynamics, Wnt/β-catenin signaling, and autophagic processes. Alterations in neurite outgrowth by SENP8 subsequently result in the impairment of excitatory synapse maturation. Our data indicate that SENP8 plays an essential role in neuronal development and is a promising therapeutic target for neurodevelopmental disorders.

Acknowledgments

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25-EP1 *25 Aug 2026*

Single-nucleus multiomics reveals a unique signature in dystrophic microglia from Alzheimer's disease patients.

Akhrorbek Akhmedov ***(Presenter)***[1], *Yongjin Yoo*[1]

Presenter: *Akhrorbek Akhmedov*

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Abstract

Microglia, key mediators of neuroinflammation, play a critical role in the development of Alzheimer's disease (AD). However, the molecular identity of specific subpopulations remains elusive. Dystrophic microglia – a distinct morphological phenotype characterized by cytorrhexis, spheroidal swelling, and beaded processes– are found in disproportionately high numbers in the postmortem brains of people with Alzheimer's disease. Despite decades of histopathological analysis, the transcriptomic characteristics of these cells and the regulatory processes that lead microglia into dystrophy are still not clearly understood.

In this study, we integrated single-nucleus RNA sequencing (snRNA-seq) and single-nucleus assay for transposase-accessible chromatin sequencing (snATAC-seq) datasets encompassing 86 donors. Microglia were resolved into nine transcriptional states, one of which was enriched for iron-handling genes (FTL, FTH1), proteotoxic stress chaperones, and ribosomal genes. We annotated this cluster as dystrophic; it displayed the largest disease-responsive transcriptional program and was placed by pseudotime analysis at the terminal endpoint of a trajectory. Multi-omic cross-validation defined a core dystrophic signature, identified , HMGA1, MYC and HSF1 as candidate transcription factor drivers, and nominated S100A9, S100A4, TXNRD1, and the complement pathway as candidate therapeutic targets for AD.

Funding. This work was supported by the Lee Jong-Wook Fellowship through KOFIH.

26-P049 *26 Aug 2026*

A dynamic landscape of lineage-defined oligodendrocytes in the mouse cortex

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Presenter: *Yuqi Cai*

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Abstract

# These authors contributed equally to this work.

Forebrain oligodendrocytes (OLs) arise from multiple developmental origins, yet whether and how distinct embryonic lineages differentially contribute to postnatal OL dynamics and repair remains unknown. In our previous work, we established combinatorial genetic strategies tor efficient tracking and direct visualization of mature OLs from different embryonic origins. These tools revised the canonical model of forebrain OL origins and provided experimental access for investigating lineage-specific development and function under physiological and pathological conditions. In this study, we further developed genetic tools that enable quantitative analysis of lineage-defined oligodendrocyte precursor cells (OPCs) and their mature OL progeny. Using these tools, we longitudinally tracked the distribution of cortical OPCs and OLs during postnatal development and following demyelination insults. Our results reveal lineage-, age- and region-dependent differences in OPC proliferation, OL differentiation and regenerative responses. Together, these findings reveal lineage-dependent patterns of cortical OPC/OL dynamics during postnatal development and regeneration, and establish a genetic framework for dissecting how developmental origin influences myelination and remyelination in the mouse cortex.

Circuit Dynamics and Oscillations

25-P043 *25 Aug 2026*

Voltage imaging with ASAP7 reveals decoupled simple and complex spike synchrony in Purkinje cells in vivo

Qiyuan Liang ***(Presenter)***[1], *Yukun A. Hao*[2,3], *Sungmoo Lee*[2,3], *Huiqi Zhang*[1], *Guangnan Tian*[1], *Michael Z. Lin*[2,3], *Michael Häusser*[1]

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Abstract

Purkinje cells (PCs) are the sole output neurons of the cerebellar cortex and key to motor coordination and learning. They integrate massive streams of sensorimotor information via parallel fibers to modulate high-frequency simple spikes (SS), while simultaneously receiving potent "error signals" from climbing fibers that trigger low-frequency complex spikes (CS). The synchrony of complex spikes is a well-established mechanism for encoding motor errors and regulating synaptic plasticity, but the spatiotemporal organization of SS remains poorly understood. This gap exists because calcium imaging lacks the temporal resolution to capture fast SS firing (60–100 Hz), while electrophysiology lacks spatial information.

Here, we overcame these limitations by combining the latest negatively tuned genetically encoded voltage indicator (GEVI) ASAP7 with Acousto-Optic Deflector (AOD)-based random-access two-photon microscopy. This system enables inertia-free, multi-point scanning to achieve kilohertz sampling rates for recording voltage signals across populations of Purkinje cell somata in awake mice. The fast kinetics of ASAP7 enabled the first optical resolution of SS dynamics with single-spike fidelity. Our preliminary results demonstrate that the synchrony of simple and complex spikes is decoupled, consistent with the distinct input pathways modulating CS and SS. By simultaneously mapping the spatial synchrony of both simple and complex spikes, this toolkit opens a new window into the spatiotemporal codes underlying cerebellar computation.

This project is supported by JC STEM Lab of Neural Computation, and the National Institutes of Health (NIH) BRAIN Initiative (Grants U01 NS103464, RF1 MH114105, and 1R01NS123681)

25-P044 *25 Aug 2026*

Sustained astrocyte-neuron coupling marks an inference state in the hippocampus revealed by duration-explicit state modeling

Zhenyuan Wang ***(Presenter)***[1]

Presenter: *Zhenyuan Wang*

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Abstract

The ability to infer threat, extending conditioned fear to cues never directly paired with harm, depends on the hippocampus binding separately learned associations into a coherent prediction. Astrocytes are increasingly implicated in shaping hippocampal ensemble activity, yet whether they participate in the transitions that constitute inferential reasoning has remained unknown, in part because neuronal and glial signals interact over markedly different timescales that conventional analyses cannot jointly resolve. To address this, we develop a Hidden Semi-Markov Model that infers the sequence of latent brain states from simultaneous neuronal spiking and astrocytic calcium activity, recorded through a custom optoelectrode in dorsal CA1 of freely behaving mice. Unlike standard hidden Markov models, which assume that states decay at a constant rate and so cannot represent how long a computation is held, our framework models the dwell time of each state explicitly, allowing it to detect sustained neuro-astrocyte coupling and to distinguish a deliberative state from transient ones. The model resolves four recurring states, a resting state, a transient perception state, a prolonged inference state, and a freezing state tied to defensive behavior. The ordered progression into the inference state emerges only after an inferential association is learned, its occupancy predicts an animal's fear response to the indirectly associated cue, and within it astrocytic calcium signals couple tightly to neuronal firing and consistently lead it in time. These results identify astrocytes as active temporal organizers of hippocampal inference and provide a general framework for dissecting neuro-glial computation across cognitive states.

25-P045 *25 Aug 2026*

Astrocytic G-Protein-Coupled Receptors Signaling in the Hippocampus Modulates Neuronal Computation Underlying Inferential Fear Memory Through L-Lactate in Mice

Zhongqi Charles Fu ***(Presenter)***[1], *Zhen WANG*[1], *Ying LI*[1]

Presenter: *Zhongqi Charles Fu*

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Abstract

Higher-order forms of emotional fear require inferential associative learning and memory. Whether and how the astrocytes modulate the internal models for fear inference are not known. Here, we show that following paired auditory-visual stimuli training, the direct visual-foot shock fear conditioning can generate indirect auditory inference fear memory. By computational analysis of electrophysiology recording we show that the hippocampal neuronal forward-looking code participates in the emotional fear inference. Manipulation of dCA1 astrocytes by expressing the G-coupled receptors hM3q and hM4Di bidirectionally modulates fear inference. Specific knockdown of astrocytic Excitatory amino acid transporter 2 impairs fear inference. locally injecting L-Lactate into dCA1 rescued the associations memory deficit. Our results suggest that hippocampal neuron contributes to reasoning by compute a prospective code for inferred fear associations. Astrocytic G-protein-coupled receptor, glutamate transporter and L-lactate signaling play a key role in regulating the processing of inferred aversion emotion associations by higher-order internal models.

25-P046 *25 Aug 2026*

Low-frequency electrotherapy for neocortical epilepsy depends on sensory deficits

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Presenter: *Yoon Ji Kwon*

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Abstract

Neuromodulation for epilepsy most frequently utilizes high-frequency stimulation to suppress seizure activity, and low-frequency stimulation (LFS) when the former fails. Both protocols are known to induce synaptic plasticity, yet it is not known whether the mobilization of plasticity mechanisms is required to suppress seizure. In addition, it has not been examined how cortical neuromodulation may be shaped by sensory loss and subsequent altered cortical plasticity. In this study, the mGluR1/5-activating paired-pulse LFS (pp-LFS) protocol was delivered to the primary auditory cortex (A1) surface via graphene-based electrocorticography (ECoG) arrays in mouse models of noise-induced hearing loss (NIHL) and picrotoxin (PTX)-induced neocortical epilepsy. In non-seizure animals, pp-LFS induced long-term synaptic potentiation (LTP) in the A1 surface layers both in vivo and in brain slices, whereas pp-LFS-LTP was significantly disrupted in animals with acquired NIHL. In the PTX model, cortical pp-LFS effectively suppressed the progression of epileptiform spikes and behaviour. Lastly, using NIHL as a plasticity-impaired model, we demonstrate that pp-LFS-induced plasticity is required for its anti-epileptic effects, as NIHL animals exhibited increased rather than suppressed seizure-like activity after pp-LFS. This study proposes pp-LFS as an mGluR1/5-driven neuromodulation protocol for the treatment of neocortical epilepsy, and explicitly demonstrates that sensory deficits shape the outcome of seizure electrotherapy in the epileptic brain.

RGC, CityUHK 11101725

25-P047 *25 Aug 2026*

Day-night dynamics of brain states and behaviors revealed by 24-hour stereoelectroencephalography signals from epileptic patients

Ting Yu ***(Presenter)***[1], *Yao CHEN*[2], *Chuanliang HAN*[3], *Rosa H. M. CHAN*[4], *Vincent C. K, CHEUNG*[1]

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Abstract

Many basic physiological processes in the brain and body are regulated by the brain's circadian rhythms. Yet, little is known about the neural underpinnings, dynamics, and functions of the day-night cycles of whole-brain activity in humans. Here, we exploited the stereoelectroencephalographic (SEEG) electrodes implanted in 4 epileptic patients (118-165 channels per subject) for monitoring seizures to probe activities of multiple cortical and deeper brain regions throughout the day. Continuous 24-hour SEEG and synchronized video data of the subjects were recorded for 2-7 days for brain state-behavior correlations. Throughout, subjects behaved normally without restrictions. Filtered SEEGs were re-referenced (bipolar method). Videos were manually annotated for different behaviors. Brain states were characterized by SEEGs' power spectral density (PSD) and functional networks based on correlations and coherence between channels. Unsupervised k-means clustering was used to identify common brain states over 24-hour periods. Similarities between timing of occurrence of brain states and behaviors were calculated using Jaccard coefficient. We first identified several recurrent frequency boundaries (~8, 13, 33, 65 Hz) which appeared as distinct discontinuities in PSD heatmaps and delineated frequency bands with distinct sleep-wake modulations. White-matter channels exhibited increased delta-band PSD and reduced high-frequency PSD during sleep. Brain states classified from interregional correlations showed state-dependent network organization, with eating-related states characterized by widespread inverse co-modulation and sleep-related states, by increased positive co-modulation. Coherence analysis revealed stable interhemispheric insular coupling in the delta band throughout the day, strong amygdala-hippocampal coupling in multiple bands during sleep and phone use, and two distinct beta-band sleep states involving language-related and hippocampal-limbic networks. Our findings show that coordinated day-night cycles of activity can be identified in multiple brain regions, but their temporal co-fluctuation and spectral coupling are flexibly modified to accommodate specific behaviors. Work supported by CUHK (SBS & GCNI) and Hong Kong RGC (STG1/M-401/24-N).

25-P048 *25 Aug 2026*

Organization of Posterior Parietal Inputs to the Retrosplenial Cortex in Mice

Haruka Umeno ***(Presenter)***[1], *Ken-Ichiro TSUTSUI*[1], *Shinya OHARA*[1]

Presenter: *Haruka Umeno*

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Abstract

Successful navigation depends on the integration of allocentric and egocentric spatial information. The retrosplenial cortex (RSC) is thought to play a central role in this process by integrating spatial inputs from multiple brain regions. The RSC is anatomically divided into the granular RSC (gRSC) and dysgranular RSC (dRSC). Previous studies in rodents and primates have suggested that these subdivisions receive distinct spatial inputs: the gRSC primarily receives allocentric information from the hippocampal formation, whereas the dRSC receives egocentric information mainly from the posterior parietal cortex (PPC). Although hippocampal inputs to the gRSC have been extensively studied, partly because of their relevance to memory and allocentric navigation, the detailed organization of PPC inputs to the RSC remains poorly understood.

Here, we reexamined PPC inputs to the RSC in mice. To map inputs to the RSC, we injected retrograde adeno-associated virus (AAV) expressing a fluorescent protein into the RSC and found that both subdivisions receive inputs from the PPC, in contrast to previous reports. Among PPC subregions, retrogradely labeled neurons were particularly abundant in the medial PPC (mPPC), indicating that the mPPC is a major source of input to the RSC. We next used an anterograde AAV to visualize mPPC projections to the RSC. Consistent with the retrograde tracing results, mPPC axons were densely distributed in both the gRSC and dRSC.

To identify the postsynaptic targets of this pathway, we combined optogenetics with patch-clamp recordings in acute brain slices. Channelrhodopsin-2 was expressed in mPPC neurons to selectively stimulate their axons, and light-evoked responses were recorded from RSC neurons to determine which cell types receive mPPC input.

Together, these findings suggest that the gRSC, in addition to the dRSC, is a major target of parietal input. This revised organization provides new insight into how the RSC processes egocentric information relevant to spatial navigation.

25-P050 *25 Aug 2026*

Synfire Chains in Theta-nested Gamma Oscillations balances Prediction and Vigilance

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Abstract

Traditional views attribute vigilance primarily to the sensorimotor system. However, emerging experimental evidence implicates hippocampus does interact with locomotor processes in active environmental sampling and forward planning. Thus, we propose that hippocampal theta-nested gamma oscillations (TGOs) support both predictive planning for reward retrieval and vigilance against unexpected threats, implemented via synfire chains (SFCs). Through computational model using a biologically plausible spiking neural network model, we reproduce key experimental observations and exploit chain length and separation in SFC to demonstrate the positive correlation between theta frequency and locomotion velocity optimally balances predictability and alertness. These findings provide a unified mechanistic account of how TGOs coordinate planning and vigilance in the hippocampus during goal-directed navigation. Specifically, theta oscillations support self-location awareness, gamma oscillations enhance predictive coding, and their coupling ensures sufficient temporal windows for prospective planning.

Funding. This work was supported partly by the National Natural Science Foundation of China (Grant No. 12175242), the Natural Science Foundation of Zhejiang Province (Grant No. LZ24A050007), the Research Initiation Project of Zhejiang Lab (No. K2022KI0PI01), and the Zhejiang Lab Open Research Project (No. K2023KI0AA03).

Cognition and Behavior

24-P002 *24 Aug 2026*

Comprehensive Mapping of Neuronal Inputs to dorsal CA1 Using Retrograde Tracing to Elucidate Memory Mechanism

Yik Lok Chung ***(Presenter)***[1], *Hao-Yu XU*[1], *Pak-Kan Jacque IP*[1,2]

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Abstract

Objective

The trisynaptic pathway, involving the entorhinal cortex, dentate gyrus, CA3, and CA1 regions of the hippocampus, is a key theory explaining memory mechanisms, but it is far from capturing the full complexity of the process. Emerging research indicates that various cortical regions significantly contribute to memory, highlighting the need for detailed neural mapping. This study aims to provide a comprehensive mapping of the neuronal inputs to the CA1 region to gain deeper insights into memory coordination.

Methods

The study utilized rabies viral vectors to trace excitatory neurons connected to the hippocampal CA1. Brain tissues were sectioned and imaged to map neuronal input regions. QuPath and ABBA software were used to quantify labelled cells, and specific laminar layers and AP coordinates that transmit signals to CA1 were identified.

Results

Analysis revealed that over 50% of neuronal inputs to CA1 originate locally within the hippocampus, specifically from CA1, CA3, and the dentate gyrus. the CA1 also receive major projection from cortical regions including the entorhinal cortex, with both medial and lateral parts showing distinct connections. Other regions such as the retrosplenial and perirhinal cortices exhibit significant ipsilateral connectivity with CA1. We extended our investigation to the perirhinal cortex, employing the same tracing technique to disynaptically map the upstream regions of the perirhinal cortex that project to the CA1 region. Our findings indicate that PERI-CA1 neurons receive inputs from various sensory association cortices, including olfactory, visual, and auditory cortices.

Conclusion

The study quantified the regions providing input to CA1 and identified specific laminar layers potentially involved in spatial learning and memory. Future research will focus on how these upstream regions contribute to different memory processes, employing single- cell sequencing to observe transcriptomic changes during various memory tasks and in memory-associated disease states.

Funding. This work was supported by Lo Kwee-Seong Biomedical Research Fund (J.I), RGC General Research Fund (14119924) Faculty Innovation Award (FIA2020/A/04) from the Faculty of Medicine, CUHK (J.I.), Hong Kong RGC Area of Excellence Scheme (AoE/M-604/16; J.I.), Hong Kong RGC Theme-based Research Scheme (T13-605/18-W; J.I.), Hong Kong PhD Fellowship Scheme (PF22-70986; Y.L.C.).

24-P010 *24 Aug 2026*

The Influence of Affective State Changes on Executive Skills in Valorant Players

Rhia Rajeevan ***(Presenter)***[1]

Presenter: *Rhia Rajeevan*

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Abstract

This study examined the impact of affective state changes on executive functioning in young adult male Valorant gamers. Using a pre-post design, 70–80 participants completed the Positive and Negative Affect Schedule (PANAS) before and after a 30-minute gaming session, followed by the Executive Skills Questionnaire (ESQ). Results showed a significant decrease in positive affect (t=-5.26, p=1.55e-06) and an increase in negative affect (t=4.80, p=8.84e-06) post-gameplay. Regression analysis revealed that increased negative affect significantly impaired flexibility(p=0.035), goal-directed persistence(p=0.013), task initiation(p=0.0339), planning/prioritization(p=0.0038), and working memory(p=0.02). Positive affect was positively associated only with stress tolerance(p=0.0371). These findings highlight the emotional sensitivity of executive functioning in both recreational and competitive gaming contexts.

24-P011 *24 Aug 2026*

Hippocampal Cholinergic Dysregulation Underlies Cognitive Deficits in Mice Exposed to Nano-Neonicotinoid Pesticides

*Dhanshree Sayangrushi Borkar **(Presenter)**[1], Rajesh Singh Yadav[1], Dnyaneshwari Shivshankar Pande[1], Riya Tyagi[1], Shivendra K Chaurasiya[2]*

Presenter: *Dhanshree Sayangrushi Borkar*

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Abstract

Background

The use of nanoformulations of pesticides raises concerns about their potential toxicity and harmful effects. Research highlights the advantages of these pesticides, but studies assessing their neurotoxic effects on non-target organisms are very limited. Hence, it is important to study these nanopesticides to assess the severity of neurotoxic effects.

Objective

The present study investigates the impact of nano-imidacloprid and nano-acetamiprid, both individually and in combination, on cognitive behaviour, cholinergic function and, genetic expression in the hippocampus of the mouse brain.

Methods

Male BALB/c mice (4-6 weeks) were divided into four groups: Control, T1 (Nano-imidacloprid, 25 mg/kg b.w.p.o.), T2 (Nano-acetamiprid, 25 mg/kg b.w.p.o.), and a combination treatment, T3 (Half of both doses), and administered nanoformulations through oral gavage. After 28 days of treatment, mice were sacrificed, and the hippocampus was dissected from the brain. The Y-maze spontaneous alternation and novel arm preference test were performed to assess learning and memory in mice. Cholinergic functions were measured through gene expression (AChE, Bax, Bcl-2, Caspase 3 & 9) using RT-PCR.

Results

A significant decrease in the spontaneous alternation was observed in mice treated with nanopesticides as compared to controls, indicating impaired short-term spatial working memory. Nanopesticide-treated mice exhibited a much lower percentage of entries and significantly less time spent in the novel arm compared to controls. Altered AChE gene expression in the hippocampus of nanopesticide-treated mice was observed as compared to controls. Increased expression of Bax, Caspase-3, and Caspase-9, accompanied by reduced Bcl-2 levels, indicates activation of apoptotic pathways. These findings support nano-neonicotinoid-mediated neurotoxicity involving hippocampal cholinergic disruption and learning and memory impairment.

Conclusion

The present findings demonstrate that subchronic exposure to nanoformulated neonicotinoids disrupts hippocampal cholinergic homeostasis and induces molecular alterations that impair learning and memory.

24-P012 *24 Aug 2026*

Cognitive Polygenic Scores and Executive Function Performance in Schizophrenia Spectrum Disorders

*Victoria Plakunova **(Presenter)**[1], Margarita Alfimova[1], Ekaterina Semina[1], Yulia Chaika[1]*

Presenter: *Victoria Plakunova*

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Abstract

Executive functions are related cognitive control processes supporting goal-directed behavior, including cognitive flexibility, interference control, and working-memory updating. GWAS indicate that common executive function has a distinct polygenic architecture and overlaps with psychiatric vulnerability, whereas intelligence is highly polygenic [1, 2]. Whether these predispositions are reflected in controls and schizophrenia-spectrum patients remains unclear.

We examined associations of polygenic scores for executive function and intelligence with executive-control measures in schizophrenia-spectrum patients (n = 215) and controls (n = 186), aged 29.1 ± 8.8 years. Performance was assessed using TMT-B (Trail Making Test Part B), the Stroop Golden interference index [3], and an executive-function composite. TMT-B time was log-transformed, control-standardized, and inverted; Golden scores were control-standardized. Models included

age, sex, group, and genetic principal components; stratified analyses were performed, and negative symptoms were examined using PANSS (Positive and Negative Syndrome Scale).

In the total sample, cognitive polygenic scores showed nominal associations with TMT-B performance (β = 0.090, p = 0.032). Stratified analyses suggested that the associations were driven by controls: higher cognitive polygenic scores were associated with better TMT-B performance (β = 0.171, p = 0.023) and executive-function composite scores (β = 0.151, p = 0.038), whereas no comparable associations were observed in patients. No consistent associations were found for the Stroop Golden interference index. In patients, higher PANSS negative symptoms were associated with poorer TMT-B performance (β = −0.227, p = 0.002), but not with the interference index (β = 0.016, p = 0.821).

These findings suggest that cognitive polygenic scores may be more directly reflected in executive-task performance in controls, whereas in schizophrenia-spectrum disorders this relationship may be obscured by clinical heterogeneity.

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24-P013 *24 Aug 2026*

Evaluation of cognitive performance following Auditory Beat Stimulations in healthy young adults

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Abstract

Background & Objectives

Executive functions (EF) include attention, working memory, cognitive inhibition, and cognitive flexibility are the goal-directed higher order cognition, regulated by the prefrontal cortex. Auditory Beat Stimulation (ABS), particularly binaural beats, has emerged as a non-invasive method of brainwave entrainment, influence the neural activity and cognitive processes. However, evidence regarding its effects on EF remains inconclusive. This study aims to examine the effects of different forms of ABS on EF and their impact on cognition in healthy young adults.

Methods

A double-blind, crossover study was conducted with 30 Indian healthy young adults (mean age: 22.5 ± 3.7). Participants underwent randomly 3 separate ABS sessions, each of 20 minutes duration at a frequencies of 2 Hz (Delta), 6 Hz (Theta), and 10 Hz (Alpha). Each ABS session was with 2 weeks gap between sessions to washout the effect of prior ABS session. EF were evaluated before and after each intervention using PEBL (version 2.0). The tests used were Berg Card Sorting Test (BCST), Corsi Block-Tapping Test (CBTT) and MathPro test to evaluate cognitive flexibility, visuospatial memory, and arithmetic performance respectively. Cognitive scores changes following each ABS were compared pre and post-intervention using paired Student's t-tests.

Results

BCST demonstrated that all three ABS sessions significantly increased the number and shorten the reaction time for correct responses. Total BCST scores showed significant improvement following Theta ABS ($p < 0.026$) and Alpha ABS ($p < 0.025$). Reaction time in MathPro test was significantly shorter for correct responses after Delta, Theta and Alpha ABS, suggesting a positive effect of ABS on cognitive processing and arithmetic task.

Conclusion

ABS of 6 and 10 Hz has the potential to neuro-modulate, can be used for brainwave entrainment to imrove cognition. Further research needed to evaluate its efficacy in cognitive decline patients for cognitive restoration and rehabilitation.

24-P014 *24 Aug 2026*

The role of KIF5B in localization of RNA-binding proteins and specific synaptic modifications in living mouse brain

Hei Man Charlotte Lam ***(Presenter)***[1], *Cora Sau Wan Lai*[1]

Presenter: *Hei Man Charlotte Lam*

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Abstract

KIF5B is a ubiquitously expressed kinesin-1 motor protein that drives anterograde intracellular transport of cargoes along microtubules. Germline loss of KIF5B is embryonically lethal, indicating that it is essential for maintaining basic cellular functions across multiple cell types. Conditional knockout of KIF5B in CaMKIIα-Cre–expressing neurons disrupts transport of the RNA-binding protein fragile X mental retardation protein (FMRP) to spatially-targeted dendritic spines, resulting in impaired learning and memory formation in mice. Beyond neurons, increasing evidence suggests that the molecular composition of dendritic spines is shaped not only by soma-derived mRNAs and motors within neurons, but also by astrocytic transport and extracellular vesicle–mediated exchange of RNA and proteins. While molecular motors such as kinesins are essential for these astrocyte functions, whether KIF5B in astrocytes directly participates in these processes, and how this influences spine plasticity and behavior, remain unknown. This research aims to establish mechanistic links between intracellular RNA-binding protein (RBP) transport, postsynaptic structural remodeling, and learning-related behavioral deficits by combining two-photon (2P) imaging with behavioral analysis in KIF5B conditional knockout mice, thereby elucidating how KIF5B contributes to synaptic plasticity during learning.

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24-P015 *24 Aug 2026*

Value-Based Choice Under Delay and Uncertainty: Links to Interoceptive, Autonomic, and Prefrontal Processes

Suhhyun Park ***(Presenter)***[1], *Seoyoung Choi*[2], *Sanghoon Han*[1,2]

Presenter: *Suhhyun Park*

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[2] *Department of Psychology, Yonsei University, Seoul, Korea, Korea, Republic of*

Abstract

Individuals differ in how they evaluate future rewards that are delayed, uncertain, or both. Although delay discounting and probability discounting have been widely used to study value-based choice, delay and probability are often examined separately, leaving less known about how they are combined within a single choice context. We examined whether individual differences in this integration were related to interoceptive, autonomic, and prefrontal responses. Participants completed standard delay and probability discounting tasks, an integrated decision-making task, a heartbeat counting task, and self-report measures of interoceptive and psychological traits. During the integrated task, participants chose between a safe option and a probabilistic delayed reward while cardiac activity was recorded using PPG and prefrontal hemodynamic activity was measured using fNIRS. Choices varied with both probability and delay: participants selected the probabilistic delayed reward more often when reward probability was high and delay was short, and shifted toward the safe option as uncertainty and temporal cost increased. Importantly, these effects differed across individuals, suggesting variability in sensitivity to delayed and uncertain rewards. Prefrontal hemodynamic responses were greater during choices involving smaller subjective value differences and were associated with individual differences in probability and delay sensitivity. Interoceptive accuracy, interoceptive confidence, and heart rate variability were also associated with choice adjustment, choice stability, and prefrontal engagement. These findings suggest that complex reward choices involving both delay and uncertainty are related to coupled variation in behavior, cardiac physiology, and prefrontal activity.

24-P016 *24 Aug 2026*

Attention and mind wandering is not binary: Exploring the EEG markers of intermediate state between attention and mind wandering

*Amritharekha P **(Presenter)***

Presenter: *Amritharekha P*

Abstract

[Abstract not available]

24-P017 *24 Aug 2026*

Multi-level analysis of stroke-induced cognitive impairment

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Abstract

Objectives

This study investigated remote hippocampal cognitive impairment induced by focal cortical ischemia via distal middle cerebral artery occlusion (dMCAO) in mice and explored its underlying spatiotemporal mechanisms.

Methods: Cognitive function was evaluated using Barnes and T-maze tests. RNA sequencing and qPCR identified and validated differentially expressed genes. Intravital two-photon microscopy tracked blood-brain barrier (BBB) leakage and cerebrovascular remodeling. Glial cells and microvessels were investigated in the peri-infarct and ipsilateral hippocampal regions at different phases post-stroke. Microglial dynamics were quantified via skeletonization and fractal analysis. Synaptic spine density was visualized using epitope-preserving magnified analysis of the proteome (eMAP).

Results

dMCAO induced a delayed, time-dependent deficit in long-term memory during the chronic phase. Transcriptomic profiling revealed a hippocampal-specific downregulation of cognition-associated genes (Npas4, Egr1, Btg2, Adrb1). qPCR confirmed a distinct spatiotemporal shift in gene suppression, transitioning from acute cortical dominance (day 3) to chronic hippocampal-predominant repression (days 60 and 90). Parallel neurovascular pathology showed acute BBB leakage, progressive glial reactivity (acute cortical activation transitioning to chronic hippocampal dominance with microglial process retraction and reduced fractal complexity), and chronic microvascular atrophy. Furthermore, eMAP imaging demonstrated a progressive loss of dendritic spines on pyramidal neurons expanding spatially from the infarcted cortex to the remote ipsilateral hippocampus. Crucially, the timelines of transcriptional silencing, late-stage hippocampal neuroinflammation, and synaptic attrition directly mirrored the delayed behavioral deficits.

Conclusion

Cortical ischemia triggers progressive cognitive decline driven by a causal cascade of chronic hippocampal transcriptional suppression, neurovascular damage, glial reactivity, and synaptic degeneration, establishing a robust pathological timeline for post-stroke secondary neurodegeneration.

Acknowledgements

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24-P018 *24 Aug 2026*

Refinement of task representations in the cortex supporting flexible multitask performance

*Shuting Wang **(Presenter)***[1,2], *Yun Zhu*[2], *Chunyue Li*[3], *Wing-Ho Yung*[2], *Ya Ke*[1]

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Abstract

Executing multiple tasks simultaneously, commonly seen in daily lives such as talking while walking, is a manifestation of the flexibility of our cognitive functions. However, humans have limited ability in performing such tasks, which is often exacerbated in a variety of neurological diseases. Deciphering the mechanism underlying this type of cognitive flexibility in human has been hampered by the poor spatiotemporal resolution of neuroimaging methods. To facilitate in-depth investigation of their neural underpinning using animal model, we developed a novel behavioral paradigm in mouse. Mice were trained in a task combining a cognitive and a motor task mimicking distracted car-driving. In this paradigm, the animals learned to manipulate a lever (like operating the steering wheel) during which they needed to discriminate between two auditory cues in a go/no-go test (i.e., cognitive decision-making). We observed interference in both tasks in the early stages. With training, some animals were able to partially restore their performance. Using single-neuron and population analyses, we revealed that multitask performance need a dynamic balance across neuronal ensembles, integrating principles of competition, coordination, and prioritization. The higher cortical regions gradually adapted over training to support flexible multitasking. Together, our findings provide a comprehensive framework for understanding how parallel processing is organized across cellular, population, and computational levels.

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24-P019 *24 Aug 2026*

Cholinergic Modulation of Spatial Learning in the Perirhinal Cortex

*Xingru Xiao **(Presenter)***[1], *Haoyu Xu*[1], *Zhongjie Zhang*[1], *Jacque Pak Kan Ip*[1,2]

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Abstract

The perirhinal cortex (PRH) serves as a critical anatomical hub bridging the neocortex and the hippocampus. However, the precise upstream mechanisms regulating PRH activity and its subsequent information transmission to the hippocampus remain unclear. In this study, we investigated how the cholinergic system gates these processes. Using single-cell RNA sequencing and Allen Brain Cell (ABC) Atlas data, we profiled receptor gene expression in the PRH and found that cholinergic receptors are highly expressed in layer 2/3 and layer 6 glutamatergic neurons. Based on these expression patterns, we hypothesized that acetylcholine (ACh) in the PRH dynamically regulates spatial learning by modulating cognitive map formation. To test this, we employed fiber photometry paired with a GRAB ACh sensor to record real-time cholinergic dynamics in mice performing a spatial working memory task. Our results revealed a prominent ACh rise that reflects spatial cue-triggered reward prediction, as demonstrated by significantly higher signal amplitudes in correct trials compared to incorrect trials. Crucially, this cholinergic signal progressively declined from Day 1 to Day 7 of training. This attenuation indicates that ACh in the PRH encodes environmental uncertainty and attentional demand rather than static reward value. As maze navigation becomes automated with learning, the requirement for attentional recruitment—and thus cholinergic activity—significantly diminishes. Together, these findings demonstrate that cholinergic modulation in the PRH dynamically gates cognitive learning during spatial learning.

Funding: This work was supported by the Hong Kong Research Grants Council (RGC) General Research Fund (14119924), the Lo Kwee-Seong Biomedical Research Fund (J.I.), the Faculty Innovation Awards (FIA2020/A/04) from the Faculty of Medicine, the Chinese University of Hong Kong, and Gerald Choa Neuroscience Institute Research Program Fund.

24-P020 *24 Aug 2026*

Distractor effects in decision making are related to divisive normalisation and feature inhibition

*Jing Jun Wong **(Presenter)**[1], Nicole H.L. Wong[1], Jessie Y.S. Choy[1], Bolton K.H. Chau[1,2,3]*

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Abstract

Human decision making can be influenced by the presence of distractors that contain irrelevant information. However, there is yet a consensus on whether distractors facilitate or impair choice quality. One reason why past findings have sometimes contradicted each other is because they often involved complex multi-attribute tasks, which required applying intricate value models before the key distractor effects could even be tested. As a result, conclusions about distractor effects could be confounded by the validity of the value models. To test distractor effects directly, the current study employed a simple perceptual decision-making task. Participants had to judge which of the two sets of moving dots had the highest motion strength (i.e., greater number of dots). The distractor was a third set of moving dots that ought to be ignored, with the motion strength and direction (i.e., either tilted away or towards from the direction of the highest motion strength) systematically manipulated. Across six experiments, we consistently observe that greater motion strengths of the distractor led to a decrease in accuracy, i.e., negative distractor effect. Furthermore, performance also decreased when the distractors tilted closer towards the direction associated with the correct option. Computational models revealed that the distractor effects observed in behaviour can be explained by a combination of two classical theories in neurophysiology. Specifically, the distractor effect can be accounted for through divisive normalisation, while the orientation effect is captured by a dual feature inhibition mechanism. Our work illustrates distractors can impair choice quality through mechanisms explainable by classical neurophysiological principles.

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24-P048 *24 Aug 2026*

Burden of Idiopathic Developmental Intellectual Disability Attributable to Lead Exposure in Northeast Asia, 1990–2023: A Systematic Analysis for the Global Burden of Disease Study 2023.

*BARAKA WANJARA[3], Ramadhan Mlekwa **(Presenter)**[3], Wansoo Kim[1], Bilguuntuguldur Samaindagva[3], Jaewon Khil[2], Ha Won Lee[2], Minji Jeon[2], Hye Jun Kim[2], Seogsong Jeong[2]*

Presenter: *Ramadhan Mlekwa*

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Abstract

Background

Lead severely harms children's neurodevelopment. Long-term comparison of lead-attributable Idiopathic Developmental Intellectual Disability (IDID) and Population Attributable Fractions (PAFs) aligned with leaded-gasoline bans across Northeast Asia countries remain scarce.

Method: Using GBD 2023 estimates, we assessed lead-attributable IDID years lived with disability (YLD), absolute numbers, and PAFs among children aged 0–14 years in Northeast Asia from 1990 to 2023. IDID was operationally defined using International Classification of Diseases codes. Average annual percentage changes (AAPCs) were estimated by log-linear regression, and pre- versus post-ban PAF trends were compared.

Results

Lead-attributable IDID YLDs declined significantly in all five countries, with faster relative declines in Republic of Korea and Japan and slower declines in Mongolia, China, and Democratic of People's Republic of Korea. The PAFs of IDID YLDs attributable to lead exposure showed a decreasing pattern after the leaded gasoline ban. In the Democratic People's Republic of Korea, where a leaded gasoline ban was not implemented, the PAF did not change in both 1990 and 2023.

Conclusion

Despite marked declines in lead-attributable IDID burden in both rate and absolute numbers across Northeast Asia from 1990 to 2023, substantial cross-country inequalities persist, driven by differences in economic development, geographic factors, and leaded gasoline ban implementation. These findings support urgent population-wide strategies and stronger public health policies to reduce lead exposure, particularly in higher-burden settings. Funding

This research was supported by Bio-Data Industry Professional Training Program through the Korea Institute for Advancement Technology (KIAT) funded by the Ministry of Trade, Industry and Energy (RS-2025-02214034). Acknowledgement

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24-P049 *24 Aug 2026*

Burden of Idiopathic Developmental Intellectual Disability Attributable to Lead Exposure in Northeast Asia, 1990–2023: A Systematic Analysis for the Global Burden of Disease Study 2023.

Baraka Wanjara ***(Presenter)***[3], *Ramadhan Mlekwa*[3], *Wansoo Kim*[1], *Bilguuntuguldur Samaindagva*[3], *Jaewon Khil*[2], *Ha Won Lee*[2], *Minji Jeon*[2], *Hye Jun Kim*[2], *Seogsong Jeong*[2]

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Abstract

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Conclusion

Despite marked declines in lead-attributable IDID burden in both rate and absolute numbers across Northeast Asia from 1990 to 2023, substantial cross-country inequalities persist, driven by differences in economic development, geographic factors, and leaded gasoline ban implementation. These findings support urgent population-wide strategies and stronger public health policies to reduce lead exposure, particularly in higher-burden settings. Funding

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25-P001 *25 Aug 2026*

The role of SPARCL1 in exercise-induced synaptic plasticity and cognitive enhancement

Yunxiao Zhong ***(Presenter)***[1], *Jiasui Yu*[1], *Suk Yu YAU*[1]

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Abstract

SPARCL1 is a matricellular protein that mediates cell–matrix interactions and plays critical roles in synapse formation, plasticity, and maintenance. However, whether SPARCL1 underlies the cognitive benefits of physical exercise remains unknown. Here, we aimed to evaluate the effects of SPARCL1 on exercise-induced synaptic plasticity and cognitive enhancements. Wild-type (WT) and SPARCL1-knockout (KO) male mice underwent four weeks of treadmill training, followed by cognitive assessments including the Y-maze, novel object recognition (NOR), and location object memory (LOM). Exercise significantly improved cognitive performance in WT mice, whereas these benefits were completely abolished in SPARCL1-KO mice. AAV-mediated SPARCL1 overexpression in astrocytes in the hippocampal CA1 region of sedentary mice mimicked the cognitive benefits of running. Electrophysiological recordings revealed that SPARCL1 overexpression enhanced synaptic transmission in the CA1 neurons, characterized by increased sEPSC amplitude and NMDA/AMPA ratio, though reduced release probability. Together, these findings demonstrate that SPARCL1 is both necessary and sufficient for exercise-induced cognitive enhancement and synaptic plasticity.

25-P002 *25 Aug 2026*

Involvement of α7 Nicotinic Acetylcholine Receptor-Signaling in Social Behavior Impairments in the Stressed Mice

Yukihiro Noda ***(Presenter)***[1], *Mizuki Uchida*[1], *Masaki Kano*[1], *Norio Ozaki*[2], *Akira Yoshimi*[1]

Presenter: *Yukihiro Noda*

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Abstract

Smoking is considered a form of self-medication for psychosis, including nicotine (NIC) dependence, through stimulation of nicotinic acetylcholine receptors (nAChRs) in psychiatric disorders. However, the effects of NIC on neuropsychological functions and the underlying molecular mechanisms remain unclear. In this study, we investigated the effects of (-)-NIC on emotional behaviors, intracerebral expression of nAChR subunits, and morphological changes in swim-stressed mice.

Male C57BL/6J mice (7-weeks old) were subjected to swim stress for 15 min. Subsequently, the mice received drugs administration for 7 days (days 2–8) and were subjected to the swim test and social interaction test on day 8, or the conditioned place preference test on days 9–13. On day 8, the mice brains were removed and used for neurochemical analyses. All experiments were performed in accordance with the Guidelines for Animal Experiments of Faculty of Pharmacy, Meijo University.

Stressed mice showed impaired social behavior, reduced phosphorylation levels of Akt, CaMKII, and ERK, and decreased thickness of the pyramidal neuronal layer in the hippocampus. Repeated administration of (-)-NIC and a selective α7nAChR agonist attenuated social behavior impairments in stressed mice. The attenuating effects of (-)-NIC were blocked by a selective α7nAChR antagonist. Repeated administration of (-)-NIC also ameliorated the reduced phosphorylation levels of Akt, CaMKII, and ERK, as well as morphological abnormalities in the hippocampus, without inducing conditioned place preference.

These findings suggest that hippocampal α7nAChR signal pathways play an important role in social behavior impairments in stressed mice and that abnormal neuronal morphology mediated through these pathways contributes to development of such impairments. Activation of α7nAChRs may therefore represent a promising therapeutic target for emotional impairments associated with stress-related disorders.

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25-P003 *25 Aug 2026*

Sustained Behavioral Stress Effects of Inescapable Foot Shocks on Male Sprague-Dawley Rats

Kerstin Mariae Matias ***(Presenter)***[1], *Sharriz Anne Cruz*[1], *Adrian Paul Tan*[1], *Gregory Quirk*[2], *Bryan Paul Bulatao*[1,3], *Richelle Ann Manalo-Cabalinan*[1,4]

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Abstract

Depression affects 3.3 million adults in the Philippines. Despite the global efforts in addressing this issue, the lack of an effective animal model for depression-like symptoms remains a challenge. Hence, this study aimed to use inescapable foot shocks (IFS) and explore the extent of their effects in inducing depressive- and anxiety-like behaviors in male Sprague-Dawley rats. Sixteen rats were randomly assigned to either IFS (n=8) or control (n=8) groups. Rats in the IFS group were exposed to a 6-day IFS (60 15s-shock, 0.85mA, ITI=15-20s). All rats subsequently underwent immediate behavioral assessment (Day-4 post-IFS): open field test (OFT), social novelty test (SNT), and escape test (ET). Four rats each from the IFS and control groups were retained for a late behavioral assessment at Day-11 post-IFS. After 6-days of IFS, stressed rats showed a significant reduction in weight gain compared to the control group (two-way RM ANOVA main effect of time x stress interaction: p=0.034). They also exhibited decreased time in the center during OFT during both immediate and late tests (immediate: control=63.8s vs IFS=27.8s, p=0.011; late: control=39.8s vs IFS=13.0s, p=0.027), suggesting persistent anxiety-like behavior one week after stress. IFS rats also showed a delayed latency to escape shock in the late, but not immediate, test (immediate: control=13.3s vs IFS=23.1s, p=0.165; late: control=3.4s vs IFS=29.6s, p=0.029), indicating learned helplessness. In the social novelty test, stressed rats showed preference for social novelty comparable with the control group (immediate: control=0.663 vs IFS=7300, p=0.172), but they excreted more fecal boli during the test (immediate: control=0 vs IFS=2.625, p=0.017), suggesting that their social novelty recognition remained intact under stress. Our findings suggest that IFS induces persistent behavioral deficits associated with depression and anxiety in rats, without impairing social behavior.

This work was funded by DOST-PCHRD, Philippines.

25-P004 *25 Aug 2026*

Tumor Necrosis Factor-Alpha Upregulation and Behavioural Alterations in a Preclinical Model of Hypertensive Cerebral Small Vessel Disease

Siti Nurulnabila binti A Rahaman ***(Presenter)***[1], *Sayyidah Maryamul Azra' Zul Ramli*[1], *Che Mohd Nasril Che Mohd Nassir*[2], *Muhammad Zulfadli Mehat*[1], *Hafizah Abdul Hamid*[1]

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Abstract

Cerebral small vessel disease (CSVD) is a leading microvascular pathology underlying cognitive impairment and vascular dementia, with white matter lesions (WMLs) representing one of its pathological structural hallmarks. While hypertension drives WML progression through an immune-mediated neuroinflammation, the precise mechanisms of neuroinflammation during early phase CSVD remain poorly characterized. This study investigates age-related behavioural changes and neuroinflammatory cytokine expression in a preclinical model of hypertensive CSVD. Age-matched spontaneously hypertensive-stroke prone (SHRSP) rats and normotensive Wistar Kyoto (WKY) rats were randomly allocated into three age graoups: 8, 14 and 42 weeks. Systolic blood pressure and body weight were monitored weekly. Locomotor activity, exploratory behaviour and recognition memory were evaluated using the open field test (OFT) and novel object recognition test (NORT). The expression of TNF-α, IL-1β and IL-6 was quantified by Western blot. Significant age- and strain-related differences were observed in physiological, behavioural and neuroinflammatory parameters. SHRSP demonstrated elevated blood pressure and lower body weight compared with WKY controls. In OFT, SHRSP demonstrated greater exploratory behaviour at 8 and 14 weeks, followed by a significant decline at 42 weeks. In the NORT, SHRSP exhibited a progressive reduction in discrimination index by 42 weeks, indicating progressive memory impairment. Western blot analysis showed that age and strain were statistically significant determinants of TNF-α upregulation, with SHRSP maintaining higher baseline levels throughout than WKY controls. However, downstream IL-1β and IL-6 were undetectable, suggesting limited activation of secondary inflammatory cascade in the studied CSVD stages. Hypertensive CSVD in SHRSP is associated with

early behavioural hyperactivity, subsequent deterioration in exploratory behaviour and progressive recognition memory impairment. The upregulation of TNF-α alongside the undetectable downstream cytokine suggests that TNF-α-mediated signalling pathways may predominate during the early phase of hypertensive CSVD, preceding the broader neuroinflammatory cascade. This study was funded by the Ministry of Higher Education (FRGS/1/2019/SKK08/UPM/02/5).

25-P005 *25 Aug 2026*

The Standardization Of a Combined Stress Model for Studying Stress-Related Behavioural Phenotypes in Female Wistar Rats

Kumar Nischay Jaiswal ***(Presenter)***[1], *Kalyan Vijayalakshmi*[1], *B.N. Srikumar*[1]

Presenter: *Kumar Nischay Jaiswal*

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Abstract

Depression and anxiety disorders affect women nearly twice as men, yet the vast majority of preclinical stress research has been conducted in male rodents. Female rodents exhibit inherent stress resilience that renders single-stressor paradigms insufficient to produce consistent behavioural phenotypes, creating a critical gap in female-specific stress neurobiology research. We hypothesized that combining social defeat stress (SDS) with chronic immobilization stress (CIS) would cumulatively overcome this resilience threshold. Three independent experiments were conducted in female Wistar rats (2–2.5 months). Experiment 1 examined SDS per se (10 days; retired breeder females as residents). Experiment 2 examined CIS per se (2 hours/day, 10 days). Experiment 3 examined combined CIS+SDS. Each stressed group was compared against its own normal control cohort using independent samples t-tests. Depression- and anxiety-like behaviours were assessed using the Sucrose Preference Test, Forced Swim Test (FST), Open Field Test (OFT), and Elevated Plus Maze (EPM). SDS per se produced no significant behavioural changes across any measure compared to its own normal control. CIS per se, similarly failed to produce significant depression- or anxiety-like behaviour. In contrast, combined CIS+SDS animals showed significantly increased total immobility and last four-minute immobility in the FST ($p<0.05$), indicating behavioural despair. Both OFT and EPM revealed significantly reduced locomotor activity in the combined group. Within OFT, animals showed significantly reduced time in the centre zone and significantly increased time in the periphery, reflecting anxiety-like thigmotaxis. EPM did not reveal anxiety-like behaviour beyond the locomotor reduction. Sucrose preference remained unaffected across all three experiments. Neither social defeat nor immobilization stress alone was sufficient to produce behavioural deficits in female Wistar rats. Their combination produced a reproducible phenotype of behavioural despair and anxiety-like avoidance, validating combined CIS+SDS as a reliable and translatable model for investigating the neurobiology of stress in females.

25-P006 *25 Aug 2026*

The Underlying Mechanisms of Targeted Memory Reactivation During Sleep on Fear-Induced Memories

Lingjun Jin ***(Presenter)***[1], *Qiyu Zheng*[1], *Xiaoqing Hu*[2], *Cora Sau Wan Lai*[1,2]

Presenter: *Lingjun Jin*

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Abstract

Sleep is essential for memory consolidation, particularly during non-rapid eye movement (NREM) sleep. Targeted memory reactivation (TMR) during NREM sleep can influence this process, enhancing memory when delivered during slow-wave sleep (SWS) while attenuating it during non-slow-wave (NS) sleep. In this study, we investigated the impact of TMR applied during spindle activity, which is a 10–14 Hz oscillation pattern generated from the thalamic reticular nucleus (TrN) that mainly occurs during NS sleep, following fear conditioning in mice. A closed-loop system was used to identify the spindle and deliver the TMR stimulus during the sleep recording. Memory retention was evaluated using freezing behaviour in a subsequent fear recall test. We found that spindle-targeted TMR, administered after additional exposure to the conditioning context, attenuated fear memory expression during short-term recall. The optogenetic results suggested that the circuit involving TrN and the frontal association area (FrA) played a crucial role in this effect. Current behavioural findings suggest that sleep spindle activity defines a temporally precise window in which TMR can selectively modulate fear memory consolidation, offering new insights into the interplay between sleep microarchitecture and memory processing. By

understanding the effect of TMR during sleep, we may know how memory consolidation is influenced during sleep and potentially inform new approaches for memory-related intervention in human.

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25-P007 *25 Aug 2026*

Social Exposure During Conditioning in Rats Reduces Conditioned Place Preference for Morphine, but not for Methamphetamine

Gabriela Ilona Janairo[1], Johanna Munar[1], Cynthia Grace Gregorio[2], Gregory Quirk[1], Rohani Cena-Navarro ***(Presenter)***[1]

Presenter: *Rohani Cena-Navarro*

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Abstract

Social exposure during abstinence reduces addictive behavior in animal models (Venniro et al., 2022). However, it is not known whether social exposure during conditioning can reduce the acquisition of addictive behavior. We addressed this question for two commonly abused drugs: the opioid morphine (MO) and the stimulant methamphetamine (MA), using conditioned place preference (CPP). Male and female Sprague-Dawley rats received i.p. injections of either MO (7.5 mg/kg) or MA (1 mg/kg) for 5 days in a CPP chamber either alone (drug-alone group) or with a sex-matched cagemate (drug-social group). A saline-alone and a saline-social group served as controls. After 8 days of abstinence, the level of CPP (rat tested alone) was significantly higher in both drug-alone groups compared to saline-alone controls (MO $p<0.001$; MA $p<0.001$). CPP in the MO-social group was significantly lower than MO-alone group ($p=0.010$) and did not differ from saline-alone controls ($p= 0.105$). When separated by sex, this reduction in MO-social CPP was only significant for females, although MO-social males showed lower levels of drug-primed reinstatement following extinction compared to MO-alone males ($p=0.035$). Social exposure also had an anxiolytic effect in females, but not in males, in an open field test ($p=0.011$). For MA, there was no significant effect of social exposure on CPP, reinstatement, or anxiety-like behavior. Our findings suggest that social exposure reduces the addictive effect of repeated morphine administration, resulting in a "social buffering" of conditioning. The selectivity of this effect for MO (vs MA) is consistent with the involvement of the endogenous opioid system in social exposure, which may reduce its susceptibility to morphine-induced changes (Van den Berg et al., 1999). Our findings suggest (at least for opioids) that the likelihood of developing SUD may be determined by the social context in which drug exposure occurs.

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25-P008 *25 Aug 2026*

Weak structural connections shape human cognition through nonlinear connectome scaling

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Abstract

Human cognition is supported by brain structural connectivity. Although weak connections are abundant in mammalian connectomes, weak connections are often discarded or downweighted because of tractography uncertainty and their functional relevance to human cognition and brain function remains an open question. Across multiple datasets and

tractography pipelines, we show that weak connections are not merely tractography noise. When connectivity weight is interpreted through a nonlinear weighting framework, weak connections make measurable contributions to cognitive prediction, functional-connectivity simulation, and structure-function coupling. These effects are selective: nonlinear weighting improves prediction of general cognitive ability and memory more than crystallized intelligence or processing speed, consistent with weak connections preferentially expanding the modal repertoire of brain networks and supporting both large-scale integration and fine-grained segregation. We further show that weak connections include reproducible and functionally informative subsets organized along systems-level and transcriptomic gradients. These findings suggest that weak connectivity is an essential component of human brain organization under nonlinear scaling.

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25-P009 *25 Aug 2026*

Exploring the synaptic plasticity of the PRC-CA1 neural pathway related to memory

Jiyang Li ***(Presenter)***[1], *Haoyu Xu*[1], *Jacque Pak Kan IP*[1,2]

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Abstract

Memory encoding relies on intricate neural networks within the medial temporal lobe. While the entorhinal cortex is the traditional gateway to the hippocampus, the direct perirhinal cortex to CA1 (PRC-CA1) monosynaptic pathway remains understudied. This project explored the synaptic plasticity and functional architecture of the PRC-dCA1 pathway. Structurally, retrograde tracing confirmed robust monosynaptic projections from the PRC to the dorsal CA1 (dCA1). Electrophysiologically, extracellular field potential recordings demonstrated functional synaptic transmission and revealed that PRC activation significantly modulates spike-timing-dependent plasticity (STDP) at dCA1 synapses. Behaviorally, chemogenetic activation of this pathway led to enhanced learning and memory performance in mice. To dissect the underlying microcircuit, optogenetics combined with whole-cell patch-clamp recordings revealed that PRC excitatory inputs project onto both pyramidal neurons and local inhibitory interneurons within the dCA1. Furthermore, a feedforward inhibitory loop was identified, where PRC-targeted interneurons directly inhibit local CA1 pyramidal cells. To validate the functional dynamics of this circuit during active memory processing, future plans will employ two-photon in vivo calcium imaging. This advanced imaging technique will allow the real-time tracking of neuronal ensemble activity in both the PRC and dCA1 as mice perform object-recognition and spatial memory tasks. By monitoring calcium transients in specific cell types, we aim to elucidate how the PRC-CA1 loop encodes object-identity information and coordinates synchronized population activity in vivo. Together, these findings uncover a novel circuit mechanism for memory modulation.

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25-P010 *25 Aug 2026*

Chronic Exposure to Ambient Roadside PM2.5 Induced Anxiety-like Behavior And Altered Gene Expression in the Hippocampus: a Preclinical Study

Zonghao Ma ***(Presenter)***[1], *Hussain Akhlaq*[1], *Fuxiang LI*[1], *Suk Yu YAU*[1]

Presenter: *Zonghao Man*

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Abstract

Background

Chronic exposure to environmentally relevant concentrations of traffic-related fine particulate matter (PM2.5) may affect neurobehavioral outcomes, but its underlying mechanisms remain unclear. We examined behavioral outcomes and gene expression changes in the lung and hippocampus after 12 months of exposure to roadside ambient PM2.5.

Methods

Male C57BL/6 wild-type mice at 4-5 weeks old were housed in real-time exposure chambers supplied with filtered air or roadside ambient air continuously for 12 months at 23 ± 2 ℃ and approximately 60% relative humidity. Depression- and anxiety-like behaviors were assessed using a series of behavioral tests, including the sucrose splash test, light/dark box test, and open field test. Hippocampus samples were collected for transcriptomic analysis, and pathway enrichment was performed using differentially expressed genes (DEGs).

Results

Twelve-month ambient PM2.5 exposure significantly increased anxiety-like behavior, without significant effects on depression-like behavior assessed by the sucrose splash test. In the hippocampus, 340 DEGs were identified (192 upregulated, 148 downregulated). Tryptophan metabolism was the only significantly enriched KEGG pathway among downregulated DEGs (padj = 0.0248; 3 DEGs: Lao1, Tph1, and Aldh8a1). Additional downregulated candidates, including Gnb3 and Cyp2d26, mapped to the serotonergic synapse pathway, together suggesting disrupted hippocampal serotonin/kynurenine neurochemistry as a candidate mechanism for the observed anxiety-like behavior.

Conclusions

Twelve-month exposure to PM2.5 increased anxiety-like behavior in mice and altered hippocampal gene expression, notably in hippocampal tryptophan metabolism, providing candidate genes and pathways for further validation.

Acknowledgment

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25-P011 *25 Aug 2026*

Micro-circuitry and beneficial effects of auditory perceptual learning

*Liyin Xiao **(Presenter)***[1], *Cora S.W. Lai*[1,2]

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Abstract

Auditory perceptual learning has been found to restore the ability to process information through intensive training in sound detection and discrimination, especially in age-related hearing deficits. However, the underlying mechanism of auditory learning in improving cognitive functions and memory remains unknown. In this study, we found that mice who experienced GO/NOGO auditory training showed significantly improved performance in the novel object recognition test (NORT). Dendritic spine structural plasticity and functional plasticity of calcium activity in pyramidal neurons (PNs) and parvalbumin-positive GABAergic interneurons (PVINs) were investigated in the primary auditory cortex and other brain regions by employing in vivo two-photon imaging and fiber photometric recording. The temporal association (TeA) was known as a sensory integration hub for higher-level processing, which plays a role in higher-order functions such as auditory discrimination, memory, and emotion processing. Optogenetic inhibition of PVINs in the TeA in mice after completing auditory training during the NORT exploring phase greatly impaired the animal's ability to distinguish between familiar and novel objects. We suggest that the auditory training may remodel the processing and function of different brain regions beyond the auditory system, which are associated with cognitive improvement. On top of that, our preliminary experiment showed that aged mice that underwent auditory perceptual training displayed enhanced object discrimination in NORT, suggesting that auditory perceptual learning may have a positive impact on neural functioning in the aged population.

25-P049 *25 Aug 2026*

A comparison of Chronic Restraint Stress and Inescapable Footshock Stress models in Female Rats

Sharriz Anne Cruz ***(Presenter)***[1], *Kerstin Mariae Matias*[1], *Adrian Paul Tan*[1], *Via Joyce Cariaga*[1], *Gregory Quirk*[1,2], *Bryan Paul Bulatao*[1,3], *Richelle Ann Manalo-Cabalinan*[1,4]

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Abstract

Chronic restraint stress (CRS) and inescapable footshock stress (IFS) are established rodent models of depression that induce behavioral changes. While various behavioral assays are used to evaluate depression-like behaviors, their sensitivity may differ across stress paradigms. Moreover, it remains unclear which assays capture the behavioral effects of CRS and IFS. This study assessed the sensitivity of commonly used behavioral tests in detecting depression-like behaviors induced by CRS or IFS. Female Sprague-Dawley rats (8 weeks old) were assigned to control or stress conditions for either CRS or IFS. IFS rats were exposed to 60 randomized footshocks (0.85mA, 15s) over 35min/day for 6 days, while CRS rats underwent 2.5h/day restraint in plastic cones for 5 consecutive days, followed by a 2-day rest period then another 2-day restraint. Following stress exposure, rats were evaluated using behavioral tests assessing anhedonia, sociability, self-care, and anxiety-like behavior. Both IFS and CRS reduced the sucrose preference ratio, indicating stress-induced anhedonia (IFS=0.636 vs control=0.852, p=0.0329; CRS=0.677 vs control=0.878, p=0.0337). In the splash test, CRS rats showed increased number of grooming (CRS=19.19, control=5.13, p=0.0453) and duration (CRS=92.44s, control=26.81s, p=0.0295) following application of a sucrose solution to the fur, suggesting enhanced stress-related grooming behavior, while IFS did not show this effect. Neither stress protocol produced significant effect in the elevated plus maze, social novelty test, or rail suspension test. There was also no significant decrease in bodyweight in either stress model, suggesting relatively mild stress effects under the present conditions. Overall, these findings suggest that the sucrose preference test is a sensitive measure for detecting stress-induced anhedonia across both paradigms, while the splash test may be particularly useful for identifying behavioral changes associated with restraint. These results may help guide behavioral test selection for future studies using female rodent models of stress-related disorders.

25-P051 *25 Aug 2026*

Effect of α7 nicotinic acetylcholine receptor stimulation in social behaviors in juvenile mice exposed to social defeat stress

Masaki Kano ***(Presenter)***[1], *Mayu Ozaki*[1], *Niina Banno*[1], *Mizuki Uchida*[1], *Norio Ozaki*[2], *Akira Yoshimi*[1], *Yukihiro Noda*[1]

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Abstract

The efficacy and safety of antidepressants for juveniles and adolescents with depressive symptoms caused by psychosocial stress is poor. The nicotinic acetylcholine receptor α7 subunit (α7nAChR) signal pathways are involved in the regulation of mental functions and/or neuroinflammation. In this study, we investigated the effects of an α7nAChR agonist in social behaviors in juvenile mice exposed to social defeat stress.

Juvenile (3-week-old), male C57BL/6J mice were exposed to social defeat stress for 10 consecutive days. A social interaction test was performed on the day following the last stress exposure (day 11). A selective α7nAChR agonist was administered 30 min before the test. Immediately after the last stress exposure or behavioral test, the mice brains were removed for biochemical analyses. All experiments were performed in accordance with the Guidelines for Animal Experiments of Nagoya University School of Medicine and Meijo University Faculty of Pharmacy.

Stressed mice exhibited impaired social behaviors and decreased α7nAChR expression in the prefrontal cortex (PFC). The expression levels of phosphorylated Akt and STAT3, which play the important roles in neuroinflammation, neurodevelopment, and neurogenesis, were also decreased in the PFC of stressed mice. Treatment with the selective α7nAChR agonist attenuated both social behavioral impairments and the decreases in phosphorylated Akt and STAT3 expressions. In addition, the TNF-α expression levels and Iba-1 immunoreactivity were increased in the PFC of stressed mice, indicating TNF-α-related microglial activation.

These results suggest that neuroinflammation, neurodevelopmental, and neurogenic pathways mediated through α7nAChR-Akt/STAT3 signal pathways are involved in social behavior impairments induced by juvenile social defeat stress. Targeting α7nAChR may represent a novel therapeutic strategy for stress-related psychiatric disorders in adolescents with adverse juvenile experiences.

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25-P052 *25 Aug 2026*

Sex-specific differences in sucrose preference across a 12-hour test in Sprague Dawley rats

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Abstract

The sucrose preference test (SPT) is a behavioral test used to assess anhedonia in rodent models of depression, in which rodents are given a free choice between a sucrose solution or plain water and their consumption is measured over time. A higher predilection towards the sucrose solution is considered normal behavior while decreased sucrose preference is a marker for anhedonia. Despite its frequent use, no standardized protocol exists for this test, and studies vary in the period of time during which sucrose preference is measured. In this study, we aim to determine if there are changes in sucrose preference over time by measuring sucrose preference at different time points. Sixteen male and twenty female Sprague-Dawley rats were subjected to the SPT for twelve hours during the dark phase. Their consumption was measured every four hours, and the sucrose preference (Weight sucrose solution consumed ÷ (Weight sucrose solution consumed + Weight water consumed)) was compared for the early (1st-4th hour interval), mid (5th-8th hour interval), and late (9th-12th hour interval) periods. Female rats showed a statistically significant difference in sucrose preference across time (one-way RM ANOVA, $F(1.548, 29.41)=7.810$, $p=0.0037$), with increased sucrose preference at the late period ($\bar{x}=0.8285$) compared to the early ($\bar{x}=0.7100$, $p=0.0113$) and mid ($\bar{x}=0.7670$, $p=0.0314$) periods. Male rats, however, exhibited no significant difference in sucrose preference between the time periods ($\bar{x}$ early=0.7675; $\bar{x}$ mid=0.7831; $\bar{x}$ late=0.8400, one-way RM ANOVA, $F(1.316, 19.74)=1.621$, $p=0.2233$). Our data show a sex-specific rise in sucrose preference throughout the 12 hour test performed in the dark phase, suggesting that the timing of data collection for the SPT is important in females. Indeed, averaging over the entire 12 hour timepoint, as usually done, may miss potential treatment effects. We propose that measurements for the SPT be conducted at multiple time points across a testing session.

25-P053 *25 Aug 2026*

The role of anterior piriform cortex in olfactory associative learning and decision making in a GO/NO-GO task

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Abstract

Olfaction conveys rich contextual information and is continually shaped by experience as animals learn to associate odors with rewarding or aversive outcomes. The anterior piriform cortex (APC), a major hub of the olfactory cortex, plays a critical role in odor perception and learning. However, how APC neurons dynamically encode olfactory information across learning stages during decision-making remains poorly understood. To address this, we trained head-fixed mice in a go/no-go associative task combined with population calcium recordings, circuit mapping, and causal perturbations to probe APC function. Using fiber photometry, we monitored and tracked population-level APC neural activity during task performance, revealing the temporal dynamics underlying learning and decision-making. We used anatomical tracing to characterize the input-output circuits that can support the neural dynamics in APC. Optogenetic inhibition of APC activity altered behavioral responses, revealing a causal role of APC in odor-guided choice behavior. Together, our results provide insights into how

APC circuits encode and transform olfactory information during learning, contributing to a better understanding of the neural mechanisms underlying sensory-driven adaptive behavior.

Study supported by RGC CRF (C1134-25G)

25-P054 *25 Aug 2026*

Working memory from intrinsically generated ramping activity

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Abstract

Classical working memory models often rely on attractor-type mechanisms, where neural activity reaches a fixed point and remains stationary to maintain stimulus information. However, recurrent neural network (RNN) models can exhibit a rich variety of dynamics beyond these simple attractors. To explore more general working memory mechanisms, we trained RNNs on delayed-response tasks such as the two-alternative forced-choice task (2AFC). We found that RNNs with ReLU neurons show a previously undescribed "slow-branch" solution, where activity rapidly transitions to one of two branches corresponding to the stimulus, then slowly ramps along the selected branch during the delay to maintain working memory. We show that these branches correspond to nonlinear eigenvectors of the connectivity W, and that truncating W along them faithfully reproduces the trained slow-branch dynamics, whereas classical eigen-decomposition and low-rank (SVD) approximations fail to do so. We further developed a generative Gaussian low-rank model and derived precise conditions on network parameters for the emergence of slow-branch dynamics, establishing an analytical link between connectivity structure and the resulting dynamics. The ramping regime of our model matches the slow ramping activity widely observed during delay periods in mouse premotor areas. Moreover, after a perturbation, both the model and the recordings relax back to the original branch on correct trials but switch to the opposite branch on error trials, reversing the choice. While existing explanations attribute the ramping activity to external input, our model shows it can arise intrinsically from local recurrent connections and directly contribute to working memory. More broadly, the theoretical tools we introduce, including nonlinear eigenvector analysis, are useful for understanding trained RNNs in general.

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25-P055 *25 Aug 2026*

Prediction Errors Shape Memory Organization in Cross-Modal Language Processing: An Electroencephalography Study of N400 and Free Recall

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Abstract

Introduction

Humans use contextual cues to predict upcoming language, but it remains unclear whether prediction errors affect only recall accuracy or also the organization and fluency of memory retrieval. This study examined how category-based predictions shape free recall in a cross-modal language task.

Methods

Forty healthy Korean-speaking, right-handed adults completed a visual-auditory predictive coding task while electroencephalography (EEG) was recorded using a CGX-Dry system. Each trial presented a visual category cue or neutral cue, followed by an auditory Korean noun. Three within-participant conditions were compared: Match, in which cue and target categories matched; Trap, in which the target violated the cued category within the current block context; and Neutral, in which no trial-level category cue was provided. After each block, participants completed an odd-even distractor task and a 90-second typing-based free recall phase. Behavioral measures included recall accuracy, Adjusted Ratio of Clustering (ARC), local integration/isolation, inter-response time (IRT), and key-logging indices.

Results

Trap trials elicited larger N400 event-related potential responses than Match trials, indicating semantic prediction error. However, prediction error did not uniformly increase recall accuracy. Instead, Trap items followed by stronger P600/late positive complex (LPC) responses were more often integrated into category-based recall clusters, whereas Trap items with enhanced N400 but weak LPC activity appeared as isolated or poorly organized recalls. Key-logging analyses showed that integrated Trap items were retrieved with smoother category transitions, while isolated Trap items showed longer retrieval latencies.

Conclusion

These findings suggest that prediction error benefits memory organization only when the violated input is re-integrated into an existing semantic structure, linking electrophysiological markers of prediction violation and reanalysis to free recall organization.

25-P057 *25 Aug 2026*

Functional Impairment without Detectable Diffusion MRI Changes in Experimental Cerebral Small Vessel Disease

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Abstract

Background

Cerebral small vessel disease (CSVD) is a major contributor to vascular cognitive impairment, but early functional changes may not always be detectable using conventional neuroimaging approaches. This study examined whether behavioural alterations in a preclinical CSVD model are accompanied by changes in diffusion MRI metrics.

Methods

Male stroke-prone spontaneously hypertensive rats (SHRSP) and Wistar Kyoto (WKY) controls were assessed at 8, 14, and 42 weeks. Behavioural performance was evaluated using the open field test, novel object recognition test, and Morris water maze. Brain MRI was performed using a 3.0T scanner with diffusion tensor imaging. Whole-brain and hippocampal diffusion metrics, including fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, were analysed.

Results

SHRSP rats demonstrated age-associated behavioural alterations, including reduced locomotor activity, loss of novelty preference at 42 weeks, and less consistent spatial learning performance in aged animals. Despite these behavioural changes, diffusion MRI measures remained largely preserved. Whole-brain and hippocampal analyses showed no significant effects of strain, age, or strain × age interaction on fractional anisotropy, mean diffusivity, axial diffusivity, or radial diffusivity.

Conclusion

Behavioural impairment in SHRSP rats may occur despite preserved conventional diffusion MRI metrics. These findings suggest that functional changes in CSVD may precede detectable microstructural abnormalities using standard diffusion MRI measures, highlighting the need for more sensitive imaging or network-based approaches for early CSVD detection.

25-EP3 *25 Aug 2026*

Conscientiousness Moderates the Effect of Brief Mindfulness Practice on Neural Responses to Errors

*Yiyao Huang **(Presenter)**[1], Lezhi Liu [1], Xiaoqian Yu[1]*

Presenter: *Yiyao Huang*

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Abstract

Mindfuless is theorized to promote both attentional regulation and nonjudgmental acceptance of internal experiences, yet its effects on neural responses to errors remain inconsistent. Previous studies suggest that personality traits may modulate error

monitoring and explain these variabilities. The current study examined whether conscientiousness and neuroticism moderated the effect of a brief mindfulness intervention on error monitoring, as indexed by the error-related negativity (ERN) and error positivity (Pe). Meditation-naïve university students (n = 121) were randomly assigned to either a 10-min mindfulness breathing group or a TED talk control group in a pretest-posttest between-subjects design. Participants completed a Flanker task before and after the intervention, while brain activity was recorded by electroencephalography (EEG). Controlling for age, gender, and baseline performance, moderation analyses did not show that either conscientiousness or neuroticism moderated the effect of group on behavioral measures (correct reaction time (RT), error rate and post-error slowing (PES)). However, conscientiousness significantly moderated the effect of group on ΔPe, $F(1, 82) = 4.402$, $p = .039$, $\Delta R^2 = .049$, suggesting that only individuals with high conscientiousness showed a significant group difference, with the mindfulness group showing lower ΔPe compared to the control group. No significant moderation was found for neuroticism on either ΔERN or ΔPe. The Pe indexes neurocognitive mechanisms related to the conscious evaluation of motivationally significant events. Mistakes are often personally salient for individuals with high conscientiousness, who care strongly about accuracy and performance. Consequently, highly conscientious individuals in the control condition became increasingly engaged with, concerned about, or attentive to their errors over time, whereas mindfulness practice attenuated this tendency through nonjudgmental acceptance, as reflected by smaller Pe changes.

26-P001 *26 Aug 2026*

Social Decision-Making Following Adverse Experiences

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Abstract

Social decision-making describes how individuals choose among various options under a social context. Disruptions in these processes can contribute to neuropsychiatric disorders with social dysfunctions, yet how adverse experiences shape social decision-making remains unclear. Here, we examined the effects of social defeat on decision-making in male mice using a two-choice social reward task, in which animals could choose either to deliver a reward to both themselves and a partner, or to obtain the reward only for themselves. Three-chamber sociability test and sucrose preference assays showed that our social defeat paradigm induced social avoidance without producing anhedonia-like behavior. Based on baseline choice preferences, mice were classified as prosocial or selfish. Social defeat abolished the pre-existing choice patterns in both groups, indicating that adverse social experience can disrupt stable preferences in social decision-making. cFos analysis further revealed reduced neuronal activity in nucleus accumbens after social defeat, regardless of baseline social preference. Together, these findings suggest that social defeat reshapes social decision-making by abolishing choice preferences and suppressing activity in brain regions involved in social valuation and reward processing.

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26-P002 *26 Aug 2026*

Neural circuits of eye movement desensitization and reprocessing in fear extinction

Guowei Zhang ***(Presenter)***[1]*, Beth Wing Lam So*[1]*, Wenyuan Xie*[1]*, Xiaoqian Liu*[1]*, Cora Sau Wan Lai*[1]

Presenter: *Guowei Zhang*

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Abstract

Eye Movement Desensitization and Reprocessing (EMDR) is a common psychiatric clinical practice for post-traumatic stress disorder (PTSD), yet relapse is common, individual variability is substantial, and the neural mechanisms remain largely unknown. We developed an EMDR-like paradigm in a PTSD-relevant mouse model using auditory cued fear conditioning, followed by tone-specific extinction (CS+) with alternating bilateral sensory stimulation (ABS). Here, we found that CS-ABS treatment significantly reduced fear responses during extinction, as well as in short-term and long-term recall, indicating successful recapitulation of the EMDR paradigm. In vivo two-photon imaging in the frontal association cortex revealed that CS-ABS enhanced extinction-associated dendritic spine formation. Notably, compared with pure tone extinction, extinction with ABS resulted in newly formed spines that were more clustered near eliminated spine "hotspots" and persisted longer, indicating targeted structural remodeling specific to ABS-mediated extinction. Functionally, photometric recording showed

that CS-ABS shifted the PL/IL balance toward IL dominance during both extinction and recall, suggesting a potential cortical rebalancing mechanism in EMDR. We further discovered that systemic methylphenidate (MPH) facilitated the long-term benefits of CS-ABS, pointing to the involvement of dopaminergic system in EMDR. Building upon that, we demonstrated the necessity of the VTA–IL dopaminergic projection: optogenetic inhibition of this pathway during CS-ABS completely abolished fear attenuation, confirming that VTA–IL dopamine signaling is essential for EMDR-like effects. Together, these findings show that alternating bilateral sensory stimulation drives fear reduction via prefrontal spine clustering and IL-dependent rebalancing, with VTA–IL dopamine as an essential pathway. MPH may serve as an adjunct to enhance EMDR efficacy and highlights the importance of dopamine in EMDR therapy.

26-P003 *26 Aug 2026*

Posterior perirhinal cortex directs dorsal CA1 cognitive map formation

Haoyu Xu ***(Presenter)***[1], *Zhongjie Zhang*[1], *Jacque Pak Kan Ip*[1,2]

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Abstract

The hippocampus forms cognitive maps that guide flexible behavior. Within this structure, dorsal CA1 (dCA1) balances representational flexibility and stability during learning, but the regulatory circuit mechanisms remain unknown. Here, using monosynaptic retrograde tracing and single-neuron projectome analysis, we identified a previously underexplored direct projection from the posterior perirhinal cortex (pPRH) to dCA1. Chemogenetic silencing of these neurons impaired acquisition but not recall of a spatial-contextual task. Learning was accompanied by dCA1 orthogonalization across contexts while maintaining stable feature coding. Silencing this pathway abolished both orthogonalization and stability. Unexpectedly, stability loss preceded and prevented flexible remapping, showing that stronger stability supports greater flexibility. Thus, pPRH provides contextual input necessary for dCA1 to stabilize task-relevant representations, which in turn enables the flexible orthogonalization underlying adaptive cognitive maps.

26-P004 *26 Aug 2026*

Olfactory Temporal Order Memory Deficits Induced by vHPC-to-mAON Neural Circuit Inhibition in Early Alzheimer's disease

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Abstract

Objectives

Olfactory memory is impaired at early stages of Alzheimer's disease (AD), yet underlying mechanisms remain poorly understood. This study identifies olfactory temporal order memory impairment as a pivotal preclinical event and investigates its hippocampal-olfactory circuit basis.

Methods

Olfactory episodic memory (temporal order, spatial, and novel odor recognition), visual temporal order memory, and odor-sequence learning task were assessed across ages in 3xTg AD mice and wild-type mice. Ventral hippocampus (vHPC) activity and vHPC-to-pars medialis of the anterior olfactory nucleus (mAON) projection were monitored by fiber photometry during behavioral tests. Optogenetic inhibition of vHPC-to-mAON output was subsequently performed in wild-type mice to test causal necessity.

Results

We reveal for the first time that 3xTg AD mice exhibit progressive olfactory memory decline from 3 to 12 months. At 3 months, they show selective deficits in olfactory temporal order memory, preceding impairments in olfactory spatial memory, odor recognition, and visual temporal order memory. These deficits were accompanied by aberrant vHPC activity during memory retrieval. Furthermore, mAON-projecting vCA1 neurons transmitted abnormal odor-sequence, rather than odor-specific information to mAON, correlating with impaired performance and suggesting vHPC–to-mAON circuit

dysfunction as a key mechanism. Optogenetic inhibition disrupted olfactory temporal order memory retrieval and odor-sequence learning in wild-type mice. Notably, 3-month-old AD mice exhibited partial rather than complete vHPC–mAON dysfunction.

Conclusions

Impaired olfactory temporal order memory may precede visual episodic deficits and reflect earlier hippocampal dysfunction. Aberrant vHPC output to mAON may contribute more critically to early olfactory deficits than peripheral olfactory impairment, highlighting hippocampal–olfactory circuit restoration as a promising strategy for early AD intervention.

26-P005 *26 Aug 2026*

Establishing Octopus as a Systems Neuroscience Model for Studying Complex Cognition

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Abstract

The octopus exhibits a large and complex nervous system, a rich behavioural repertoire, and advanced learning capabilities. Having diverged from the vertebrate lineage approximately 550 million years ago, coleoid cephalopods nonetheless converged on complex nervous systems and sophisticated cognitive traits, offering a unique opportunity to investigate fundamental principles underlying brain organization and the evolution of intelligence.

Despite their promise as neuroscience models, progress in cephalopod neuroscience has been limited by challenges in long-term husbandry, the lack of species-adapted molecular and neural recording technologies, incomplete neuroanatomical frameworks, and the absence of quantitative behavioural paradigms linking neural activity to cognition. To address these barriers, we have established Hong Kong's first octopus vivarium and an integrated systems neuroscience platform for cephalopod research. We have developed stable surgical access to the octopus brain, enabling high-density Neuropixels recordings and calcium imaging in vivo. In parallel, we are developing quantitative behavioural assays, including visual looming paradigms, to investigate innate anti-predation behaviours such as camouflage and jet-propelled escape responses. To provide an anatomical framework for these studies, we are using tissue clearing and high-throughput anatomical imaging methods such of Volumetric Imaging with Synchronized on-the-fly-scan and Readout (VISoR) to construct digital brain atlases and mesoscale connectomes for multiple local octopus species, including Amphioctopus fangsiao, A. aegina, A. marginatus, and Octopus sinensis. Together, these advances establish a foundation for systems-level investigations of the neural circuits that generate complex behaviour and cognition in octopuses.

This project is supported by JC STEM Lab of Neural Computation.

26-P006 *26 Aug 2026*

The role of serotonin in fear conditioning and fear extinction

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Abstract

The post-traumatic stress disorder (PTSD) is characterized by excessive expression of fear and impaired fear extinction, which cause tremendous cost for individual and society. Serotonin (5-HT) is widely recognized as a vital neurotransmitter that regulates the higher cognitive functions, especially in the sensory processing, decision making, and emotion regulation. Recently, there are a lot of studies on selective serotonin reuptake inhibitors (SSRIs) in PTSD, but the mechanism of SSRIs in PTSD and the precise role of 5-HT in fear learning and extinction are still unknown. The two subregions of medial prefrontal cortex, infralimbic cortex (IL) and prelimbic cortex (PL), were believed to play a central role in fear conditioning and extinction. Here we will explore the dynamic relationships between 5-HT level and the neural circuits between PL/IL, amygdala, and dorsal raphe nucleus that underlying fear learning by using photometry, optogenetics, 5-HT sensors, and behavior experiments.

26-P040 *26 Aug 2026*

The Investigation of impact of sleep fragmentation on brain inflammation, metabolism and cognitive behaviour

Krit Lee ***(Presenter)***[1], *Ka-Hing Wong*[1,2], *Raymond Chuen-Chung Chang*[3], *Cheng Wai-yin, Nano*[1,2]

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Abstract

Until recently, several studies suggest that disruption in circadian rhythm, often caused by shift work or jet-lag and diseases such as neurodegeneration, may induce cognitive impairments and exacerbate the disease progression. While the underlying mechanisms remain elusive, it is suggested that gut microbiome disruption may be involved. In fact, emerging studies has suggested that gut and brain are closely connected via the microbiota. The gut microbiome has played a crucial role in regulating neuroimmune systems, while neurological diseases can disrupt gut microbiome and lower its diversity, eventually accelerating cognitive decline. These findings suggested that targeting the gut, such as administrating dietary fibers and metabolites, may attenuate neuroinflammation and cognitive impairment.

To investigate if gut pre-treatment can attenuate the circadian disruption-induced cognitive impairments, we first established a sleep fragmentation rodent model by placing the mouse cages on orbital shakers, which were set to oscillate periodically (10s at 140 rpm followed by 60s of rest), during the daytime (12 hrs). This non-invasive technique has been known for inducing sleep disruption with minimal stress and anxiety caused. The mice were sleep fragmentated for approximately two weeks. During this 2-week experiment, the mice were administrated with butyrate (50 mg/kg) or β-glucan (2 mg/kg) daily via jelly feeding, as gut-protective treatments. Afterwards, acute inflammation was induced by i.p. injecting lipopolysaccharides (LPS) (2mg/kg). Behaviour tests including open-field, novel object recognitions (NOR) and Y-maze were performed 5 days after LPS injections. We also studied the involved metabolic changes in vivo via magnetic resonance spectroscopy at different timepoints after LPS injection (4 hours, 48 hours, 14 days).

We observed overall changes in the MRS spectrum across the groups. This suggests a different approach in understanding how circadian disruptions impact brain metabolism and potentially affect neuroinflammation and cognitive decline.

26-P052 *26 Aug 2026*

PTPRN Sets the Threshold for Hippocampus-Dependent Memory Formation by Constraining AMPAR-Dependent Synaptic Potentiation

Jiexin Chen ***(Presenter)***[1], *Lili Wang*[1], *Mingrui Wang*[1], *Zhuo Huang*[1]

Presenter: *Jiexin Chen*

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Abstract

Not every experience is converted into long-term memory, suggesting that the brain sets a threshold for memory formation. How this threshold is regulated at the molecular level remains poorly understood. Here, we investigated the potential role of protein tyrosine phosphatase receptor type N (PTPRN) in hippocampus-dependent memory. Loss of PTPRN selectively enhanced long-term spatial and contextual memory, whereas CA1-specific re-expression of PTPRN attenuated these effects. At the synaptic level, PTPRN deficiency was associated with increased postsynaptic GluA1-containing AMPAR function and enhanced long-term potentiation, without detectable effects on long-term depression. Together, these findings suggest that PTPRN may contribute to the regulation of hippocampal synaptic plasticity and influence the threshold for long-term memory formation.

Computational and Theoretical Neuroscience

24-P021 *24 Aug 2026*

MDSGA-Net: A Multi-Scale Dynamic Sparse Graph Adversarial Network for Cross-Subject EEG Emotion Recognition

Han Cui ***(Presenter)***[1], *Yuge Zhu*[1], *Baishen Huang*[2], *Shaojia Huang*[2], *Tao Xu*[1]

Presenter: *Han Cui*

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Abstract

Cross-subject electroencephalogram (EEG) emotion recognition remains challenging because substantial inter-subject variability induces distribution mismatches in both temporal patterns and inter-channel relationships, limiting generalization to unseen users. Existing approaches typically emphasize either feature-level domain adaptation or graph-based channel modeling, while adaptive relational learning and subject-invariant representation learning are seldom integrated within a unified framework. To address this limitation, a multi-scale dynamic sparse graph adversarial network (MDSGA-Net) is proposed. The framework couples a multi-scale temporal encoder, a dynamic sparse graph learner with branch-wise learnable graph priors, and a gradient-reversal-based subject-adversarial branch, so that hierarchical EEG dynamics, sample-adaptive channel interactions, and subject-invariant cues are jointly captured. Under a strict leave-one-subject-out (LOSO) protocol, MDSGA-Net attains 91.41% ± 5.17% accuracy, 91.37% ± 4.73% Macro-F1, and 98.86% ± 0.87% AUC on SEED, together with 81.30% ± 4.42% accuracy, 81.13% ± 4.41% Macro-F1, and 96.68% ± 1.05% AUC on SEED-IV, surpassing representative domain-adaptation and graph-based baselines on both benchmarks. Ablation studies further confirm that subject-adversarial alignment and graph sparsity regularization contribute complementary gains. By delivering stable and interpretable cross-subject EEG decoding without per-user calibration, the proposed framework offers a practical computational basis for affective brain–computer interfaces, mental-state monitoring, and personalized healthcare applications.

24-P022 *24 Aug 2026*

Data Compression Through the Lens of Synaptic Competition: A Bio-Inspired Approach

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Abstract

Synaptic competition is a neuronal phenomenon based on spike-timing-dependent plasticity (STDP) and the conditions of limited resources. Since synaptic competition leads to distinct outcomes across different neurons, it inevitably induces information reorganization and loss. In our study, we first found that the dimensionality of data processed by the synaptic competition model was significantly reduced. Subsequently, we verified the information in the compressed data and confirmed that valid information was successfully preserved. Finally, we applied this data compression method to a task on the MNIST dataset and found that its performance was significantly superior to PCA, a widely used data compression method. These results fully demonstrate the feasibility of the synaptic competition mechanism as a data compression method, and also indirectly reveal the reason why neurogenesis is restricted to only one layer, as well as how valuable old memories are preserved during the formation of new memories. The present study suggests that issues related to adult neurogenesis deserve further exploration in the future.

24-P023 *24 Aug 2026*

Representational drift under spontaneous activity - self-organized criticality enhances representational reliability

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Abstract

Neural systems face the challenge of maintaining reliable representations amid variations from plasticity and spontaneous activity. In particular, the spontaneous dynamics in neuronal circuit is known to operate near a highly variable critical state, which intuitively contrasts with the requirement of reliable representation. It is intriguing to understand how reliable representation could be maintained or even enhanced by critical spontaneous states. We firstly examined the coexistence of the scale-free avalanche in the spontaneous activity of mouse visual cortex with restricted representational geometry manifesting representational reliability amid the representational drift with respect to the visual stimulus. To explore how critical spontaneous state influences the neural representation, we built an excitation-inhibition network with homeostatic plasticity, which self-organizes to the critical spontaneous state. This model successfully reproduced both representational drift and restricted representational geometry observed experimentally, in contrast with randomly shuffled plasticity which causes accumulated drift of representational geometry. We further showed that the self-organized critical state enhances the cross-session low-dimensional representation, comparing to the non-critical state, by restricting the synapse weight into a low variation space. Our findings suggest that spontaneous self-organized criticality serves not only as a ubiquitous property of neural systems but also as a functional mechanism for maintaining reliable information representation under continuously changing networks, providing a potential explanation how the brain maintains consistent perception and behavior despite ongoing synaptic rewiring.

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24-P052 *24 Aug 2026*

Integrative Prioritization of Schizophrenia Risk Variants, Genes, Brain Regions, and Cell Types Using GWAS and Brain Atlas Resources

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Abstract

Schizophrenia is one of the most prevalent and debilitating neuropsychiatric disorders worldwide and is highly polygenic. Numerous genome-wide association studies (GWAS) have identified schizophrenia risk loci. However, while these studies have identified numerous risk loci, they are often limited to link genetic risk to disease-relevant molecular and cellular processes. Identifying the brain regions and cellular populations associated with these genetic variants is crucial for translating genetic associations into mechanistic insights and understanding the biological pathways underlying schizophrenia pathogenesis. Here, we developed an integrative computational pipeline that systematically connects schizophrenia-associated variants to candidate genes, brain regions, and disease-relevant cell types.

Schizophrenia GWAS summary statistics from the Psychiatric Genomics Consortium (PGC) were analyzed using a chromosome-wise framework combining brain-region-specific expression quantitative trait locus (eQTL) colocalization, MAGMA gene analysis, and single-nucleus RNA sequencing (snRNA-seq) based Human Brain Atlas cell type profiling. Colocalization analysis prioritized SNP–gene associations across basal ganglia and cortical regions, including INO80E and LINC01068. In parallel, MAGMA analysis and cell-type profiling identified medium spiny neurons (MSNs), hippocampal neurons, and deep-layer intratelencephalic neurons as cell populations enriched for schizophrenia-associated genetic signals.

Genes were ranked by schizophrenia association and cell-type specificity. Among MSN-associated genes, DRD2 emerged as a highly prioritized candidate. Interrogation of the DRD2 locus identified rs2514218, a variant previously associated with schizophrenia risk and antipsychotic treatment response, supporting the biological relevance of the DRD2–MSN pathway.

This framework enables systematic prioritization of SNP–gene–brain region and gene–cell type relationships and provides a foundation for future integration of cell-type-specific eQTL resources to directly map risk variants to brain cell types. The framework is readily adaptable to other neuropsychiatric and neurodegenerative disorders, facilitating systematic investigation of genetic risk at cellular resolution.

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25-P012 *25 Aug 2026*

Task-Driven Network Reconfiguration and Dynamic Organization During Motor Imagery in Acute Ischemic Stroke

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Abstract

Background

Upper-limb dysfunction is a major source of post-stroke disability. Conventional electroencephalography (EEG) analyses emphasize local oscillatory markers such as event-related desynchronization (ERD), which capture only circumscribed cortical engagement and may be insufficient to characterize dysfunction of distributed motor networks. Whether acute stroke disrupts the brain's capacity to reconfigure functional networks during motor imagery (MI), and whether network-level measures add information beyond local markers at the individual level, remains unclear.

Methods

MI-EEG was analyzed in 50 patients with acute ischemic stroke and 54 healthy controls during imagery of the ipsilesional and contralesional hand. A multi-level framework compared local activation (mu/beta-band ERD), static coordination (mu-band weighted phase-lag index), task-driven reconfiguration (rest-to-task connectivity distance and edge-redistribution variability), and dynamic organization (multilayer flexibility; hidden Markov modeling of latent states). Group differences used non-parametric permutation inference with Benjamini–Hochberg false-discovery-rate (FDR) correction and prespecified covariate-adjusted sensitivity analyses. A planned head-to-head analysis tested whether reconfiguration distance explained National Institutes of Health Stroke Scale (NIHSS) variance beyond bilateral mu-band ERD.

Results

Stroke patients showed markedly reduced rest-to-task reconfiguration bilaterally (ipsilesional and contralesional both $q = 6.0e\text{-}5$), reduced multilayer flexibility at loose and strict coupling ($q = 0.016$; $q = 0.033$), and group-specific latent-state recruitment. All primary findings survived age and sex adjustment. ERD effects were selective and specification-dependent. Within the stroke cohort, reconfiguration did not add NIHSS variance beyond bilateral mu-band ERD (delta R-squared < 0.001, $p = 0.871$); variance decomposition showed comparable unique contributions from bilateral ERD (3.8%) and reconfiguration (4.3%), with the largest joint contribution in their shared variance (7.3%).

Conclusions

Network-level and local-oscillatory measures are complementary descriptors of acute-stroke motor-system function at different levels of analysis, not a hierarchy in which network metrics supersede ERD. Longitudinal, adequately powered replication is required before individual-level clinical claims can be made.

25-P014 *25 Aug 2026*

Emergence of Cortical Hierarchy in Harmonizing Functional and Effective Connectome with Large-Scale Biophysical Modeling

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Abstract

Incorporation of cortical hierarchy improves fitting of functional connectome (FC) from structural connectome (SC) using reduced Wong-Wang model. However, its necessity remains unknown due to difficulty in model training as well as limited

data modality. Here, we developed a connectome-based back-propagation training procedure that enables nodal parameters to be trained independently across cortical nodes, thereby exploring nodal heterogeneity with full degrees of freedom. We then introduced effective connectome (EC) from direct electrical stimulation dataset F-TRACT, and adopted a two-step training pipeline that integrates information from both EC and FC. In the well-trained model, hierarchical specialization anatomically emerges that recurrent strength and intrinsic noise level both increase along the hierarchical axis from sensory-motor to association areas. Moreover, we found an empirical divergence that node strength of EC is positively correlated with hierarchy, whereas node strength of FC shows negative correlation. With demonstrated impact of heterogeneity of node dynamics as to modeled node strength, we finally illustrated a unique relationship between hierarchy, connectomes and model parameters. Our cross-modality work highlights the underlying organization of brain-wide dynamics, by paving the way for deep learning enforced biophysical modeling.

25-P015 *25 Aug 2026*

Delving into unsupervised Hebbian learning from artificial intelligence perspective

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Abstract

Unsupervised Hebbian learning is a biologically inspired algorithm designed to extract representations from input images, which can subsequently support supervised learning. It presents a promising alternative to traditional artificial neural networks (ANNs). Many attempts have focused on enhancing Hebbian learning by incorporating more biologically plausible components. Contrarily, we draw inspiration from recent advances in ANNs to rethink and further improve Hebbian learning in three interconnected aspects. First, we investigate the issue of overfitting in Hebbian learning and emphasize the importance of selecting an optimal number of training epochs, even in unsupervised settings. In addition, we discuss the risks and benefits of anti-Hebbian learning in model performance, and our visualizations reveal that synapses resembling the input images sometimes do not necessarily reflect effective learning. Then, we explore the impact of different activation functions on Hebbian representations, highlighting the benefits of properly utilizing negative values. Furthermore, motivated by the success of large pre-trained language models, we propose a novel approach for leveraging unlabeled data from other datasets. Unlike conventional pre-training in ANNs, experimental results demonstrate that merging trained synapses from different datasets leads to improved performance. Overall, our findings offer fresh perspectives on enhancing the future design of Hebbian learning algorithms.

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26-P007 *26 Aug 2026*

Lag-Dependent Directional Organization and Entropy-Production Readouts in the Human Motor Network During Task fMRI

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Abstract

Background

Directional organization in task-evoked brain networks remains difficult to quantify from functional MRI. We developed a conservative framework to characterize non-equilibrium directional structure in motor-task BOLD dynamics using publicly available CoSpine motor fMRI data.

Methods

We analyzed 22 subjects from the brain-only motor-task cohort of OpenNeuro ds005884, each with left- and right-hand motor runs. Four retained motor-network clusters were examined without assigning specific anatomical subregion labels.

Lagged functional connectivity was computed at $\tau = 1$ and $\tau = 2$ TRs after within-run z-normalization. Directional structure was summarized using antisymmetric lagged irreversibility, source-sink hierarchy scores, and pair-KL entropy-production rate under a linear-Gaussian approximation. A ridge-regularized surrogate directed-coupling readout was used to estimate source-sink topography. Robustness was assessed with run-bootstrap, subject-bootstrap, leave-one-out analyses, paired permutation tests, and specification-curve checks.

Results

Subject-level rankings were highly concordant across directional indices. Pair-KL entropy-production rate correlated strongly with mean absolute irreversibility and hierarchy score at both lags, with Spearman ρ ranging from 0.81 to 0.87. Irreversibility and hierarchy showed near-identical subject rankings, with $\rho = 0.95$ at $\tau = 1$ and $\rho = 0.96$ at $\tau = 2$. At $\tau = 2$, motor_cluster_03 emerged as the most source-like node and motor_cluster_04 as the most sink-like node, with stable recovery across resampling analyses. Cross-lag analysis revealed higher entropy-production rate at $\tau = 1$ but greater accumulated hierarchy asymmetry at $\tau = 2$.

Conclusions

Motor-task fMRI dynamics show internally consistent directional structure and reproducible source-sink organization. Entropy-production rate and accumulated asymmetry provide complementary readouts of lag-dependent broken detailed balance in task-driven brain dynamics.

26-P008 *26 Aug 2026*

Robust inference of brain connectome reveals cortical circuit pathophysiology in psychiatric disorders

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Abstract

Understanding how anatomical connectivity gives rise to large-scale brain dynamics remains a central challenge in neuroscience.Here we introduce gradMFM, a multi-step gradient-based optimization framework that infers latent structural connectivity (SC) and regional circuit heterogeneity from empirical functional connectivity (FC) and its dynamics (FCD).The optimized regional parameters preserve a consistent hierarchical organization across cortical parcellations, supporting its biological interpretability.Cross-species validation in macaque and marmoset datasets shows that gradMFM-inferred SC aligns more closely with tracer-derived projections than diffusion MRI estimates, particularly for long-range connections.Applying gradMFM to major depressive disorder (MDD), we construct disease-specific whole-brain models that can reproduce disease-specific FC abnormalities and reveal reduced hierarchical differentiation together with altered projections involving MDD-related cortical regions.Together, these findings establish a principled route for inferring hidden anatomical architecture from spontaneous brain activity and for linking structural coupling, functional dynamics, and disease-specific network pathology.

26-P009 *26 Aug 2026*

A Dynamical Route to Emergent Criticality in Training Deep Neural Networks

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Abstract

Power-law spectra are widely observed in deep learning, from Hessian and Fisher spectra to empirical gradient covariance. These scale-free statistics are often interpreted as signatures of criticality, and self-organized criticality has repeatedly been proposed as a possible organizing principle of neural-network training. However, existing accounts largely treat power laws as phenomenological observations or properties measured after training. What is missing is a dynamical mechanism explaining how training drives initially unstructured gradient statistics toward critical-like organization.

We identify such a mechanism by modeling the empirical gradient covariance as an exponential moving average updated by rank-one gradient outer products. We show that its spectrum self-organizes through preferential amplification, the eigenspace analogue of preferential attachment in complex networks. Directions with larger gradient variance become increasingly likely to attract future gradient projections, creating a rich-get-richer process that destabilizes isotropic gradient statistics and generates power-law spectra without imposing scale-free structure by hand.

We establish this mechanism primarily in unsupervised learning and show that the spectral exponent is experimentally tunable: repeated samples, input masking, and data noise systematically reshape the power law. When perturbed data remain learnable, the spectra continue to satisfy the predicted scaling relation; when learning is disrupted, the relation breaks down. Beyond eigenvalues, the same amplification process induces structural concentration, with dominant modes localizing on a small subset of weights and aggregating onto a small number of nodes, providing a dynamical route to sparse updates and simplified neuron-level representations. We further show that analogous behavior extends to supervised learning.

These results recast criticality in deep learning from a static spectral signature to a generative dynamical mechanism, suggesting that self-organized learning dynamics may offer a useful complex-systems framework for understanding the emergence of structured, sparse, and potentially more generalizable representations.

Disorders of the Nervous System

24-P001 *24 Aug 2026*

Dopaminergic Dysfunction Underlying Motivational Symptoms in Parkinson's Disease using Neuromelanin-Sensitive MRI

Hui Zhang ***(Presenter)*** [1], *Miriam Vignando*[1], *Shirley Pang*[1], *Shu-Leong Ho*[1], *Raymond Chan*[1], *Mitul A Mehta*[1], *Henry Mak*[1], *David Shum*[1]

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Abstract

Background

Beyond the hallmark motor symptoms, apathy has emerged as a core non-motor and motivational dysfunction in Parkinson's disease (PD), intrinsically linked to progressive dopaminergic neuronal loss. In contrast, impulse-control disorders (ICDs) are typically iatrogenic phenomena resulting from dopaminergic overstimulation of an already compromised neural system. Consequently, apathy is thought to reflect the primary neurodegenerative dopaminergic deficit. Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) enables in-vivo assessment of dopaminergic neuron integrity within the substantia nigra (SN), serving as a non-invasive biomarker of nigral degeneration. Although reductions in SN neuromelanin signal have been consistently observed in PD, the relationship between nigral neuromelanin alterations and apathy remains unclear, particularly regarding hemispheric asymmetry and domain-specific dimensions of apathy.

Methods

Forty-two participants were included: 16 healthy controls (HC), 16 PD with abnormal motivational expressions (PD-AME) and 10 with predominantly motor symptoms (PD-motor). SN integrity was quantified using NM-MRI. Four quantitative NM-MRI metrics were derived: (1) mean SN neuromelanin contrast-to-noise ratio (NM-CNR), (2) total SN volume, (3) laterality index (LI) of SN volume, and (4) LI of SN signal intensity. Apathy severity was assessed using Starkstein Apathy Scale (SAS) and Geriatric Apathy Scale (GAS).

Results

PD-AME participants showed significantly reduced NM-CNR ($p = 0.02$) and higher apathy scores compared with HC ($p < 0.001$). Ordinal regression showed that lower dopaminergic medication dose, greater motor symptom severity, larger SN volume, and higher nigral asymmetry predicted more severe cognitive/social apathy (GAS-1) (Model statistics: Model $\chi^2(9) = 17.2$, $p = 0.046$; Nagelkerke $R^2 = 0.49$).

Conclusions

Nigral asymmetry, rather than overall degeneration, appears critical for motivational dysfunction in PD.

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24-P024 *24 Aug 2026*

Informative Value of Baseline Regional Brain Volumetry for Cognitive Outcomes Following Donepezil Treatment in Alzheimer's Disease

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Abstract

Background

Clinical responses to donepezil vary considerably among patients with Alzheimer's disease. Identifying neuroimaging biomarkers associated with differential cognitive trajectories following donepezil treatment may help predict therapeutic efficacy and optimize patient selection.

Methods

Patients with Alzheimer's disease who initiated donepezil therapy after baseline cognitive assessment were classified into two groups according to longitudinal cognitive outcomes: a cognitive decline group and a cognitively stable group. Brain volume ratios of multiple cortical and subcortical regions were obtained from structural neuroimaging performed prior to

treatment initiation. Group differences in regional brain volumes were analyzed using analysis of covariance, adjusting for age and sex. False discovery rate (FDR) correction was applied to account for multiple comparisons.

Results

After adjustment for age and sex, the cognitively stable group demonstrated significantly larger amygdala volume at baseline compared with the cognitive decline group (β = 0.025, p = 0.004), which remained significant after FDR correction. In addition, bilateral accumbens volumes were significantly greater in the stable group and survived FDR correction. In contrast, hippocampal volume and other subcortical structures showed no significant associations with cognitive outcomes following donepezil treatment.

Conclusions

Preserved volumes of the amygdala and accumbens at baseline were associated with cognitive stability after donepezil initiation in patients with Alzheimer's disease. These findings suggest that limbic and reward-related brain structures may serve as imaging biomarkers for predicting cognitive response to donepezil, beyond traditional hippocampal measures.

24-P025 *24 Aug 2026*

Blood-Based Biomarkers for Alzheimer's Disease in Down Syndrome: A Systematic Review of Plasma p-tau217 and Neurofilament Light

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Abstract

Background

Adults with Down syndrome (DS) experience widespread accumulation of Alzheimer's disease (AD) brain pathology due to genetic overproduction of amyloid-beta protein. Utilizing ultra-sensitive plasma biomarkers can break diagnostic bottlenecks caused by baseline intellectual disabilities, allowing for early preclinical screening.

Objectives: To compare the diagnostic accuracy via Area Under the Curve (AUC) metrics, testing profiles, and cohort demographics of plasma p-tau variants, and the Aβ42/Aβ40 ratio for early-stage AD detection in adults with DS.

Methods

We reviewed literature published between 2019 and 2026. Target cohorts included adults with DS stratified into cognitively stable, mild cognitive impairment (MCI-DS), or AD dementia (DS-AD) groups. Continuous demographics and cohort sizes were evaluated across analytical platforms in R using non-parametric Kruskal-Wallis tests to rule out cohort selection bias.

Results

Nineteen studies representing a pooled sample of 4,857 participants were analyzed. The data revealed a strict platform: plasma p-tau217 test was predominantly run by Meso Scale Discovery (MSD) assay, while 100% of plasma Aβ42/Aβ40 analyses utilized the Single Molecule Array (Simoa) platform.

Diagnostic evaluation demonstrated that plasma p-tau217 achieved robust staging performance (AUC=0.88). For complementary biomarkers, NfL plasma panel profiling demonstrated an exceptional clinical Sensitivity of 100% and Specificity of 71% (AUC=0.91). Peak standalone diagnostic discrimination was achieved via Simoa-based p-tau181 (AUC=0.99) and p-tau212 (AUC > 0.96). Concurrently, Kruskal-Wallis testing verified that mean baseline control ages were highly uniform across testing groups (Simoa: 41.4±4.4 years vs. MSD: 40.3±4.6 years; p = 0.85), confirming that reported diagnostic performance is completely free from age-skewed cohort selection bias.

Conclusions

Plasma p-tau variants processed on ultra-sensitive digital immunoassay platforms provide peak diagnostic precision for early clinical screening in the DS population.

Keywords: Down syndrome; Alzheimer's disease; plasma p-tau; Aβ42/Aβ40 ratio; early detection; assay platforms

24-P026 *24 Aug 2026*

A Non-Human Primate Model of Parkinson's Disease Exhibiting Slowly Progressive Motor Symptoms Following Nigral Injection of α-Synuclein Preformed Fibrils

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Abstract

Objective: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopamine (DA) neurons from the substantia nigra pars compacta (SNc) and the formation of Lewy bodies in remaining DA neurons, leading to a gradual decline in motor function. Recently, α-synuclein preformed fibrils (PFF) have been appreciated for developing PD model animals. However, no reports have so far been available on motor symptoms in PFF-treated animal models of PD. Common marmosets, a small non-human primate (NHP), have frequently been used as a PD model. In the present study, we attempted to establish a marmoset model of PD by stereotaxically injecting PFF into the SNc. Mutant α-synuclein fibrils were bilaterally injected into the SNc. Total locomotor activity was measured every 3 months postoperatively using MarmoDetector. Immunohistochemical analyses were performed 21 months later in both animals. Results: Two animals with bilateral PFF injections showed a slowly progressive reduction in locomotor activity over 21 months, declining to approximately half of their baseline levels. Histological analysis confirmed largely decreased DA terminals within the striatum. At least one of the two animals further exhibited a marked loss of DA neurons from the SNc and the emergence of Lewy body-like inclusions therein. Conclusions: the present results provide the first demonstration of slowly progressive motor symptoms in an NHP PD model, underscoring its potential as a preclinical platform for PD research.

24-P027 *24 Aug 2026*

Therapeutic Efficacy of 4-Hydroxyisoleucine In Experimental Rat Model Of Demyelination: Neuroprotection Through IGF-1 and GLP-1 Level Restoration

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Abstract

Background

Multiple Sclerosis (MS) is a chronic autoimmune neurodegenerative condition causing demyelination and axonal damage. Ethidium bromide (EBrD) induces focal demyelination by damaging glial cells, especially oligodendrocytes and astrocytes. 4-hydroxyisoleucine (4-HI) exhibits neuroprotective potential by regulating key signaling pathways. To our knowledge, this is the first study assessing the neuroprotective potential of 4-HI in an experimental rat model of demyelination.

Objective

This study aims to evaluate the neuroprotective potential of 4-HI in an EBrD-induced experimental rat model of demyelination.

Methods

Adult Wistar rats received EBrD injection into the intracerebropeduncle region (ICP) to induce demyelination. Animals were administered 4-HI orally at a dose of 100 or 200 mg/kg and semaglutide at 2 mg/kg. Neurobehavioral performance, pro-inflammatory cytokines, apoptotic markers, neurotransmitter levels, and hematological indices were assessed. Histopathological analysis was conducted to evaluate myelin damage, neuroinflammation, and myelin repair. Quantitative

real-time polymerase chain reaction (qRT-PCR) was performed to examine insulin-like growth factor (IGF-1) and glucagon-like peptide (GLP-1) signaling. Further, molecular docking studies were performed to predict 4-HI interactions with IGF-1R and GLP-1R.

Results

The study found that 4-HI treatment improved neuromuscular coordination, locomotion, and cognitive function. It reduced pro-inflammatory cytokines, pro-apoptotic markers, and restored neurotransmitter imbalances. Histopathological analysis revealed enhanced myelin repair, reduced neuroinflammation, normalized hematological profiles, and mitigated pathological alterations in various brain regions. Additionally, qRT-PCR showed that 4-HI administration modulated mRNA expression of IGF-1, GLP-1, and cytokines.

Conclusion

4-HI exhibits neuroprotective potential in the EBrD-induced demyelination by targeting IGF-1 and GLP-1 pathways, reducing neuroinflammation, restoring myelin integrity, and improving neurobehavioral outcomes. Our findings suggest that 4-HI holds therapeutic potential in demyelination, though further validation is needed.

24-P028 *24 Aug 2026*

Single-Nucleus Transcriptomic Analysis Reveals Impaired Dentate Gyrus Granule Neuron Maturation in the MECP2- Deficient Marmoset Hippocampus

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Abstract

Background

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily caused by mutations in the methyl-CpG-binding protein 2 (MECP2) gene. Although hippocampal dysfunction is thought to contribute to cognitive impairments in RTT, the cell type-specific molecular alterations underlying these abnormalities remain incompletely understood. Non-human primate models offer unique opportunities to investigate disease mechanisms that may not be fully recapitulated in rodents.

Methods

To characterize transcriptional alterations associated with MECP2 deficiency, we performed single-nucleus RNA sequencing of the hippocampus from MECP2-deficient and wild-type common marmosets. Cell populations were identified through unsupervised clustering and annotated using established marker genes. Differential gene expression and gene ontology analyses were conducted to identify affected biological pathways.

Results

We identified diverse neuronal and non-neuronal cell populations across the marmoset hippocampus. Comparative analysis revealed widespread but cell type-specific transcriptional alterations in MECP2-deficient animals. Dentate gyrus granule neurons exhibited the most pronounced changes, including reduced expression of genes associated with neuronal maturation, synaptic organization, and neurotransmission. In contrast, genes linked to immature neuronal states were relatively enriched in the MECP2-deficient group. Gene ontology analysis further demonstrated disruption of pathways involved in neuronal development, synaptic signaling, and circuit function. These findings suggest impaired maturation and functional integration of dentate gyrus granule neurons in the absence of MECP2.

Conclusions

Our study provides the first single-nucleus transcriptomic characterization of the MECP2-deficient marmoset hippocampus and reveals cell type-specific molecular abnormalities associated with Rett syndrome. These findings highlight disrupted neuronal maturation in the dentate gyrus as a potential mechanism contributing to hippocampal dysfunction in Rett syndrome and demonstrate the value of non-human primate models for investigating disease pathogenesis.

24-P029 *24 Aug 2026*

The Role of Parvalbumin Interneurons in Hippocampal Alzheimer's Pathology and Potential Treatment for Alzheimer's Disease

Wenyuan Xie ***(Presenter)***[1]

Presenter: *Wenyuan XIE*

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Abstract

The Role of Parvalbumin Interneurons in Hippocampal Alzheimer's Pathology and Potential Treatment for Alzheimer's Disease Early dysfunction of hippocampal inhibitory circuits is linked to memory impairment and sleep abnormalities in Alzheimer's disease (AD), yet the impact of specific inhibitory interneuron types remains unclear. Parvalbumin (PV) inhibitory interneurons regulate sleep architecture and synaptic activity, highlighting their potential for targeted intervention in AD. Our study first investigated the role of PV interneurons in the hippocampal pathology of 5XFAD mice. Longitudinal two-photon live imaging demonstrated the plaque accumulation, blood-brain barrier disruption, and PV interneuron axonal bouton density decreased significantly between 2 and 4 months of age. Meanwhile, in our sleep analysis, we found that 3-month-old 5XFAD mice showed reduced sleep and disordered sleep structure. At 4 months of age, 5XFAD mice showed spatial working memory deficits in Barnes maze test. Dorsal hippocampal immunostaining revealed progressive amyloid plaque accumulation and age-related decline in PV interneuron fluorescence. We then performed interventions targeting hippocampal PV interneurons dysfunctions and sleep disturbances. Applying either non-invasive 40 Hz acoustic entrainment or chemogenetic PV interneuron manipulation increased amyloid clearance, improved sleep and memory, and left locomotion and anxiety unaffected. Additionally, both approaches reduced hippocampal amyloid plaque in older 5XFAD mice. These results identify PV interneurons as crucial mediators of non-invasive gamma entrainment and support PV-targeted manipulation as a precise strategy to counteract early AD pathology and cognitive decline.

This work is supported by National Natural Science Foundation of China (N_HKU735/21); Research Grant Council of Hong Kong (17108821, C7074-21G, 17103922, C1024-22GF, C7011-24GF, 17102525); Health and Medical Research Fund (09200966).

24-P030 *24 Aug 2026*

Perirhinal Amyloid Pathology Disrupts Hippocampal Cognitive Maps in Alzheimer's Disease

My Linh Truong ***(Presenter)***[1], *Haoyu Xu*[1], *Zhongjie Zhang*[1], *Pak Kan Ip Jacque*[2]

Presenter: *My Linh Truong*

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Abstract

Alzheimer's disease progressively degrades neural circuits supporting spatial memory, but the cortical mechanisms that initiate this decline remain unclear. The perirhinal cortex (PRH) accumulates amyloid pathology at the earliest disease stages, preceding hippocampal degeneration, yet its causal contribution to hippocampal circuit failure is untested. To isolate this relationship, we developed a focal amyloid model restricting AAV-mediated expression of three familial AD mutations bilaterally to the PRH of wild-type mice (PRH-3XFAD) and compared behavioural and neural outcomes with the global 5XFAD model and controls. PRH-3XFAD mice recapitulated the neuroinflammatory and amyloid pathology profile of 5XFAD PRH, with transgene expression confined to the injection site, and failed to acquire the DNMP spatial working memory task. Longitudinal in vivo calcium imaging of dCA1 pyramidal neurons revealed a persistent reduction in place cell proportion and spatial information in both AD models relative to controls, with place field stability increasing across training but remaining below control levels. Sample-phase PC correlation between left- and right-trial activity did not differ across groups, indicating comparably dissociated spatial representations during the sample phase in all animals. The correlation between distinct contexts in Choice run instead decreased progressively in controls, reflecting development of context dissociation, whereas both AD models showed the opposite trajectory, with correlations rising across training.

These findings implicate PRH pathology as an upstream driver of hippocampal cognitive map failure, suggesting that spatial memory deficits in Alzheimer's disease may emerge through disrupted cortical input before hippocampal degeneration becomes established.

This study is supported by: Lo Kwee-Seong Biomedical Research Fund (J.I.), the Faculty Innovation Awards (FIA2020/A/04 to J.I.) from the Faculty of Medicine, The Chinese University of Hong Kong, and Gerald Choa Neuroscience Institute Research Program Fund (J.I.).

24-P031 *24 Aug 2026*

A novel CDD mouse model carrying a nonsense mutation R550X

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Abstract

CDKL5 is located on chromosome Xp22 and encodes a serine/threonine kinase. Mutations in the CDKL5 gene cause CDKL5 deficiency disorder (CDD), a rare neurodevelopmental disease. Affected individuals present with seizures, cortical visual impairment, hypersensitivity, intellectual disability, autistic-like phenotypes, and severe motor impairment, including hypotonia. The CDKL5 gene spans 22 exons and encodes an N-terminal catalytic domain and a C-terminal domain. Pathogenic variants in CDKL5 are distributed across both domains, but they are not uniformly scattered. Previous studies have focused on mutations in the N-terminus; however, mutations in the C-terminus have recently gained attention, as the C-terminus also plays an important role in regulating subcellular localization to ensure proper CDKL5 protein function.

R550X is a nonsense mutation caused by a C-to-T base transition at the R550 site. We previously established a CDKL5 iPSC model. Nevertheless, the in vivo effects of the R550X mutation remained unknown. Therefore, we generated an Cdkl5 R550X mouse model and found that the R550X mutation caused the mRNA degradation and protein loss. The mutant mice exhibited decrease spine density in cortical region. Furthermore, our behavioral tests demonstrated that Cdkl5 R550X mouse model recapitulates key behavioral features of CDD, including visual impairment, motor dysfunction, social novelty deficit, repetitive stereotypies, and spatial learning and memory deficits.

24-P032 *24 Aug 2026*

TPC2 Inhibition Rescues Microglial ER-phagy to Suppress STING-Driven Neuroinflammation and Cognitive Decline in Alzheimer's Disease

Xiaoming Cui ***(Presenter)***[1,2], *Aston Jiaxi WU*[1,2], *Olivia Ka-Yi HO*[1,2], *Xuejing LU*[1,2], *Maggie Ming-Ki LEUNG*[1,2], *Zhu ZHANG*[1,3], *King-Ho CHEUNG*[1,2,3]

Presenter: *Xiaoming Cui*

Abstract

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Background

Chronic neuroinflammation driven by microglial activation and the cGAS-STING pathway hyperactivation is a central driver of Alzheimer's disease (AD) progression. We previously demonstrated that exaggerated TPC2-mediated lysosomal Ca2+ release leads to lysosomal alkalization and autophagy impairment in AD. However, how this dysfunction sustains aberrant STING signaling remains poorly understood. We hypothesized that TPC2-induced lysosomal impairment disrupts ER-phagy-mediated STING degradation, thereby exacerbating neuroinflammation.

Experimental Approach

Microglial ER-phagy and STING degradation kinetics were investigated in BV2 cells and primary microglia challenged with LPS or amyloid- b1-42 (Ab1-42). The therapeutic efficacy of targeting this pathway was evaluated in 5xFAD transgenic mice using a novel small-molecule TPC2 inhibitor (T25) and a conditional, microglia-specific TPC2 knockout model (AAV-Iba1-Cre × TPC2fl/fl).

Key Findings

We found that physiological STING clearance relies heavily on intact ER-phagy. However, hyperactive TPC2 causes lysosomal alkalization that blocks this degradative pathway, resulting in STING accumulation and persistent neuroinflammation. Both pharmacological inhibition with T25 and genetic deletion of microglial TPC2 successfully rescued ER-phagy, restored STING degradation, suppressed downstream pro-inflammatory signaling, and markedly ameliorated cognitive deficits in 5xFAD mice.

Significance

This study uncovers a novel microglia-specific mechanism linking dysregulated Ca2+ homeostasis and defective ER-phagy to chronic STING activation. Modulating TPC2 represents a compelling and precise therapeutic strategy to counter neuroinflammation and cognitive decline in AD.

Acknowledgment

This study was supported by the General Research Fund of Hong Kong (GRF: 12100321 & 12102923), the Guangdong Province Natural Science Foundation (GDNSF: 2023A1515010641), and the Health and Medical Research Fund (HMRF: 20212841) to K-H.C.

24-P033 *24 Aug 2026*

Cationic Polystyrene Nanoplastics Exacerbate Alzheimer's Disease Pathological by Impairing the Microglial Autophagy- Lysosome Pathway and Triggering Neuroinflammation

*Jie XIao **(Presenter)**[1,2], Aston Jiaxi WU[1,3], Lexie Xiaoming CUI[1,3], Zhu ZHANG[1,2], King-ho CHEUNG[1,2,3]*

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Abstract

Background

Nano-plastics (NPs) are pervasive environmental pollutants capable of breaching the blood-brain barrier, yet their potential role in accelerating Alzheimer's disease (AD) pathologies remains unclear. This study systematically investigated how the surface charge of polystyrene NPs (neutral, negative, versus positive/cationic) influences microglial autophagy-lysosome function and downstream AD pathology.

Experimental Approach

The differential neurotoxic profiles of surface-charged NPs were examined in vitro using microglial cell cultures to track phagocytic uptake, lysosomal integrity, and autophagic flux. The in vivo chronic impact of cationic NP exposure on neuroinflammation, amyloid pathology, and behavioral outcomes was evaluated using 5xFAD transgenic mouse models.

Key Findings

Among the tested particles, cationic (positively charged) NPs exhibited the highest cytotoxicity, showing repaid microglial internalization and lysosomal accumulation. This buildup triggered lysosomal alkalization and degraded essential lysosomal-associated proteins, resulting in severe autophagic flux obstruction. Mechanistically, this blockade prevented the timely clearance of key inflammatory regulatory protiens, driving microglial hyperactivation. Consequently, in vivo administration of cationic NPs profoundly exacerbated cognitive and behavioral deficits in 5xFAD mice, significantly elevated amyloid-β (Aβ) plaque deposition in the cortex and hippocampus, and aggravated hippocampal neuroinflammation.

Significance

These findings demonstrate that surface charge dictates the neurotoxic potential of environmental nanoparticles. Cationic NPs accelerate AD progression by disrupting the microglial autophagy-lysosome axis, identifying these widespread nanopollutants as critical, previously unrecognized risk factors for neurodegenerative decline.

Acknowledgment

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24-P034 *24 Aug 2026*

Nell-1 is a Synaptic Organizer Promoting Hippocampal Synaptogenesis

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Abstract

Blood-based proteomic screens in Alzheimer's disease (AD) have revealed that numerous circulating proteins are dysregulated, many within pathways linked to neurodegeneration. One such protein, NELL-1 (neural epidermal growth factor-like 1), is a neuronally enriched secreted factor consistently found to be reduced in AD plasma. During aging and AD progression, rhis reduction in plasma NELL-1 levels were negatively associated with plasma neurofilament light chain level, a marker of neurodegeneration, further supporting plasma NELL-1 level is associated with neurodegeneration. To investigate whether and how NELL1 is involved in neuronal functions, we examined its expression and role in hippocampal neurons. In the adult mouse hippocampus, Nell-1 is predominantly expressed in excitatory neurons and enriched in the postsynaptic density fraction, suggesting a role of Nell-1 in synaptic function. Application of recombinant Nell-1 to cultured hippocampal neurons increased excitatory synapse density, as indicated by elevated pre- and postsynaptic puncta and their colocalization. Consistent with this structural increase, the colocalization of AMPA receptors with the postsynaptic terminals was also elevated, suggesting that the newly formed synapses are functional. Together, these findings identify Nell-1 as a synaptic organizer that promotes excitatory synaptogenesis in hippocampal neurons and suggest that decreased Nell-1 levels may contribute to synaptic dysfunction and neurodegeneration in AD.

This study was supported in part by the Research Grants Council of Hong Kong (the General Research Fund HKUST16102824), the InnoHK Initiative of the Innovation and Technology Commission (ITC) of the HKSAR Government and the Innovation and Technology Fund (ITCPD/17-9 and MHP/076/20) and the SIAT–HKUST Joint Laboratory for Brain Science (Joint Laboratory Funding Scheme [JLFS/M-604/24]).

24-P035 *24 Aug 2026*

Dysregulation of Senescence-associated genes orchestrates immune microenvironment in Parkinson's disease

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Abstract

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Background: Cellular senescence and immune dysregulation are increasingly recognized as synergistic drivers of neurodegeneration, yet the core molecular regulators linking these processes in Parkinson's disease (PD) remain poorly defined.

Methods

We integrated transcriptomic profiles from two independent cohorts (GSE8397 and GSE20163) to characterize senescence-associated signatures in the PD substantia nigra. A high-confidence set of 191 cellular senescence genes was intersected with PD-associated DEGs. To prioritize key drivers, we employed a consensus machine learning framework (LASSO, SVM-RFE, and Random Forest) and protein-protein interaction (PPI) network analysis. The identified hub genes were further validated using single-cell RNA sequencing (scRNA-seq), cultured cell lines, and an in vivo Drosophila model.

Results

We identified a robust quartet of senescence-related hub genes: HMGCR, HSPB1, ITPR1, and SDC1, that consistently classified PD pathology across cohorts. Immune infiltration analysis (ssGSEA) revealed that these hub genes are quantitatively linked to a remodelled immune microenvironment, characterized by increased infiltration of MDSCs and

neutrophils alongside a loss of CD4+ effector T cells. At single-cell resolution, these genes exhibited compartment-specific dysregulation, with a notable downregulation in vulnerable dopaminergic (DA) neurons, a pattern recapitulated in MPP+-treated cells. Finally, targeted knockdown of Hmgcr and Sdc in Drosophila significantly impaired locomotor performance, providing initial functional support for their relevance to PD-like behavioural deficits.

Conclusion

Our study identifies a core senescence-associated gene set linked to cellular aging and neuroinflammatory changes in PD. These hub genes, particularly HMGCR and SDC1, may represent candidate biomarkers and potential therapeutic targets for further investigation in PD.

This research was supported by institutional grants from Guangzhou Medical University (Grant Nos. 02-410-250201, 02-408-2501-2172).

24-P036 *24 Aug 2026*

Sub-chronic MK801 in Adolescent Mice Induces Shifts of Schizophrenia-like Positive to Negative Symptoms and Persistent Sleep Oscillatory Dysregulation

Lok In Lauren Wong ***(Presenter)***[1], *Cora S.W. Lai*[1]

Presenter: *Lok In Lauren Wong*

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Abstract

Administration of MK801 during adolescence has been used as a mouse model of schizophrenia-like symptoms, based on the NMDAR hypofunction theory. While the acute effects of MK801 are relatively consistent across studies, other behavioural effects and oscillatory disturbances remain ambiguous across studies and protocols. This inconsistency has been a major source of discrepancy between MK801 rodent models and symptoms observed in patients with schizophrenia. We examined immediate and persistent behavioural and sleep oscillatory deficits in adolescent mice treated with MK-801 (0.5 mg/kg, i.p., 7 days). We found that MK801 produced a dynamic shift from a positive to negative symptom profile from the acute to the later stage (>1 week after administration). In the acute phase, mice displayed prominent hyperlocomotion and deficits in prepulse inhibition (PPI), consistent with psychosis-like behaviour and impaired sensory gating. One week after administration, mice displayed reduced novelty preference and a trend toward hypoactivity with increased anxiety-like behaviour. Notably, latent inhibition impairment was revealed using a fear conditioning paradigm, which was the only positive-like behavioural feature that emerged at the later state. EEG analysis revealed an increase in total sleep duration accompanied by abnormal augmentation of slow-wave (SO) delta activity, consistent with a compensatory response following MK801-induced hyperactivity. Importantly, cortical gamma power during NREM sleep was reduced, and sleep spindle coupling dynamics were disrupted during the early post-treatment period and remained impaired beyond one week. Overall, these features support the notion that sub-chronic adolescent MK801 administration recapitulates both positive and negative symptoms of schizophrenia. Combined with persistent sleep oscillatory deficits, this suggests impaired thalamocortical circuit desynchrony and may interact with cognitive deficits associated with schizophrenia.

24-P037 *24 Aug 2026*

Topical Hydrogel Delivery of Small Molecules Promotes Retinal Ganglion Cell Survival and Optic Nerve Regeneration: A Drug Repurposing Strategy for Glaucoma

Linjing Mi ***(Presenter)***[1], *Yumeng Gan*[1], *Xinyu Chen*[1], *Xinting Huang*[1], *Ngan Pan Bennett Au*[2], *Roja Hadianamrei*[3], *Chi-Chiu Ko*[4], *Chi Him Eddie Ma*[1]

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Abstract

Introduction

Glaucoma remains a leading cause of irreversible blindness worldwide. Although current therapeutic strategies primarily focus on lowering intraocular pressure to decelerate disease progression, they fail to reverse visual field deficits or rescue degenerated neurons. Consequently, there is an urgent need for novel therapeutic agents that can proactively promote

axonal regeneration and restore visual function. Building upon our previous findings, we identified several FDA-approved small molecules capable of promoting axon regeneration of optic nerve and retinal ganglion cell survival, which has high potential in visual function repair and neuroprotection in the treatment of glaucoma disease.

Aim

To repurpose FDA-approved small molecule drugs for glaucoma disease treatment and to develop non-invasive topical eye administration of these small molecules.

Methods: Small-molecule candidates were encapsulated into three distinct topical delivery systems: solution, hydrogels and liposomes. Subsequently, retinal drug permeation of the prepared formulations was quantitatively evaluated to optimize the vehicle composition and dosage. The axon-regenerative efficacy of the optimized formulation was first validated using an acute optic nerve crush (ONC) model, followed by subsequent validation in both the silicone oil-induced ocular hypertension (SOHU) glaucoma model and a genetic animal model of glaucoma.

Results

Permeation assays revealed that the hydrogel formulation exhibited significantly higher retinal drug bioavailability compared to solution and liposome-based formulation.

Conclusion: The hydrogel-based eye drop holds great promise for reversing pathological progression in animal models and translating into clinical glaucoma therapy, thereby offering a novel-mechanism, high-compliance treatment strategy for patients in the future. Evaluating this optimized formulation in both the ONC and glaucoma models is therefore greatened in the following work to investigate its therapeutic efficacy.

Acknowledgement

This study was supported by the Research Grants Council Research Impact Fund (R1005-24F).

24-P042 *24 Aug 2026*

Disrupting laboratory fear memory reconsolidation with individualized, neuroimaging guided, PTSD-protective circuit TMS: A pre-clinical experiment in healthy participants

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Abstract

Post-traumatic stress disorder (PTSD) is associated with persistent intrusive memories and maladaptive fear responses, yet current first-line treatments have substantial non-response and dropout rates. Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses magnetic pulses to modulate targeted brain circuits. Continuous theta-burst stimulation (cTBS) is a brief patterned TMS protocol that is typically considered inhibitory. However, the optimal target, timing, and psychological state for TMS in PTSD remain unclear. This pre-clinical randomized experiment tests whether individualized, neuroimaging-guided cTBS targeting a PTSD-protective circuit can disrupt laboratory fear-memory reconsolidation in healthy adults.

Healthy participants will be randomized to one of three groups: (1) cTBS to the individualized PTSD-protective circuit following fear memory reactivation, (2) cTBS to a vertex control target following reactivation, (3) cTBS to the PTSD-protective circuit at rest. Participants will complete four sessions: MRI acquisition for individualized target localization, fear acquisition, memory reactivation with TMS intervention, and memory recall, extinction, reinstatement, and re-extinction. The PTSD-protective circuit target will be individualized using resting-state fMRI connectivity.

We hypothesize that participants receiving PTSD-protective circuit cTBS following memory reactivation will show reduced fear responses to the CS+ relative to the CS– during reinstatement compared with both control groups. The primary outcomes will be conditioned fear responses indexed by anticipatory pupillary responses and subjective ratings of US likelihood and CS unpleasantness. Interim behavioral and physiological findings from the ongoing study will be presented at the conference.

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24-P053 *24 Aug 2026*

FBXW12 Protects against Autism by Targeting CDYL for Degradation to Derepress SHANK2 Transcription

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Abstract

Autism spectrum disorder (ASD) has a complicated etiology involving both genetic and epigenetic factors. Hundreds of genetic risk genes have been identified to date, but little is known about the underlying epigenetic mechanisms of ASD. Here, we report that FBXW12, an F-box and WD repeat domain-containing protein, is a novel protective factor against ASD. FBXW12 acts as a neuronal activity-induced E3 ligase to target the ubiquitination and degradation of Chromodomain Y-like (CDYL), a transcription corepressor that functions as both a histone methylation reader and a crotonyl-CoA hydratase. Fbxw12 knockout mice exhibit core symptoms of ASD, including social disability and repetitive behaviors, which can be effectively rescued by lentivirus-mediated knockdown of Cdyl in the hippocampus. We demonstrate that Fbxw12-targeted Cdyl degradation is essential for hippocampal synaptic structure and function, primarily by derepressing SHANK2 transcription, while ASD-associated mutations of FBXW12 lead to defective CDYL degradation and repressed SHANK2 transcription. Our findings reveal an activity-induced regulatory axis underlying synaptic dysfunction in ASD, driven by both genetic and epigenetic mechanisms, which sheds new light on the complex etiology and supports targeting the FBXW12-CDYL-SHANK2 axis as a candidate therapeutic target for ASD.

24-EP1 *24 Aug 2026*

Phosphorylated Tau Sequesters KPNA2 to Compromise Nucleocytoplasmic Transport and Drive TDP-43 Proteinopathy

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Abstract

Microtubule-associated protein Tau (Tau) and TAR DNA-binding protein-43 (TDP-43) are two proteins known to co-aggregate in Alzheimer's disease (AD), with such co-aggregation becoming increasingly prevalent as the disease progresses. Despite evidence that Tau interacts with TDP-43 to exacerbate neuronal damage, how Tau influences TDP-43 pathology remains elusive. Here we found that Tau-P301L expression greatly increased levels of pathologically truncated TDP-43 and expanded the population of dying cells by disrupting nucleocytoplasmic transport (NCT). Immunofluorescence revealed that pathological Tau impaired nuclear import and disrupted nuclear membrane (NM) morphology in SK-N-SH cells overexpressing Tau-P301L. Using APEX2-mediated proximity labeling coupled with mass spectrometry (APEX-MS), we identified importin-α1 (KPNA2) as a novel direct interactor of pathological Tau. Mechanistically, the competitive binding of pathological Tau to KPNA2 inhibits the interaction between KPNA2 and its nuclear cargo proteins, impairing TDP-43 nuclear import and leading to its cytoplasmic retention and aggregation. Critically, increased expression of KPNA2 restored nuclear lamina integrity and NCT function, indicating that Tau-induced nuclear envelope defects are secondary to KPNA2 sequestration rather than direct Tau-mediated damage. This rescue further reduced cytoplasmic TDP-43 aggregation and cell death. Taken together, these results demonstrate that pathological Tau disrupts TDP-43 nuclear import by competitively binding KPNA2, which ultimately induces cell death. Blocking the abnormal interaction of Tau and KPNA2 may be an effective strategy to reduce Tau-TDP-43 co-occurrence, thus mitigating neurodegenerative disease progression.

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25-P013 *25 Aug 2026*

Age-related brain atrophy mediates a composite outcome of one-year ischemic stroke recurrence and all-cause mortality through YKL-40–related inflammatory pathways: a structural equation model

Xu Chang ***(Presenter)***[1], *Hao Liu*[2], *Ziyang Liu*[2], *Tao Liu*[2], *Yongjun Wang*[1], *Zixiao Li*[1]

Presenter: *Xu Chang*

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Abstract

Background

Chronological age strongly predicts adverse outcomes after ischemic stroke but does not capture the biological heterogeneity observed among similarly aged patients. Whether age-related one-year risk of stroke recurrence or all-cause mortality is conveyed through structural brain vulnerability, astroglial inflammation, or their interaction has not been quantitatively integrated within a unified framework.

Methods

We analyzed 4,305 patients with acute ischemic stroke from the Third China National Stroke Registry (CNSR-III). Baseline structural T1-weighted magnetic resonance imaging (MRI) was processed with a deep learning–based pipeline (FastSurfer) to derive left and right cerebral cortex and white matter volumes, modeled as indicators of a latent brain atrophy construct. Plasma YKL-40 (chitinase-3-like protein 1), a marker of astroglial inflammation, was quantified by enzyme-linked immunosorbent assay. Structural equation modeling (SEM) decomposed the effect of age on the one-year composite outcome of ischemic stroke recurrence or all-cause mortality into direct and indirect pathways through atrophy and YKL-40, adjusting for sex, atrial fibrillation, hypertension, and diabetes mellitus, with bias-corrected 95% confidence intervals (CIs) from 5,000 bootstrap resamples.

Results

The composite outcome occurred in 493 patients (11.6%). The total effect of age was not significant (β = -0.011; 95% CI, -0.061 to 0.037), whereas the total indirect effect was significant (β = 0.028; 95% CI, 0.005 to 0.050). Mediation was carried predominantly by YKL-40 (β = 0.026; 95% CI, 0.010 to 0.041); the independent contribution of atrophy was minimal. Indirect effects accounted for approximately 255% of the total effect, consistent with a suppressor-type pattern in which direct and indirect pathways operated in opposite directions. Mediation was consistent across sex, hypertension, diabetes, and atrial fibrillation subgroups.

Conclusions

The prognostic relevance of age in acute ischemic stroke is conveyed predominantly through astroglial inflammation, with structural atrophy contributing modestly.

China Postdoctoral Science Foundation (2025M784300); National Natural Science Foundation of China (82372040).

25-P016 *25 Aug 2026*

Medicinal Mushroom (NevG) Attenuates Neuroinflammation and Promotes Cognitive and Motor Recovery in Middle Cerebral Artery Occlusion (MCAO) Rat Model of Ischemic Stroke.

Muhammad Danial Che Ramli ***(Presenter)***[1,2]

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Abstract

Background

Ischemic stroke is a major neurological disorder, characterized by cognitive decline and sensorimotor impairment. Despite the potential of therapeutic effects and anti-inflammatory properties of medicinal mushrooms, most current research focuses on single-species effects rather than combined formulations. This gap highlights the need to investigate the potential of a combination of medicinal mushrooms named NevG, containing Lignosus rhinocerus, Hericium erinaceus, and Ganoderma lucidum, focusing on their therapeutic effects in the context of ischemic stroke. Methods

Forty adult male Sprague–Dawley rats were randomly assigned to five groups (n = 8): normal, MCAO-induced, and NevG in oral doses of 250 mg/kg, 500 mg/kg, and 1,000 mg/kg for 28 days. Ischemia was induced using the Koizumi method and

confirmed through triphenyltetrazolium chloride (TTC) staining and mNSS scoring. Cognitive abilities were assessed using the Morris water maze and T-maze tests, and sensorimotor function was evaluated using the open-field, rotarod, and pole tests. Mechanistic analyses involved measuring anti-inflammatory serum cytokine pathways (TNF-α, IL-1β, IL-6, and NF-κβ). Results: NevG significantly reduced infarct volume by 32%–58% compared with the middle cerebral artery occlusion (MCAO) group ($p < 0.05$). Cognitive performance improved, with a 25%–46% reduction in the Morris water maze (MWM) escape latency ($p < 0.01$) and an increase in T-maze spontaneous alternation. Sensorimotor functions were enhanced, as evidenced by increases in the open-field test (OFT), rotarod retention time ($p < 0.01$), and decreased descent time in the pole test. The cresyl violet staining of the neurons in the hippocampus shows improvement in pyramidal cell counts, and the ultrastructural transmission electron microscope (TEM) analysis shows better preservation of the nucleus and mitochondria, intact myelin sheath, and improved axonal integrity. Conclusion: NevG demonstrates significant neuroprotective effects in ischemic stroke, achieved through reduced neuroinflammation and improved neuronal survival, indicating its potential as a natural therapeutic agent.

25-P017 *25 Aug 2026*

Transcriptomic Analysis Reveals Neuroinflammatory, Viral-Response, and Synaptic Pathway Dysregulation in Vascular Dementia

Priya Dev ***(Presenter)***[1], *Abhishek Pathak*[1]

Presenter: *Priya Dev*

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Abstract

Background

Vascular dementia (VaD) involves complex neurochemical alterations driven by vascular injury, neuroinflammation, and metabolic dysfunction, yet its systems-level molecular architecture and distinction from Alzheimer's disease (AD) remain unclear.

Objective

To define transcriptomic and pathway-level signatures underlying neurochemical dysregulation in VaD.

Methods

RNA sequencing was performed in healthy controls (n = 15), VaD (n = 15), and AD (n = 15). Gene Set Variation Analysis (GSVA) and Reactome-based Gene Set Enrichment Analysis (GSEA) identified dysregulated pathways. Machine learning (Random Forest) enabled classification and feature prioritization, while UMAP, PCA, and clustering assessed molecular stratification.

Results

VaD showed strong enrichment of innate immune and interferon signaling pathways (NES ≈ 1.6–1.9, adjusted $p < 1\times10^{-5}$), including cytokine signaling and neutrophil degranulation, indicating robust neuroinflammatory activation. Leading-edge genes (IL1B, TNF, STAT1) supported interferon-driven inflammatory cascades. Vascular dysfunction signatures (ICAM1, VEGFA) aligned with hypoxia-response and angiogenic pathways, while viral-response pathways indicated coordinated host antiviral activation. Trajectory analysis (Control ⟶ VaD ⟶ AD) revealed a non-linear disease pattern, with vascular injury–associated signals peaking in VaD and synaptic/metabolic pathways progressively declining. GSVA clustering, UMAP, and PCA demonstrated clear group separation. Random Forest achieved high discrimination (AUC approaching 1.0), identifying immune–inflammatory, vascular–metabolic, and cytoskeletal pathways as key drivers. Pathway-integrated prioritization highlighted translational candidates including S100B (blood–brain barrier dysfunction) and CST3 (lysosomal signaling).

Conclusion

VaD exhibits a distinct neurochemical architecture defined by coordinated immune activation, vascular dysfunction, and metabolic dysregulation, representing an intermediate molecular state rather than a continuum of AD pathology. These findings identify mechanistically grounded targets for biomarker development and therapeutic intervention.

25-P018 *25 Aug 2026*

Ketogenic diet and its metabolite, the ketone body beta-hydroxybutyrate, suppress cocaine relapse by inducing an Axl- high microglial subpopulation in the nucleus accumbens

Chao Peng ***(Presenter)***[1], *Zhuo Huang*[1]

Presenter: *Chao Peng*

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Abstract

Cocaine use disorder is marked by persistent relapse vulnerability, yet effective interventions during abstinence remain scarce. The ketogenic diet (KD) and its principal metabolite beta-hydroxybutyrate (BHB) have emerged as candidate metabolic modulators of brain function, but whether they influence cocaine relapse, and through what neural substrate, is unknown. Using a rat cocaine self-administration model, we trained animals for ten days, imposed a two-week withdrawal period, and then conducted a cocaine-primed reinstatement test. Feeding a ketogenic diet during withdrawal significantly reduced reinstatement nose-poke responding relative to standard chow. Intraperitoneal BHB administration during withdrawal reproduced this anti-relapse effect, identifying BHB as the active mediator. To resolve the cellular basis, we performed single-cell RNA sequencing of nucleus accumbens (NAc) tissue from normal rats, cocaine-addicted rats receiving saline (high relapse), and cocaine-addicted rats receiving BHB (low relapse). Subclustering of microglia revealed multiple transcriptional states that grouped, by their relative abundance across conditions, into three functional subtypes: a homeostatic subtype enriched in normal animals, a disease-responsive subtype expanded after cocaine and reduced by BHB, and a BHB-responsive subtype selectively enriched in BHB-treated animals. Differential expression analysis showed that the BHB-responsive subtype was distinguished by elevated MHC class II-related genes (Cd74, RT1-Da/Db1/Ba/Bb) together with Axl and Cd68, defining an antigen-presentation and Axl-high microglial signature associated with the low-relapse state. To test causality, we bilaterally infused an Axl antagonist into the NAc during withdrawal; local Axl blockade abolished the anti-relapse effect of BHB. Together, these findings indicate that BHB suppresses cocaine relapse by inducing an Axl/MHC-II-high microglial subpopulation in the NAc, and that NAc microglial Axl signaling is a necessary effector of this protection. This work nominates ketone-body metabolism and microglial Axl as therapeutic targets for relapse prevention.

25-P019 *25 Aug 2026*

Understanding the Differential Effects of Novel Retinoids in Providing Protection in the 6-Hydroxydopamine Rat Model of Parkinson's Disease

Joseph Allison ***(Presenter)***[1], *Katarzyna Dyjach*[1], *Andy Whiting*[2], *Susan Duty*[1]

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Abstract

Parkinson's disease (PD) is the fastest growing neurological disorder affecting around 12 million people worldwide. Current treatments provide some relief of characteristic motor symptoms, but fail to address the underlying pathobiological mechanisms: α-synuclein aggregation, neuroinflammation, mitochondrial impairment, impaired proteostasis, and loss of neurotrophic support which underpin degeneration of substantia nigra pars compacta (SNpc) dopaminergic neurons. We hypothesise that novel retinoic acid receptor modulators (RAR-Ms), synthesised by Nevrargenics Ltd, will provide much-needed neuroprotection given their in vitro efficacy to mitigate against several of the above mechanisms implicated in the pathogenesis of PD.

Male Wistar rats (N=8-11 per group) were given unilateral intrastriatal injections of 6-hydroxydopamine to induce partial nigrostriatal lesions. Animals were dosed with ellorarxine (0.03 or 0.06 mg/kg) or GZ25 (0.3 or 0.8mg/kg) at 3-day intervals for 14 days. Amphetamine-induced rotations were performed, rats culled and brains dissected for assessment of dopaminergic neuron survival in the SNpc. Subsequently, a repeat 7-day study using the higher doses of ellorarxine and GZ25 was performed for RNA-sequencing analysis. ANOVA was used for statistical analysis with Dunnett's post-hoc testing.

High dose ellorarxine provided significant protection in 6-hydroxydopamine-lesioned rats, with a 20% increase in dopaminergic neuron survival. In contrast, no protection was observed with GZ25, despite evident target engagement. No significant reduction in amphetamine-induced rotations was seen with either RAR-M. Biochemical analyses such as non-canonical signalling cascades and RNA-sequencing are beginning to unravel the differential effects of these RAR-Ms.

In conclusion, our data support a neuroprotective role for ellorarxine in the 6-hydroxydopamine rat model of PD. Examination of ellorarxine's efficacy in α-synuclein models will provide further translational confidence in this approach. In contrast, GZ25 didn't provide neuroprotection, despite similar genomic effects. Unravelling the differential RNA-sequencing profiles and non-canonical signalling of these RAR-Ms will help identify the desired properties for achieving neuroprotection with RAR-Ms in PD.

25-P020 *25 Aug 2026*

Prioritizing Pathogenic Variants in Schizophrenia Genetics

Amal Abdurazakov ***(Presenter)***[1], *Ekaterina Semina*[1], *Yulia Chaika*[1], *Vera Golimbet*[1]

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Abstract

Introduction. International whole-exome sequencing studies of psychiatric cohorts have identified genes associated with schizophrenia [1, 2]. However, patient datasets contain numerous missense variants of uncertain significance (VUS). The inability to distinguish pathogenic from neutral variants complicates selecting valid experimental targets and limits clinical prognosis.

Methods. A computational model was developed based on weighted least squares meta-regression, integrating three independent parameters: (1) the evolutionary conservation of the DNA sequence, calculated via hidden Markov models using 730,000 exomes from gnomAD v4.1; (2) machine learning predictions of protein structural disruption using AlphaMissense; and (3) the estimated frequency of predicted loss-of-function (pLoF) variants.

Results. Parameter integration enabled the classification of 11,128 missense variants across the top 32 schizophrenia risk genes (SCHEMA consortium, q-value < 0.05) [3]. The genetic architecture of the pathology is primarily defined by two functional clusters: chromatin organization and neurodevelopment (ASH1L, KDM6B, STAG1, RB1CC1, SP4, ZMYM2, ZNF136, H1-4, SRRM2), and synaptic signaling and neuronal excitability (GRIN2A, GRIA3, CACNA1G, HCN4, DAGLA, DNM3, TRIO, MAGI2). This bipartite distribution aligns with the schizophrenia neurodevelopmental model, where early epigenetic migration disruptions induce downstream synaptic and cortical dysfunctions [4, 5].

Structural and population metrics exhibit high complementarity, co-classifying only 403 highly pathogenic variants. This validates the simultaneous capture of structural destabilization and evolutionary negative selection as distinct pathogenic mechanisms. The screening algorithm reduced the initial variant pool by 94%, isolating 674 variants with peak pathogenicity scores under combined classification criteria (AlphaMissense ≥ 0.564, CADD ≥ 25 and MPC ≥ 2). Notably, the CACNA1G, TRIO, and DAGLA genes were the most highly represented within this cohort of pathogenic variants. Consequently, these loci are assigned the highest priority for targeted experimental validation, encompassing in vitro functional characterization and in vivo neurobehavioral phenotyping.

Conclusion. This stratification mitigates genetic data redundancy, prioritizing experimental investigation into the molecular mechanisms underlying schizophrenia.

25-P021 *25 Aug 2026*

Cooperative Roles of CD81 with GPR56 and Collagen III to Regulate RhoA-Mediated Corticogenesis and Pial Basement Membrane Stability

Hyeryun Shin ***(Presenter)***[1], *Byung-Geun Ha*[1], *Yu-Jin Jang*[1], *Sung-Jin Jeong*[1]

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Abstract

The adhesion G-protein-coupled receptor GPR56 (encoded by ADGRG1) is critical for cortical development, regulating neuronal migration and interacts with extracellular matrix (ECM) components, including collagen III, integrin α3β1, and tetraspanins CD81/CD9. While cortical dysplasia is well-known in collagen III-deficient and Gpr56/Itga3 double-knockout models, the cooperative role of GPR56 with CD81 remains elusive in cortical development. This study investigates the functional cooperation between CD81 and GPR56 during embryonic corticogenesis. Spatiotemporal analyses (E10.5–E12.5) revealed that CD81 is robustly expressed in the neocortex and meninges, exhibiting significant co-localization with GPR56 in

neurons and astrocytes, and presence in collagen III⁺ meningeal fibroblasts (MFs) and CD34⁺ endothelial cells. Co-immunoprecipitation assays confirmed that CD81 physically interacts with GPR56 in neurons and with collagen III in MFs, serving as a structural bridge that facilitates GPR56 recruitment to the pial basement membrane. In neurons, CD81 knockdown significantly attenuated collagen III-induced RhoA activation, identifying it as a vital cofactor for GPR56-mediated signaling. In MFs, CD81 depletion disrupted the vimentin cytoskeletal network and reduced collagen III expression, impairing meningeal integrity independent of MMP-mediated degradation. Consequently, Gpr56/Cd81 double-knockout mice exhibited severe frontal brain malformations, including extensive neuronal over-migration and profound cortical dyslamination. Our findings suggest that CD81 plays a dual, cooperative role with GPR56 and collagen III in cortical formation. It facilitates neuronal migration in neurons and maintains structural integrity in the meningeal compartment, respectively. This signaling network is a fundamental regulator of architectural organization during embryonic brain development.

25-P022 *25 Aug 2026*

Pre- and postsynaptic upregulation of FasII synergistically underlies neuropathological and behavioral phenotypes in a Drosophila model of myotonic dystrophy

*Alex Chun Koon[1], Ka Yee Winnie Yeung **(Presenter)**[1], Yitao Wu[1], Lok I Leong[1], John Tsun Po Cheung[1], Zhefan Stephen Chen[1,2], Shaohong Isaac Peng[1], Noah S. Armstrong[3], C. Andrew Frank[3], Paul Magneron[4], Mário Gomes-Pereira[4], Ariadna Bargiela[5,6], Aline Huguet[4], Rubén Artero[5,6,7], Genevieve Gourdon[4], Vivian Budnik[8], Brian D. McCabe[9], Ho Yin Edwin Chan[1,2,10]*

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Abstract

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Myotonic dystrophy type 1 (DM1) is a multisystemic disorder that has been extensively studied for decades, yet our understanding of its neuropathological aspect remains rudimentary. Building on an established Drosophila model of DM1, we studied the neuropathological features of the disease by expressing untranslated expanded CUG repeats at the Drosophila larval neuromuscular junction. In this model, both pre- and postsynaptic expression of CUG repeats participate in inducing phenotypes in synaptic boutons, arbor disassembly, synaptic transmission and larval locomotor activity. We found that the expression of CUG repeats in either motorneurons or body wall muscles caused an upregulation of the cell adhesion molecule, FasII (NCAM1 in mammals), in these cells. Knockdown of fasII was sufficient to rescue bouton numbers and locomotor impairment in this model. Overexpression of FasIIC, an isoform of FasII with no cytoplasmic domain, mimicked the phenotypes of expanded CUG expression at the NMJ. Remarkably, overexpression of the FasII-A-PEST+ isoform rescued the synaptic and behavioral defects. Our study provided the foundation for a basic mechanism of synapse dysregulation in DM1.

25-P023 *25 Aug 2026*

Altered dendritic spines dynamics in CDKL5 deficiency

*Liuyou Wang **(Presenter)**[1], Shiyang YUAN[1], Jacque Pak Kan IP[1,2]*

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Abstract

CDKL5 deficiency disorder (CDD) is a neurodevelopmental condition characterized by profound visual dysfunction. More than 75% of patients with CDD exhibit cortical visual impairment, suggesting abnormal visual processing. CDKL5 is a key regulator of synaptic development. In our previous study, we found that CDKL5 deficiency led to reduced orientation selectivity index (OSI) and decreased contralateral/ipsilateral (C/I) correlation in cortical visual neurons of Cdkl5 knockout (KO) mice. However, whether these deficits are associated with alterations in dendritic spine function remains unclear. To investigate this, we performed in vivo two-photon calcium imaging to record spine calcium activity in neurons expressing GCaMP7b in the binocular visual cortex (bV1) of Cdkl5 KO and wild-type (WT) mice.

Our current results revealed that dendritic spines in KO mice showed a trend toward reduced OSI, lower C/I correlation and greater preferred-orientation differences compared with WT mice, indicating impaired tuning specificity and reduced binocular matching at the spine level. In addition, KO spines exhibited elevated calcium event rates and decreased functional correlation among spines located on the same dendritic branch. These findings suggest that CDKL5 deficiency disrupts dendritic spine function and local functional coordination in the visual cortex. Our study demonstrates that altered dendritic spine dynamics may constitute a key cellular mechanism contributing to cortical visual dysfunction in CDD. This work provides new insight into the synaptic basis of CDD pathology and suggests that dendritic spine function may represent a potential therapeutic target for alleviating visual deficits in affected individuals.

25-P024 *25 Aug 2026*

nELAVL phosphorylation by CDKL5 regulates RNA metabolism and condensates communication to promote experience- dependent maturation of the visual cortex

*Shiyang Yuan **(Presenter)**[1], Yao ZHU[1], Zhongyu ZHENG[1], Hei Matthew YIP[1], Maggie See Wing CHAN[1], Jacque Pak Kan IP[1,2]*

Presenter: *Shiyang Yuan*

Abstract

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Development of the visual cortex is activity-dependent, and light exposure after eye opening is required for proper formation of the binocular region in primary visual cortex (V1). Disruption of visual pathways can therefore impair cortical development. CDKL5 deficiency disorder (CDD), an X-linked neurodevelopmental disorder caused by mutations in the Cyclin-Dependent Kinase-Like 5 (CDKL5) gene, is one such condition. In addition to diverse neuropsychiatric symptoms, at least 75% of patients with CDD present with cortical visual impairment. However, how CDKL5 mutations lead to neuronal developmental and functional deficits remains unclear. In this study, we established a cortical visual impairment model in Cdkl5 knockout (KO) mice and performed an unbiased phosphoproteomic screen in V1. We identified the neuron-specific nELAVL family (nELAVL2/3/4, also known as HuB/HuC/HuD) as substrates of CDKL5. Because nELAVLs are RNA-binding proteins, we next examined how their aberrant phosphorylation in CDD affects mRNA expression in mouse V1 using bulk RNA sequencing. We found that several activity-dependent genes are dysregulated in Cdkl5 KO mice. To investigate how CDKL5-mediated phosphorylation of nELAVLs regulates mRNA expression in mouse V1, we observed enlarged cytoplasmic nELAVLs puncta in V1 neurons in Cdkl5 KO mice and in cells expressing nELAVL phospho-deficient (SA) mutants. This dysregulation of nELAVL condensates also led to altered composition of P-bodies and stress granules. Functionally, in vivo two-photon calcium imaging revealed impaired orientation tuning in V1 of Cdkl5 KO mice and mice with local viral-mediated nELAVL phospho-deficient mutations. Our results reveal a critical physiological role of CDKL5-dependent nELAVL regulation in activity-dependent refinement of visual cortical circuits.

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25-P025 *25 Aug 2026*

Nobiletin Activates Ambra1-Dependent Mitophagy to Rescue Cognitive Decline in Alzheimer's disease Models

*Xuejing Lu **(Presenter)**[1,2], Aston Jiaxi Wu[1,2], Olivia Ka-Yi Ho[1,2], Xiaoming Cui[1,2], Maggie Ming-Ki Leung[1,2], Min Li[1,2], King-Ho Cheung[1,2]*

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Abstract

Background

Alzheimer's disease (AD) is characterized by progressive memory impairment and cognitive decline. Accumulating evidence indicates that mitochondrial dysfunction plays a proximal role in the pathogenesis of familial and sporadic AD. Mitophagy, the selective degradation of damaged mitochondria, represents a promising therapeutic mechanism to mitigate amyloid-β (Aβ) and tau pathologies. Nobiletin, a natural compound derived from Traditional Chinese Medicine (TCM) with documented anti-aging properties, was recently identified by our group as a potent mitophagy inducer. Here, we hypothesized that nobiletin protects against AD-associated neuropathology and cognitive decline by restoring mitophagy.

Experimental Approach

The molecular mechanism underlying nobiletin-induced mitophagy were investigated in vitro using SH-SY5Y neuroblastoma cells under AD-like conditions. To evaluate therapeutic efficacy in vivo, a novel dual-reporter AD mouse model (5xFAD-mitoQC) was generated by crossing mitophagy-reporter (mito-QC) mice with 5xFAD transgenic mice, allowing spatial tracking of mitochondrial clearance.

Key Findings

Using a high-throughput screening (HTS) platform utilizing the mKeima-Red-Mito-7 probe, nobiletin was identified as a robust driver of mitochondrial clearance. Immunoblotting and confocal imaging revealed that nobiletin activates mitophagy via Ambra1-dependent pathway, operating independently of the canonical PINK1/Parkin axis. Crucially, in vivo administration of nobiletin significantly upregulated mitophagy within vulnerable brain regions, markedly reduced amyloid-β (Aβ) plaque accumulation, and effectively rescued cognitive and behavioral deficits in 5xFAD-mitoQC mice.

Significance

This study elucidates a novel, non-canonical mechanistic pathway through which nobiletin drives Ambra1-mediated mitochrondrial rejuvenation. These findings highlight the translation potential of nobiletin as a TCM-derived candidate to counter mitochondrial decay and arrest disease progression in AD.

This study was supported by the General Research Fund of Hong Kong (GRF: 12100321 & 12102923), the Guangdong Province Natural Science Foundation (GDNSF: 2023A1515010641), and the Health and Medical Research Fund (HMRF: 20212841) to K-H.C.

25-P026 *25 Aug 2026*

Neuron-Astrocyte Interaction via Astrocytic D1 Receptors in VTA-NAc Pathway Modulates Fear Memory

*Xiaoyan Ding **(Presenter)**[1], Ying LI[1]*

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Abstract

Fear memory formation is closely associated with post-traumatic stress disorder (PTSD) pathogenesis, with emerging evidence implicating dopaminergic dysfunction in PTSD development. Ventral tegmental area (VTA) dopamine neurons project to several downstream brain regions, mediating distinct fear memory modulation. Among these, DA projections to the nucleus accumbens (NAc), the reward circuit, have been proven to be a key element in fear memory. While astrocytic involvement in NAc-mediated memory regulation remains poorly understood, this study specifically investigates how NAc astrocytes modulate fear memory retrieval through dopaminergic mechanisms. Through integrated in vivo fiber photometry in free-moving mice, we monitored astrocytic calcium dynamics triggered by stress stimulation on conditioning training day,

coupled with chemogenetic activation of Gq on astrocytes and astrocytic D1R knockdown to mechanistically dissect the role of astrocytes in the modulation of memory. Our findings revealed that VTA-NAc dopamine signaling activates NAc astrocytes through D1Rs, which regulate fear learning and memory via neuron-astrocyte interaction, highlighting astrocyte D1Rs as a therapeutic target for fear-related disorders.

25-P027 *25 Aug 2026*

Direct Reprogramming Unmasks Severe Calcium Homeostatic Failure and Functional Saturation in C9orf72 Motor Neurons

Allan Patrick Stephane Remon ***(Presenter)*** [1], *Yu S.*[1], *Ren S.*[1] & *Jauch R.*[1,2]

Presenter: *Allan Patrick Stephane Remon*

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Abstract

The hexanucleotide repeat expansion in the C9orf72 gene is the principal genetic driver of amyotrophic lateral sclerosis (ALS), leading to toxic dipeptide accumulation and motor neuron death. While induced pluripotent stem cell (iPSC)-derived models have advanced our understanding of ALS, the intensive pluripotency reprogramming process can alter or mask native disease phenotypes.

To establish a more faithful disease platform, we utilized a direct conversion strategy to generate induced neural stem cells (iNSCs) and subsequently differentiate them into mature induced motor neurons (iMNs), comparing their phenotypic fidelity against traditional iPSC-derived lines.

Functional Fluo-4 AM live-cell imaging unmasked a profound hyperactive and desensitized calcium phenotype that is most cleanly recapitulated in the directly converted lineage. Patient-derived C9orf72 motor neurons exhibit an elevated resting baseline calcium level, a higher percentage of spontaneously active cells, and significantly prolonged burst durations. Crucially, kinetic classification following stimulation revealed a dramatic shift in cellular composition: control lines maintain a robust pool of classic "responsive" neurons, whereas C9orf72 lines display an overwhelming enrichment of "saturated" cells (~37–39%) characterized by a chronic inability to return to baseline and an abolished response to subsequent depolarization.

To identify the molecular candidates driving this functional saturation, we performed transcriptomic profiling of the mature lineages. RNA-sequencing revealed severe expression dysregulation of central calcium-handling machinery in mature C9orf72 iMNs. Specifically, we identified a stark downregulation of the primary cytoplasmic calcium buffer S100A6, combined with the significant upregulation of the surface L-type voltage-gated calcium channel CACNA1C and the intracellular endoplasmic reticulum (ER) calcium-release channels IP3R3 (ITPR3) and RyR3 (RYR3). Crucially, validation against clinical post-mortem datasets confirms that this transcriptomic disruption profile accurately mirrors pathology seen in patient tissues. Together, these findings demonstrate that direct reprogramming uncovers an authentic, translationally relevant phenotype of functional calcium exhaustion driven by explicit channel dysregulation in ALS.

25-P029 *25 Aug 2026*

Not where, but which: stiff dimensions prioritize candidate mechanisms in autism

Siqi Yang ***(Presenter)***[1,2], *Sida Chen*[1,2], *Zhao Chang*[1,2], *Qianyuan Tang*[1], *Changsong Zhou*[1,2,3]

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Abstract

Autism spectrum disorder (ASD) neuroimaging has revealed widespread alterations in functional connectivity, yet their mechanistic interpretation remains challenging: the same alteration may reflect developmental delay, atypical acceleration, compensation, or incidental variability. Here, we propose a sensitivity-based framework that shifts the question from where the autistic brain differs to which coordinated deviations should be prioritized as candidate mechanisms. Resting-state fMRI was modeled using a pairwise maximum-entropy model (pMEM), allowing individual brain dynamics to be represented as trajectories in model-parameter space. We characterized the geometry of this space using the Fisher information matrix (FIM), whose eigenspectrum revealed a stiff–sloppy organization: a small number of high-sensitivity directions and many

low-sensitivity, redundant dimensions. In typically developing controls (TDC), normative maturation projected preferentially onto the stiff subspace, indicating that typical development is organized along sensitivity-dominant dimensions rather than diffuse regional changes. Projecting ASD individuals onto this TDC-derived developmental sensitivity axis revealed bidirectional deviations, separating delayed-like and advanced-like patterns. These sensitivity-aligned deviations predicted social-behavioral phenotypes more strongly along stiffer FIM dimensions, demonstrating that clinical relevance depends on dynamical sensitivity rather than deviation magnitude alone. Computational perturbation along the stiff deviation axis selectively reduced the ASD brain-age gap in the delayed-like subgroup, while leaving the advanced-like subgroup largely unchanged, distinguishing timing-like mismatch from off-trajectory departure. Finally, spatial deviation maps covaried with BrainSpan developmental gene-coexpression modules enriched for neurodevelopmental risk programs, linking stiff dynamical deviations to molecular mechanisms. Together, our results provide a predictive, perturbable, and biologically grounded framework for prioritizing candidate mechanisms in ASD.

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25-P030 *25 Aug 2026*

Young Fecal Microbiota Transplantation Rejuvenates Neural Regenerative Capacity in Aged Mice via Remodelling of the Gut Microbiota-Metabolite Axis

*Xinyu Chen **(Presenter)**[1], Xinting Huang[1], Ziting He[1], Larry Tso-Lun Lo[3], Ngan Pan Bennett Au[1,2], Chi-Chiu Ko[3], Xiaowei Zhu[1], Chi Him Eddie Ma[1]*

Presenter: *Xinyu Chen*

Abstract

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Aging severely impairs axon regeneration and functional recovery following peripheral nerve injury (PNI), representing a major clinical challenge for geriatric nerve repair. Mounting evidence indicates that the gut microbiota and its derived metabolites play essential roles in modulating host physiological homeostasis, tissue repair, and neural plasticity, yet their impact on age-related regenerative decline in the nervous system remains poorly defined. Here, we investigated whether fecal microbiota transplantation (FMT) from young healthy mice could rejuvenate regenerative capacity in aged mice after PNI, and explored the underlying mechanism of the gut microbiota-metabolite axis. Aged recipient mice received FMT from young donor mice and then axon regeneration and functional recovery were systematically evaluated after PNI. Fecal samples from aged mice were subjected to 16S rRNA gene sequencing and untargeted metabolomics. A panel of top-ranked differential metabolites was further validated for pro-regenerative efficacy using dorsal root ganglion (DRG) explant cultures and in vivo PNI and optic nerve crush (ONC) models. Our results showed that FMT from young mice significantly promoted peripheral axon regeneration in aged recipients compared to non-treated controls. 16S sequencing and untargeted metabolomics revealed that FMT markedly reshaped the gut microbiota and metabolic profiling of aged mice. Functional validation confirmed that direct administration of these candidate metabolites substantially accelerated neurite outgrowth in DRG explant assays and enhanced functional nerve repair in vivo following PNI. Strikingly, these metabolites also successfully induced robust axon regeneration in the CNS after optic nerve injury. Collectively, our findings revealed that young microbiota transplantation rejuvenates age-impaired neural regenerative capacity by remodeling the gut microbiota-metabolite axis, and identifies specific microbial metabolites as novel intrinsic regulators of axon regeneration. This study highlights the gut microbiota-metabolite axis as a promising translational target for improving peripheral nerve repair and functional recovery in the aged population, with potential implications for promoting CNS regeneration.

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25-P035 *25 Aug 2026*

Combined Transcranial Direct Current Stimulation and Immersive Virtual Reality Meditation for Generalized Anxiety Disorder: A Randomized Pilot Trial

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Abstract

Introduction

Generalized anxiety disorder (GAD) is prevalent and often inadequately treated, with up to half of patients not responding to first-line interventions. While transcranial direct current stimulation (tDCS) shows promise as a neuromodulatory approach and immersive virtual reality meditation (IVRM) offers scalable, home-based delivery of mindfulness-based therapies (MBTs), their combined efficacy remains largely unexplored. This pilot study evaluated the feasibility and preliminary efficacy of a combined tDCS–IVRM intervention in GAD.

Method

In this randomized, double-blind pilot RCT, 32 adults with DSM-5 GAD (mean age = 31.06; 22.2% male) were assigned to active tDCS + VR or sham tDCS + VR. Participants completed 12 sessions across two weeks. IVRM was delivered concurrently with stimulation using standardized adapted MBT scripts. Outcomes (HAM-A; STAI) were assessed at baseline, post-treatment, and 1-month follow-up.

Result

Mixed-effects analyses revealed significant time effects across outcomes (all ps < .001), with significant Group × Time interactions for HAM_A and state anxiety (ps < .05) and a marginal interaction for trait anxiety ($p = .077$). The Active group showed robust reductions in the primary outcome ($\Delta M = 10.65$, $p < .001$), state anxiety (pre–post $\Delta M = 11.24$, $p < .001$; pre–follow-up $\Delta M = 12.18$, $p < .001$), and trait anxiety (pre–post $\Delta M = 12.00$, $p < .001$; pre–follow-up $\Delta M = 13.59$, $p < .001$), whereas changes in the Sham group were smaller and largely non-significant. No significant between-group differences were observed at individual timepoints.

Conclusion

These findings suggest that combined tDCS–IVRM may enhance anxiety reduction over time in GAD. High engagement supports feasibility as a scalable, home-based intervention. Larger trials are needed to confirm efficacy and establish comparative benefits.

25-P036 *25 Aug 2026*

The association of associative striatum glutamatergic levels and whole-brain resting-state functional connectivity in clinical high risk for psychosis

Siya Peng ***(Presenter)***[1], *Joe Kwun Nam Chan*[1], *Sherry Kit Wa Chan*[1], *Edwin Ho Ming Lee*[1], *Christy Lai Ming Hui*[1], *Eric Yu Hai Chen*[2], *Wing Chung Chang*[1]

Presenter: *Siya Peng*

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Abstract

Introduction

Dysregulation of the glutamatergic-dopaminergic system is a core pathophysiology of psychosis. Investigating individuals at clinical high risk for psychosis (CHR-P) offers a critical window into prodromal pathological changes. A characteristic of the CHR-P state is corticostriatal dysconnectivity, thought to be attributable to glutamatergic dysfunction that acts as an upstream trigger driving downstream dopaminergic dysregulation. However, how local metabolites mechanistically drive these connectivity changes remains unclear. To bridge this gap, we investigated how associative striatum (AST) glutamatergic metabolites (Glu, Gln, Glx) modulate whole-brain functional connectivity (rsFC) in CHR-P, while further elucidating their neuroreceptor-level correlates.

Methods

In this study, 62 CHR-P and 48 healthy participants initially underwent resting-state functional magnetic resonance imaging (rsfMRI) and single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS). We investigated the spatial coupling relationship between whole-brain rsFC strength across 400 brain regions linked to the left AST and individual metabolite

concentrations (defined as metabolite-rsFC edge weights). Subsequently, we applied a novel analytical pipeline to perform univariate spatial correlation analyses between glutamatergic edge weight difference maps (CHR-P minus HC) and established neuroreceptor atlases (i.e., Neuromap), followed by multiple comparison correction.

Results

Spatial coupling analysis revealed that the CHR-P group exhibited positive metabolite-rsFC coupling for three metabolites, whereas the HC group showed no significant coupling (Glu) or negative coupling (Glx, Gln). This pattern reversal was significant in correlation strength (Glu: $p = 0.030$; Glx/Gln: $p < 0.001$) and slopes (Glu: $p = 0.025$; Glx/Gln: $p < 0.001$). Spatial correlation analysis revealed that the Gln difference map showed a significant spatial correlation with the noradrenaline transporter ($r = 0.42$, pspin-fdr = 0.027).

Discussion

This study revealed that the neurotransmitter modulation on intrinsic network architecture underwent reconfiguration in the CHR-P population, which was associated with the spatial distribution of norepinephrine transporters. Our findings provide new insights into the integrated "chemical-connectivity" mechanisms of psychosis.

The study was supported by the General Research Fund (grant number: 17124715, 17127417) from the Research Grants Council in Hong Kong.

26-P010 *26 Aug 2026*

NMN Treatment Improves Remyelination and Mitochondrial Function in the Chronic Cuprizone-Induced Demyelination Mouse Model

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Abstract

Chronic demyelination in multiple sclerosis is associated with impaired remyelination, mitochondrial dysfunction, oxidative stress, and activation of cellular senescence, which limit therapeutic recovery. This study aimed to evaluate the therapeutic efficacy of nicotinamide mononucleotide (NMN) in a mouse model of chronic cuprizone-induced demyelination, with a particular focus on mitochondrial restoration as a mechanism for myelin repair. Adult mice were fed a cuprizone-containing diet for 12 weeks to induce long-term demyelination and were treated with NMN (100 mg/kg, intraperitoneally) during the final four weeks. Brain tissues were analyzed for myelin integrity, mitochondrial morphology, oxidative stress markers, and expression of myelin- and senescence-associated genes using histological staining, transmission electron microscopy, biochemical assays, and quantitative gene expression analysis. Chronic cuprizone exposure caused severe myelin disruption in the corpus callosum, reflected by increased g-ratio, reduced myelin thickness, abnormal myelin splitting, and a marked decrease in the proportion of myelinated axons. These alterations were accompanied by pronounced mitochondrial abnormalities, including disrupted ultrastructure, a substantial reduction in the mtDNA to nDNA ratio, increased lipid peroxidation and ROS, and depletion of glutathione. NMN treatment significantly reduced g-ratio, improved myelin thickness, partially restored myelin ultrastructure, and increased expression of the myelin-associated gene proteolipid protein. NMN also normalized mitochondrial morphology, restored mtDNA content, reduced oxidative stress, and suppressed the upregulation of senescence-associated genes p16 and p53, while having limited effects on cell cycle–promoting gene expression. In conclusion, NMN attenuates chronic demyelination by improving mitochondrial function and reducing cellular senescence, highlighting its therapeutic potential for chronic demyelinating disorders.

26-P011 *26 Aug 2026*

Alpha-melanocyte Stimulating Hormone Protects Retinal Neurons from Ischemia/reperfusion Injury by Regulating Ferroptosis

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Abstract

Retinal ischemia/reperfusion (RIR) injury is a significant cause of vision loss; it occurs when blood supply is restored following vascular blockage. Ferroptosis, characterized by iron-dependent lipid peroxidation, can be induced by ischemia/reperfusion injury. Alpha-melanocyte-stimulating hormone (α-MSH), an antioxidative and anti-inflammatory peptide hormone, is known for its protective effects against I/R-induced cellular damage. However, its role in RIR-related ferroptosis remains unclear. This study aimed to investigate the relationship between α-MSH neuroprotection and ferroptosis in RIR injury. Mouse photoreceptor 661w cells were subjected to oxygen-glucose deprivation/reperfusion (OGD/R) for in vitro analysis, while RIR was induced in C57BL/6J mice using the middle cerebral artery occlusion (MCAO) model for in vivo evaluation. Retinal function was assessed using electroretinography (ERG), and ferroptosis-related markers were evaluated through Western blotting, immunofluorescence staining, and metabolic assays. Notably, α-MSH enhanced the glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis, regulated iron storage (ferritin light chain, FTL), reduced levels of lipid peroxides (e.g., 4-hydroxynonenal and malondialdehyde), and preserved mitochondrial integrity following I/R-induced ferroptosis. This study provides novel insights into the neuroprotective effects of α-MSH through the regulation of ferroptosis.

26-P012 *26 Aug 2026*

Investigating the Impact of TRIP12 Mutation on Neural Development Using Human Neural Organoid Model

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Abstract

TRIP12 (Thyroid Hormone Receptor Interacting Protein 12) is an E3 ubiquitin ligase that plays a pivotal role in regulating several key cellular processes, such as protein degradation, DNA damage response, and chromatin remodeling. Mutations in the TRIP12 gene are known to be closely associated with various neurodevelopmental disorders, and its complete loss-of-function leads to early embryonic lethality, underscoring its essential role in embryonic development. However, this early lethality has hindered a detailed analysis of its specific roles during neural development. To overcome this limitation, we utilized human pluripotent stem cell (hPSC)-derived neural organoids (NO) as an in vitro neurodevelopmental model to investigate the impact of TRIP12 deficiency. While TRIP12-deficient hPSCs successfully maintained their stemness, they often exhibited concentrated cell death foci and displayed alterations in spontaneous symmetry breaking as cell colonies expanded.

Furthermore, we observed a significant retardation in the growth of TRIP12-deficient NO. Concurrently, single-cell RNA sequencing (scRNA-seq) analysis of long-term cultured NO revealed that the loss of TRIP12 disrupted regionalization and the cell composition of neuro-glial subtypes. Taken together, these findings demonstrate that TRIP12 is a critical regulator mediating diverse processes during human neural development. Ongoing analyses using this organoid model will elucidate the precise molecular mechanisms and further clarify the link between TRIP12 dysfunction and neurodevelopmental disorders such as Autism Spectrum Disorder (ASD).

26-P013 *26 Aug 2026*

The role of parvalbumin interneurons in modulating microglia functions in Alzheimer's disease

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Abstract

The role of parvalbumin interneurons in modulating microglia functions in Alzheimer's disease Alzheimer's disease (AD) is characterized by progressive cognitive decline, widespread brain atrophy, extracellular amyloid-β (Aβ) plaques, and intraneuronal tau tangles. Sleep disruption is a prominent hallmark of aging and a recognized risk factor for AD, yet the mechanistic links between altered sleep architecture and stage-specific AD pathology remain poorly understood. Microglia, the brain's resident innate immune cells, continuously survey the parenchyma to maintain tissue homeostasis and regulate synaptic plasticity. Although emerging evidence suggests that sleep states modulate microglial dynamics, how sleep impairment perturbs microglia–neuron communication and immune function in AD remains elusive. Here we show that activation of parvalbumin-positive (PV+) interneuron activity improves sleep quality, enhances gamma-band power, and transiently modulates microglial immune function to promote Aβ plaque clearance in an AD mouse model. Combining in vivo two-photon imaging, EEG, and single-nucleus RNA sequencing (snRNA-seq), we characterize how PV+ interneurons manipulate microglial states during sleep to rejuvenate microglial functions. Together, these findings establish a direct link between sleep homeostasis and microglial pathobiology, offering fresh insights into AD progression and pointing to potential neuroimmune therapeutic targets.

26-P014 *26 Aug 2026*

Genomic and Functional Investigation of the Role of CACNB1 in Autism

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Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopment condition characterized by impairments in social interaction, repetitive behavior, and communication, with a multifactorial genetic origin. Although ASD can be diagnosed as early as 18 months of age based on developmental history and behavioral observation, the limited understanding of its genetic and molecular mechanisms hampers the development of effective therapies, highlighting the urgent need for therapeutic advancements. This study aims to investigate the genomic and functional aspects of an ASD risk gene, focusing specifically on novel tandem repeat expansions in a calcium voltage-gated channel auxiliary subunit beta 1 (CACNB1) gene.

To elucidate the role of CACNB1 in ASD, we employed a Cacnb1 knockdown approach in rodent models, targeting ASD-relevant brain regions, medial prefrontal cortex (mPFC). Behavioral assessments, including the three-chamber test, open-field test, and self-grooming analysis, were conducted to evaluate the severity of social impairments and repetitive behaviors. Results indicated that mice with Cacnb1 knockdown in the mPFC exhibited heightened anxiety and reduced preference for social novelty. Furthermore, we investigated spine morphology in vivo to examine the relationship between morphological alterations and synaptic transmission. Our findings revealed that neurons with Cacnb1 knockdown displayed more mature spines, as well as higher spine protrusion density, suggesting that CACNB1 plays a critical role in the formation of mature dendritic spines.

This project aims to elucidate the complex genetics of ASD by investigating the impact of novel genetic variants on CACNB1 gene. Future work will focus on the molecular mechanisms underlying repeat expansion in CACNB1 gene and its potential contributions to the manifestation of ASD symptoms.

Funding. This work was supported by the Lo Kwee-Seong Biomedical Research Fund (J.I.), the Faculty Innovation Awards (FIA2020/A/04 to J.I.) from the Faculty of Medicine, The Chinese University of Hong Kong, and Gerald Choa Neuroscience Institute Research Program Fund (J.I.).

26-P015 *26 Aug 2026*

Employing Organoids to Explore Patients-Associated Mechanisms in CDKL5 Deficiency

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Abstract

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CDKL5 mutations cause a rare neurodevelopmental disorder with severe neurological impairment, yet the contribution of brain region-specific mechanisms to disease progression remains poorly understood. Here, we generated various brain regions-specific organoids that recapitulate key structural features of the human brain.

Using this platform, we aim to investigate whether CDKL5-related disease is accompanied by specific alterations in subtype structure. We compare organoid-derived tissues and their protein profiles with those from disease-associated Cdkl5-mutant mouse models. In parallel, we will benchmark these findings against relevant human datasets to evaluate conserved and disease-relevant molecular changes.

This study will establish a human-relevant organoid system for examining CDKL5 mutation-associated abnormalities from the perspective of neuro biology. By integrating organoid, mouse, and human data, we seek to identify potential biomarkers, pathological signatures, or intervention points that may provide new insight into CDKL5 deficiency and related rare neurodevelopmental disorders.

26-P016 *26 Aug 2026*

Targeting TRPM7 with Carvacrol Alleviates Microglial Neuroinflammation and Meliorates Cognitive Deficits in Alzheimer's disease

*Ming-Ki Maggie Leung **(Presenter)**[1,2], Benjamin Chun-Kit Tong[1,2], Aston Jiaxi Wu[1,2], Alexis Shiying Huang[1,2], Olivia Ka-Yi Ho[1,2], Xiaoming Cui[1,2], Flora Xuejing Lu[1,2], Min Li[1,2], King-Ho Cheung[1,2]*

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Abstract

Background

Dysregulation of intracellular calcium (Ca2+) homeostasis is a critical driver of chronic neuroinflammation in Alzheimer's disease (AD). The transient receptor potential melastatin-7 (TRPM7) channel acts as an inflammatory molecular switch in peripheral macrophages and is highly expressed in the central nervous system. However, its role in modulating neuroinflammatory microglial phenotypes remains poorly understood. This study evaluated the therapeutic potential of targeting TRPM7 using carvacril, a natural compound derived from traditional Chinese medicine, to mitigate AD-associated neuroinflammation.

Experiemtnal Approach

Neuroinflammatory responses were modeled in mouse and human microglial cells stimulated with lipopolysaccharides (LPS) or interferon-gamma (IFN-γ). The regulatory effects of TRPM7 inhibition on cytoplasmic Ca2+ dynamics and pro-inflammatory phenotypes were assessed in vitro. Furthermore, the in vivo therapeutic efficacy of the TRPM7 inhibitor carvacrol was evaluated in 5xFAD transgenic mouse models.

Key Findings

LPS and IFN-γ stimulation significantly elevated inatracellular Ca2+ levers and promoted a robust pro-inflammatory microglial phenotype. Pharmacological inhibition of TRPM7 with carvacrol effectively suppressed these cytosolic Ca2+ surges and dose-dependently mitigated microglial neuroinflammatory responses. Crucially, in vivo administration of carvacrol markedly enhanced amyloid-b (Ab) plaque clearance and successfully rescued cognitive deficits in 5xFAD mice.

Significance

This study reveals a novel mechanism wherein TRPM7 execution drives microglial activation and perpetuates neuroinflammation via aberrant Ca2+ signaling. Targeting TRPM7 with carvacrol represents a promising, translationally viable therapeutic strategy to combat chronic neuroinflammation and cognitive decline in neurodegenerative diseases.

Acknowledgment

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26-P017 *26 Aug 2026*

Developing experimental strategies for neuromuscular organoid maturation to model late-onset spinal muscular atrophy

Jessica Jianghan Lu ***(Presenter)***[1], *Alex To*[1], *Chao Liang*[2], *Rio Sugimura*[1], *Sang Jin Lee*[2], *Martin Cheung*[1]

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Abstract

Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by homozygous mutations in the SMN1 gene, leading to motor neuron degeneration and muscle atrophy. Current treatments slow symptom progression but cannot restore lost neurons, making early intervention critical. However, diagnostic delay persists in adult-onset SMA (types III and IV) due to their poorly understood pathogenic trajectory. Patient-derived neuromuscular organoids (NMOs) provide a promising platform for modelling SMA, yet current NMOs lack sufficient maturation to recapitulate the gradual neurodegeneration characteristic of adult-onset SMA. This project aims to apply established brain organoid maturation strategies to NMOs for modelling late-onset SMA. These strategies include: vascularisation of NMOs via fusion with vascular organoids, transplantation of NMOs into vascularised organs of immunodeficient mice, and epigenetic-drug-induced acceleration of neuronal maturation. Fusion with vascular–immune organoids successfully generated vascularised NMO assembloids, which integrated CD31+ vasculature and showed increased NeuN and ChAT expression, suggesting enhanced neuronal and motor neuron maturation. Transplantation of NMOs into immunodeficient mice enabled host vascular integration and the emergence of neural tube-like structures, demonstrating the capacity of in vivo cues to drive tissue organisation. Finally, epigenetic modulation using DOT1L and EZH2 inhibitors increased NMO neuronal activity measured by calcium imaging. Enhancing NMO maturation will improve understanding of SMA type III/IV pathogenesis, inform optimal therapeutic windows, and identify new targets to enhance treatment efficacy.

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26-P018 *26 Aug 2026*

Mechanism-Based Drugs and Oligogenic Refractory Epilepsy

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Abstract

Refractory epilepsy is sometimes associated with an oligogenic background. However, the gene-gene interaction of oligogenic background is easily overlooked in genetic diagnosis. Two recent typical studies about oligogenic refractory epilepsy would guide the mechanism-based drug selection for this complex neural disorder.

One case, with a missense variant in CACNA1A and a truncating variant in CELSR2, suffered from developmental epileptic encephalopathy for more than twenty years. Digenic mutant Drosophila were established to mimic the patient's genotype, and it was found that the CACNA1A variant was concluded as a Gain-of-Function mutation and acted as the major pathogenic driver within this digenic system. Inhibiting the function of CACNA1A during development, via either genetic (CACNA1A KD) or pharmacologic (pregabalin) approaches, can completely rescue the severe seizure phenotype of the digenic mutation model. The other case suffered from complex focal epilepsy for nine years. Compound heterozygous variants in UBR4 and LRP1, and a de novo truncating variant in OPHN1 were identified. LRP1 was identified as the major risk gene in the UBR4-LRP1-OPHN1 trigenic background by using machine learning on trigenic Drosophila experimental

data. Transcriptome sequencing indicated that epileptic pharmacoresistance was triggered by irregulating of ASIC gene family. Based on that, ketogenic diet would be the target therapy for the UBR4-LRP1-OPHN1 trigenic case.

The oligogenic effects in neurological disorders require animal models for investigation, as behavioral and electrophysiological studies are necessary and specific to neurology research. Drosophila is one of the ideal options due to its short lifespan, powerful genetic manipulation, and efficient use of ethological and electrophysiological assays. It can help physicians rapidly identify the major pathogenic variant and design precision medicine strategies for patients. This is especially critical for neurodevelopmental disorders, which typically have a limited therapeutic window.

26-P019 *26 Aug 2026*

Liquid Biopsy for Glioblastoma Immune Evasion by Plasmonic Biosensing of Exosomal PD-L1 or PD-1 from Tumor Cells and Their Associated Microglia

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Presenter: *Lina Bao*

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Abstract

Glioblastoma (GBM) is a highly aggressive brain tumor with limited options for early diagnosis and effective treatment, partly due to the restrictive blood-brain barrier (BBB). Glycolytic reprogramming is a key metabolic feature of GBM, leading to increased lactate production. Elevated lactate levels are closely associated with PD-L1 upregulation and enhanced exosome secretion. These exosomes can cross the BBB and enter peripheral circulation, where exosomal PD-L1 may contribute to systemic immune suppression by interacting with PD-1 on T cells.

However, the use of exosomal PD-L1 and PD-1 derived from GBM cells (GMs) and GBM-associated microglia/macrophages (GAMs) as peripheral biomarkers remains insufficiently explored. Non- or minimally invasive detection strategies using ultrasensitive, label-free optical biosensors are still limited.

In this study, we found that PD-L1 or PD-1 expressions were markedly increased in GMs, GAMs, and their derived exosomes, especially under lactate-enriched conditions. These findings support exosomal PD-L1 and PD-1 as potential biomarkers reflecting the immunosuppressive GBM microenvironment.

To enable ultrasensitive detection, we developed an Au-Pt bimetallic nanoislands (BNIs)-based localized surface plasmon resonance (LSPR) biosensor. This platform sensitively detected elevated PD-L1 levels on exosomes derived from lactate-treated GMs. Importantly, the biosensor further detected increased PD-L1 or PD-1 levels in immunocapture-enriched exosomes from GMs and GAMs, as well as in total serum exosomes from GBM mouse models and patients.

Overall, our results demonstrate that the Au-Pt BNIs LSPR biosensor enables rapid, label-free, and ultrasensitive detection of exosomal PD-L1 and PD-1 in blood. This platform provides a promising liquid biopsy strategy for minimally invasive monitoring of GBM immune evasion and therapeutic response.

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26-P020 *26 Aug 2026*

Developing a peptide inhibitor to alleviate GGGGCC-induced C9ALS/FTD by suppressing RNA and protein toxicities

*Hui Zhen Chen **(Presenter)**[1], CHEN, Gang[2], CHAN, Ho Yin Edwin[1,3]*

Presenter: *Hui Zhen Chen*

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Abstract

The GGGGCC hexanucleotide repeat expansion in the C9orf72 gene is the predominant genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two neurodegenerative disorders characterized by progressive neuronal degeneration. The pathogenic mechanisms involve the accumulation of GGGGCC repeat RNA, which forms RNA foci and undergoes repeat-associated non-ATG (RAN) translation, leading to the production of dipeptide repeat (DPR) proteins. These toxic species collectively drive cellular dysfunction and neurotoxicity. Thus, targeting the expanded GGGGCC RNA in

C9ALS/FTD may represent a potential therapeutic strategy. We designed HZX1 to neutralize expanded GGGGCC RNAinduced toxicity. In vitro characterization demonstrated that HZX1 exhibits high affinity and specific binding to GGGGCC RNA. Functional validation in cellular models of C9ALS/FTD revealed that HZX1 effectively inhibits GGGGCC RNA-induced cell death.

26-P048 *26 Aug 2026*

Panaxatriol Ginsenoside Attenuates Ischemic Stroke Injury by Inhibiting Neuronal Apoptosis and Neuroinflammation via STAT3 inhibition

*Yan Pan **(Presenter)** [1,2,3], Yi Li [2,3], Xiaohe Han [2,3], Chi Wai Lee[1], Shiqing Zhang [2,3], Lei Shi [2,3], Ken Kin Lam Yung[4]*

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Abstract

Stroke includes ischemic and hemorrhagic types, with ischemic stroke being the primary one, characterized by high morbidity, mortality, disability and recurrencerates, it significantly impacts patients'daily lives and imposes a heavy burden on families and society. To date, the intravenous thrombolysis with tissue plasminogen activator (t-PA) remains the most important pharmaceutical treatment for the acute phase of ischemic stroke via restoring cerebral blood flow. However, its clinical utility is severely limited by a narrow therapeutic window and the inherent risk of hemorrhagic transformation. Therefore, there is an urgent need to identify new and effective drugs. Natural products serve as an important source for discovering innovative drugs, and ginseng, a precious medicinal plant, possesses various pharmacological effects such as anti-inflammatory and antioxidant properties. Among its main active ingredients, ginsenosides of the panaxatriol type are of particular interest. However, research on their anti-ischemic stroke effects is limited. This study aims to explore the anti-ischemic stroke effects and mechanisms of panaxatriol ginsenoside (PG1).

Internal States and Homeostasis

24-P038 *24 Aug 2026*

State-dependent plasticity of the olfactory cortex regulates novel food learning

Esther Fung Yin Ngo ***(Presenter)***[1,2], *Nanqin LI*[1,2], *Chun Yue Geoffrey LAU*[1,2]

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Abstract

"Is this new food safe for me to eat?" The ability to assess nutritional content of novel food and incorporate into dietary regimen enhance the chance of survival in animals. A new food exudes complex smell (olfactory information) that can be detected from afar, providing first line of information to create new perception. The anterior piriform cortex (APC) is located one synapse downstream of the olfactory bulb and is the largest olfactory area for odor discrimination, perception, learning and memory. While hunger is well-known to modulate multiple neural circuits to promote food-seeking behavior and consumption, how it modulates the APC for novel food learning is less explored. Here, we investigated whether acute fasting in mice can alter their exploration for novel food and neural representation in the APC. We first characterized the mice's food foraging and intake by developing a new food learning paradigm where laboratory mice were exposed (trained) to a new food (peanut butter; PB) that is more palatable and rewarding. When given a choice of familiar food chow and PB, fasted, naïve mice preferred the laboratory chow. Surprisingly, the fasted mice preferred it over the laboratory chow after training to PB. The exposure to PB strongly activated the APC neurons and enhanced structural excitatory synapses. The population response to PB odor also increased among the APC principal neurons in odor assay coupled with fiber photometry. Chemogenetic inhibition of the APC prevented the mice from acquiring this learned preference for PB but did not abrogate the preference for innate pheromone odors, nor the recall of learned PB odor. These results illuminate the role of a higher olfactory region, the APC, in learning and recall of novel food substances. Our findings will pave the way for discovering neural circuits that link sensory information to control of feeding behavior.

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25-P028 *25 Aug 2026*

Intranasal Delivery of Melatonin-loaded Lipidic Nanocapsules Ameliorates Systemic Inflammation-Triggered Circadian Desynchrony and Neuroinflammation

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Abstract

Circadian rhythms play a critical role in regulating immune function and behavior, and disruptions to these rhythms are increasingly linked to systemic inflammation and neuroinflammation. This study aimed to investigate the effects of melatonin-loaded lipidic nanocapsules on systemic inflammation induced neuroinflammation and disruptions in circadian rhythms, in comparison with melatonin. Here, we induced systemic inflammation in C57BL/6J mice using intraperitoneal (i.p.) injections of lipopolysaccharide (LPS). The i.p. injection of LPS disrupted diurnal expressions of circadian clock genes and proinflammatory cytokines, inducing inflammatory responses in liver and brain tissues. Intranasal delivery of MEL-LNC treatment modulated diurnal rhythmicity of circadian clock genes and proinflammatory cytokines, and reduced neuroinflammation. These modulatory effects outweighed those observed following the conventional melatonin treatment. These findings underscore the therapeutic potential role of melatonin-loaded lipidic nanocapsules for ameliorating circadian disruption and neuroinflammation under challenge.

25-P056 *25 Aug 2026*

Advancing Personalized Self-Regulation Neuroscience Through Multimodal Prediction of HRV Biofeedback Response

*Sumin Kim **(Presenter)**[1], Sungwoo An, Sanghoon Han[1]*

Presenter: *Sumin Kim*

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Abstract

Introduction

Heart rate variability biofeedback (HRV biofeedback) is a non-invasive self-regulation approach that provides real-time physiological information to support autonomic and emotional regulation. However, training response varies across individuals, and objective predictors of benefit remain insufficiently characterized. This study examined whether pre-intervention prefrontal functional connectivity measured with functional near-infrared spectroscopy (fNIRS), PPG-derived HRV indices, and inhibitory control performance predicted response to VR-based HRV biofeedback.

Methods

Healthy adults were assigned to either a real HRV biofeedback condition or a control condition presenting random HRV-like information. Participants completed three laboratory visits. At each visit, resting-state fNIRS and photoplethysmography (PPG) were recorded before and after training. PPG signals were used to derive heart rate and HRV indices, including RMSSD and SDNN. Participants also completed an emotional Go/No-Go task assessing inhibitory control and questionnaires measuring emotion regulation, anxiety, and stress. In the real biofeedback condition, visual feedback in VR reflected the participant's physiological state, whereas in the control condition, the displayed HRV-related information was not linked to real-time physiology.

Results

VR-based HRV biofeedback produced selective physiological changes rather than broad improvement across all outcomes. Compared with the control condition, the real biofeedback condition showed greater increases in PPG-derived HRV indices, particularly RMSSD, whereas self-reported stress and emotional state improved modestly in both groups. Emotional Go/No-Go performance showed practice-related improvement across visits, with limited condition-specific effects. Task-based fNIRS analyses indicated that baseline prefrontal connectivity was associated with individual variability in HRV change, but pre–post intervention changes were less consistent.

Conclusion

These findings suggest that VR environment biofeedback may primarily modulate autonomic regulation, while behavioral and neural effects vary across individuals. A multimodal framework combining fNIRS, PPG-derived HRV, behavior, and self-report may help identify who benefits most from biofeedback-based self-regulation training.

26-P021 *26 Aug 2026*

Rab23 modulates the ciliary and membrane trafficking of MC4R to regulate leptin–melanocortin axis

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Abstract

Carpenter Syndrome (CS) is a rare genetic disorder characterized by various clinical manifestations, including obesity, craniofacial malformations, and polydactyly. Mutation in the RAB23 gene, which encodes a small GTPase, is the causative factor for CS, yet the mechanisms linking RAB23 dysfunction to disordered energy balance remain poorly explored. Here, we investigated the role of Rab23 in central control of feeding by selectively deleting Rab23 in neural progenitor cells at ~E10.5 by using Nestin-Cre crossed with Rab23-floxed homozygous mutant. Mice with CNS-specific Rab23 loss developed hyperphagia-driven obesity, displayed hypothalamic leptin resistance (blunted leptin-induced pStat3) and reduced Mc4r expression. Consistent with impaired leptin signaling pathway, MC4R agonist failed to suppress food intake in mutants. To test whether hypothalamic neuronal loss of Rab23 is sufficient for this deficit, we delivered an adeno-associated virus expressing Cre under the Synapsin-1 promoter (AAV-hSyn-Cre) to the hypothalamus, which reproduced the reduced feeding

suppression to MC4R agonist. Furthermore, restoring Rab23 in hypothalamic neurons recovers leptin–melanocortin signaling activation and the feeding response, indicating that hypothalamic Rab23 is necessary to maintain melanocortin-dependent regulation of food intake. In addition, AAV-mediated Mc4r overexpression in the hypothalamic neuron rescued agonist responsiveness in vivo. Mechanistically, Rab23-deficient neurons showed mislocalization of ciliary MC4R and reduced primary ciliation in the hypothalamus, indicating impaired ciliary-dependent receptor positioning. In cultured cells, Rab23 depletion increased MC4R at the cell surface and impaired agonist-induced internalization, suggesting Rab23 regulates both membrane trafficking and ciliary MC4R dynamics to modulate hypothalamic leptin-melanocortin signaling. Together, these findings identify Rab23 as a critical regulator of the leptin–melanocortin signaling pathway, acting through both neuronal leptin responses, MC4R ciliary and membrane trafficking, and provide a potential mechanism for CS-associated obesity.

26-P022 *26 Aug 2026*

A thalamocortical circuit with central lateral nucleus and anterior cingulate cortex optimizes flight behavior via subcortical areas

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Abstract

Innate defensive behavior is vital for animal survival and must be actively regulated to elicit appropriate responses. This study identifies a pathway from the central lateral thalamic nucleus (CL) to the posterior anterior cingulate cortex (pACC) that optimizes sound-induced flight behavior. We demonstrate, using anatomical tracing and physiological recordings, that both pACC-projecting CL neurons and their target pACC neurons encode key variables of this behavior, such as sound intensity and flight speed. Functional manipulations reveal that the CL-pACC pathway functions as a 'brake' on flight: activation suppresses it, while silencing facilitates it. Mechanistically, CL projections primarily drive layer 5 pACC neurons, which activate GABAergic neurons in the zona incerta (ZI), inhibiting the superior colliculus (SC) in its deep layers. Additionally, this pathway boosts visual responses in SC's superficial layers, likely improving navigated flight. By regulating subcortical areas and enhancing visual responses, the CL-pACC pathway prevents overreaction and supports adaptive flight, thereby increasing survival.

26-P023 *26 Aug 2026*

Modulation of Sexual Behavior by Social Defeat in Male Mice

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Abstract

The perception of sexual attractiveness and the expression of sexual behavior can be shaped by prior intense experiences, including fear- and stress-related states. However, the neural mechanisms through which such experiences influence subsequent sexual responses remain poorly understood. Here, we investigated the behavioral and neural basis of prior social stress exposure for female preference and subsequent mating behavior in male mice. We found that this social defeat consistently increased male mice's preference for females and facilitated subsequent mating behaviors. To identify the neural basis underlying this phenomenon, we performed neural activity mapping and in vivo fiber photometry recordings, which identified the medial amygdala (MeA) as a candidate region engaged during both social defeat and subsequent sexual behavior. Optogenetic manipulations further showed that MeA activity is required for social stress-induced enhancement of mating behavior. Calcium imaging revealed overlapping MeA neuronal ensembles recruited across social defeat and mating, suggesting a shared neural substrate linking these behavioral states. Complementary in vitro patch-clamp recordings showed

that this behavioral state is accompanied by increased excitability of MeA neurons. Together, these findings implicate the MeA in linking social defeat to transient changes in subsequent sexual behavior.

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26-P024 *26 Aug 2026*

Role of BMP signaling in the regulation of cerebrospinal fluid extracellular vesiclebiogenesis in choroid plexus

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Abstract

Cerebrospinal fluid (CSF), which directly contacts the central nervous system (CNS), plays an important role in shaping the CNS extracellular microenvironment and its development and functioning. One of the main components of CSF is extracellular vesicles (EVs), which can serve as transport vehicles for important molecules such as nucleic acids, proteins, metabolites, and signaling molecules. However, the mechanisms underlying CSF production remain poorly understood. Most of the CSF is produced by the choroid plexus (CP), an epithelial tissue located in each brain ventricle. Our previous studies have found that the depletion of transcription factor Sox9 in mouse CP resulted in EVs decrease in the CSF. Additionally, the expression of pSMAD1/5, an important signaling molecule in the canonical Bone Morphogenic Protein (BMP) signaling pathway, was reduced in CP epithelial cells of Sox9 conditional mutant mice. Furthermore, CP treated with a pharmacological inhibitor of the BMP signaling pathway exhibited lower CD63 expression, a classic EV marker. Hence, we hypothesize that BMP may affect the biogenesis of CSF EVs in CP. To test this hypothesis, we used two BMP inhibitors with different mechanisms: BMP receptor inhibition Dorsomorphin and the BMP antagonist Noggin. We first determined the role of BMP on EV by analyzing the expression of EV markers: CD63 and CD9. Further, to identify the stage of EV biogenesis affected by BMP, we detect the expression of selected markers for the different stages of EV biogenesis process—ranging from endosomes to exosomes. In the future, we will identify the BMP ligand related to EVs formation in CP, and the associated molecular mechanism will be investigated. In conclusion, this study aims to explore the role of BMP signaling in the regulation of CSF EV biogenesis within the CP of the CNS and its relationship to CNS development and functioning.

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26-P025 *26 Aug 2026*

Pilot Study of Whole-Brain c-Fos Imaging in a Suncus murinus Model of Cisplatin-Induced Emesis

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Abstract

Background

Chemotherapy-induced nausea and emesis (CINV) remains a major clinical challenge, and its underlying central neural mechanisms are not fully understood. Because common laboratory rodents do not vomit, Suncus murinus provides a valuable model for investigating emetic pathways. This study aimed to establish a three-dimensional whole-brain c-Fos imaging approach using light sheet fluorescence microscopy (LSFM) to map neuronal activation associated with cisplatin-induced emesis in Suncus murinus.

Methods

Adult male Suncus murinus were treated with saline (10 ml/kg, i.p.) or cisplatin (10 mg/kg, i.p.), and emetic and spontaneous behaviours were recorded for 2 h. After behavioural assessment, animals were perfused, and brains were collected for optical tissue clearing using an iDISCO+-based protocol. Cleared brain hemispheres were immunolabelled for c-Fos and imaged using LSFM. Fluorescence intensity in coronal brain sections containing brainstem regions was analysed using ImageJ.

Results

Cisplatin treatment induced emesis in 6 out of 6 animals, comprising 6.7 ± 1.1 episodes of retching and vomiting, 34.2 ± 6.4 retches, and 6.3 ± 0.9 vomits, with a median latency of 42.3 min (interquartile range: 36.9–47.5 min). Three-dimensional LSFM imaging successfully detected c-Fos immunofluorescence in brainstem regions involved in emesis, including the area postrema and nucleus tractus solitarius, as well as forebrain regions including the hypothalamus and cortex. Further analysis of coronal brain sections showed that fluorescence intensity in the area postrema and nucleus tractus solitarius was higher in cisplatin-treated animals than in saline-treated controls.

Conclusion

This pilot study established a three-dimensional whole-brain c-Fos imaging approach in Suncus murinus. The method enabled visualization of cisplatin-induced neuronal activation in key emesis-related brain regions and may provide a useful platform for investigating the central mechanisms of CINV. However, further development of a complete Suncus murinus brain atlas is required to support accurate whole-brain regional quantification.

Acknowledgement

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26-P039 *26 Aug 2026*

Effects of Lignosulfonate on Emotional Behavior and Stress Responses in Male Rats

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Abstract

Lignosulfonate, a by product of paper manufacturing, is known for its antioxidant, adhesive, and chelating properties. However, its use has been mainly industrial, and its physiological effects in mammals remain unclear. Previous studies have shown inconsistent effects of lignin rich diets on steroid hormones, with plasma corticosterone levels increasing in female rats, whereas salivary and fecal cortisol levels decreased in pregnant Meishan sows. These findings suggest that lignin may influence steroid hormones through the HPA axis, although the mechanism is not fully understood. Therefore, because steroid hormone fluctuations can affect organs and emotional behavior, further evaluation of lignin's physiological effects is needed. This study examined the effects of dietary lignosulfonate on anxiety like behavior, organ weights, and restraint stress induced plasma corticosterone response in male rats. Four groups were prepared: control, 10% cellulose, 2% lignin, and 10% lignin. Starting from 3 weeks of age, Wistar Imamichi male rats were fed standard feed or feed mixed with lignosulfonate. The cellulose group containing cellulose was included as a negative control to distinguish lignin specific effects. At 9 weeks of age, anxiety-loke behavior was assessed using the open field test and elevated plus maze. At 10 weeks, blood sampling was conducted after restraint stress exposure for 0, 15, or 120 minutes.. The blood was collected without anesthesia, plasma was isolated, and corticosterone levels were measured using ELISA. Organ weights were also subsequently measured. Body weight at 10 weeks was significantly lower in the 10% lignin group than in the control and 2% lignin groups. Kidney weight was highest in the 10% lignin group, whereas the cellulose group had a significantly lower kidney weight than the control. No effects were observed for anxiety like behavior or plasma corticosterone levels. Further studies are needed to clarify dose dependent effects and underlying mechanisms.

26-P050 *26 Aug 2026*

A recurrent septo-subfornical circuit drives water seeking

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Abstract

# These authors contributed equally to this work.

Water seeking is a fundamental survival behavior essential for fluid homeostasis, yet the precise neural pathways governing this behavior remain unclear. Here we identify a septal glutamatergic circuit that selectively facilitates water seeking. Recurrent switching linear dynamical system (rSLDS) modelling reveals thirst-dependent organization of the neural-behavioral dynamics of subfornical organ (SFO)-projecting medial septum (MS) CaMKII-expressing glutamatergic (MS-CaMKII) neurons during goal-directed water seeking. Activation of these MS-CaMKII-SFO neurons enhances locomotion and specifically promotes water seeking in water-restricted mice, whereas time-locked inhibition of the MS-CaMKII-SFO circuit impairs water-seeking behavior. A recurrent excitatory SFO-MS circuit conditionally amplifies dehydration signals, transforming interoceptive thirst signals into goal-directed water-seeking behavior. This work establishes a new conceptual framework for understanding how the brain converts homeostatic need into organized, goal-directed water-seeking behavior.

Neural Methods and Technology

25-EP2 *25 Aug 2026*

Fixation with the two-carbon dialdehyde glyoxal facilitates multiscale label-free 3D brain imaging in mice

*Haruka Takano **(Presenter)**[1], Takanobu Nakazawa [2,3], Ryota Hashimoto [3], Hitoshi Hashimoto [1,3–7]*

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Abstract

A recent data-driven analysis of brain MRI images from 5,604 participants by the Cognitive Genetics Collaborative Research Organization (COCORO) consortium, led by co-speaker R. Hashimoto, identified four brain biotypes across major psychiatric disorders. Although these biotypes are expected to pave the way for objective diagnostic methods due to their correlation with cognitive and social functions, elucidating their underlying biological mechanisms requires detailed analyses using disease model mice. To advance research in this direction, we recently developed FAST (block-FAce Serial microscopy Tomography), a macro-to-meso whole-brain imaging system designed to compare inter-individual variations in brain structure and activity in animal models in an unbiased manner.

In the present study, we achieved high-precision analysis of brain structures using FAST combined with a glyoxal-based fixation protocol, which yields high autofluorescence for increased anatomical contrast. Although endogenous autofluorescence is typically weak, we found that glyoxal-fixed brains displayed approximately 11-fold higher autofluorescence than paraformaldehyde (PFA)-fixed brains, enabling high-quality imaging without fluorescent labels. Compared with PFA-fixed tissue, glyoxal-fixed brains exhibited slight shrinkage and weight reduction, but these parameters remained stable over time. Furthermore, we confirmed that the application of an autofluorescence quenching reagent enabled clear post hoc c-Fos immunostaining.

Although autofluorescence is typically considered background noise in immunostaining, we leveraged glyoxal-enhanced autofluorescence as a robust signal for 3D imaging and subsequently suppressed it to enable immunofluorescence analysis. This autofluorescence is also highly useful for the 3D reconstruction of post hoc immunofluorescence images by aligning them with the original FAST images. In summary, leveraging the discovery of enhanced autofluorescence in glyoxal-fixed brains, we employed a 'counterintuitive' approach to establish a label-free, high-definition 3D structural analysis method that remains compatible with post hoc immunostaining. By providing a robust, brain-structure-based framework, this approach will contribute to elucidating the biological mechanisms underlying psychiatric disorders.

26-P026 *26 Aug 2026*

LATeNT: A novel light-activated tetanus neurotoxin for conditional synaptic inhibition

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Abstract

Current optogenetic silencing tools, including NpHR, Arch, and GtACRs, suppress neuronal activity through membrane hyperpolarization or inhibitory ion conductance. However, these approaches can induce rebound excitation, perturb ionic homeostasis, and broadly alter neuronal excitability rather than directly suppressing synaptic transmission. To overcome these limitations, we developed Light-Activated TeNT (LATeNT), a synapse-specific optogenetic silencing tool that inhibits vesicle release through light-dependent cleavage of the SNARE protein VAMP2. Using structure-guided protein engineering and directed evolution, we generated a compact single-chain LATeNT capable of rapid and reversible optical control of synaptic transmission in vivo. LATeNT functions across multiple brain regions and long-range projections, with synaptic

transmission recovering within 24 hours after light withdrawal. Using LATeNT, we identified a hippocampal interneuron population involved in anxiety-like behavior and demonstrated a requirement for postsynaptic SNARE-dependent endocannabinoid release during depolarization-induced suppression of inhibition (DSI). Together, these findings establish LATeNT as a versatile platform for inducible, reversible, and spatially precise suppression of vesicle-mediated cellular communication.

26-P027 *26 Aug 2026*

Establishing C. elegans nervous system biophysical atlas by systematic electrophysiology recording

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Abstract

There are many theories about how behavior is controlled by the nervous system. Testing and refining these theories would be greatly facilitated if we could accurately simulate an entire nervous system, replicating brain dynamics in response to various stimuli and contexts. However, modeling a nervous system by reconstructing biological circuits requires understanding each neuron output/input relationship which is determined by its intrinsic biophysical properties. Current efforts focusing on the modeling mammalian nervous system is limited by recordings from only a fraction of many complex subsystems. To address this problem, we chose C. elegans as our research model, which has a simple and well-defined nervous system with only 302 neurons and a complete connectome, making it possible to uncover the entire circuit with single-cell resolution. Guided by empirical data and the available connectome information in C. elegans, we aim to construct a circuit-level model that can simulate information flow and network dynamics, and motor output. We plan to systematically record every neuron type in C. elegans using our in vivo whole-cell patch-clamp method to achieve this goal. Here we present our progress on our systematic electrophysiological recording from worm neurons. Ultimately, we will work with theorists to attempt to construct a conductance-based system-level model that can help us understand how brain direct behavior.

26-P028 *26 Aug 2026*

A Rapid and De-Risked Blood-to-Nerve-Cell Manufacturing Platform for Personalized Treatment of Neurological Disorders

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Abstract

Neurological disorders present a massive healthcare burden, but current cell therapies face two major bottlenecks. First, donor-derived allogeneic cells require chronic, high-risk immunosuppression to prevent rejection. Second, therapies utilizing pluripotent stem cell intermediates carry a residual risk of tumor formation. To address these operational challenges, we designed an autologous reprogramming platform intended to streamline cell manufacturing and minimize safety risks by targeting a direct somatic-to-neural lineage transition.

Leveraging our group's work in decoding the structural and molecular logic of pioneer transcription factors, we utilized directed molecular evolution to engineer a high-performance SOX17 variant. Applying this factor aims to drive the direct, efficient conversion of human somatic blood cells into induced neural stem cells (iNSCs). Empirically, our blood-to-iNSC platform drastically optimizes manufacturing timelines, shortening the generation time of neural stem cells by approximately three weeks compared to standard pluripotent protocols. Furthermore, the resulting iNSCs successfully preserve somatic aging hallmarks, making them uniquely suited for modeling late-onset diseases.

In short, this rapid manufacturing platform offers a scalable strategy to generate personalized nerve cells directly from a patient's own blood. By accelerating production timelines and preserving donor age signatures, this technology provides a promising path forward for developing safe, autologous clinical treatments and disease models.

26-P029 *26 Aug 2026*

Rapid rescue of despair behaviors by sonogenetic neuromodulation of the mPFC-DRN pathway

*Ting Lei[1,3], Quanxiang Xian **(Presenter)**[1,3], Danni Li[1], Min Su[1], Yong Wu[1], Xuandi Hou[1], Jianing Jing[1], Yizhou Jiang[1], Xiaohui Huang[1], Kin Fung Wong[1], Jiejun Zhu[1,2], Jinghui Guo[1], Zhihai Qiu[1,2], Lei Sun[1]*

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Abstract

Sonogenetics combines genetic tools and low-intensity ultrasound to non-invasively modulate specific neuronal populations and circuits, exhibiting potential for treating brain diseases.

This study examines sonogenetics' potential in a mouse depression model, targeting excitatory medial prefrontal cortex (mPFC) neurons projecting to the dorsal raphe nucleus (DRN). Projecting neurons were induced to express a mechanosensitive ion channel, and alterations in patterns of neuronal activation and despair-like behaviors upon sonication were evaluated. Sonogenetics selectively activated targeted excitatory mPFC neurons projecting to the DRN, enhancing real-time DRN neuronal activity and serotonin release, with no observed tissue damage or astrocytic/microglial activation. Tail suspension and forced swim tests revealed that sonogenetically activating this pathway rapidly reversed despair-like behaviors in stressed mice, whereas effects observed upon mPFC sonication were abrogated by functionally silencing downstream DRN neurons, and this effect is fully recapitulated by selective inhibition of DRN serotonergic neurons alone.

Collectively, this study constitutes the first demonstration of the potential for a circuit-targeted sonogenetic therapeutic approach for relieving despair behaviors. Our findings establish sonogenetics as a non-invasive, cell-type-specific tool for both basic circuit dissection and potential therapeutic translation in mood disorders.

26-P030 *26 Aug 2026*

Indicator-invariant Domain Generalization for Spike Inference based on Calcium Imaging

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Abstract

Understanding how numerous neurons communicate with each other to generate movements and cognition is a central goal in neuroscience. Electrophysiology offers direct access to electrical neural spikes, but it is invasive and of low throughput. Calcium imaging has emerged as a powerful alternative because it can monitor the activity of large neuronal populations simultaneously. In calcium imaging, neurons are labelled with calcium-sensitive fluorescent indicators. When a neuron fires, the brightness changes, which can then be converted into fluorescence traces for individual neurons. Calcium imaging thus assesses neuronal electrical activity indirectly based on the above surrogate optical signal. Spike inference attempts to provide the reverse mapping of the fluorescence traces back to the neural electrical activities.

Existing spike inference methods perform good in dataset-independent manner, but the domain shifts within

different datasets have not been fully eliminated. A bottleneck in spike inference is the domain shift attributed to varying calcium indicator types, which hampers the robustness of models. In this paper, an indicator-invariant domain generalization approach is proposed. To better exploit the fundamental information from different types of calcium traces, the training data is first divided into three classes based on indicator properties. Taking this marginal distribution as label, the supervised adversarial training is applied to align the indicator domain shifts. Besides, the encoded features are utilized as adversarial input for indicator-invariant learning, where a style projector and the signal integral weights are proposed to filter uninformative indicator features. Finally, supervised learning is adopted to construct mapping between calcium trace and spike rate. The spike inference performances are validated in the experiments. It is proved that the proposed method achieves significant superior results compared with existing methods with correlations of 64.58% and bias of 0.15, revealing the efficiency and generalization across neurons.

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26-P031 *26 Aug 2026*

Sensitive Identification of Low-Frequency Somatic Mobile Element Insertions via End-to-End Segmentation and Classification of Long-Read Sequencing

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Presenter: *Ziting He*

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Abstract

Mobile elements (MEs), such as LINE-1, Alu, and SVA elements, can undergo retrotransposition in human neural stem cells, creating brain somatic mobile element insertions (MEIs) in simple or complex forms. Specific ME segments, such as LINE-1 5' promoters and 3' poly(A) signals, are implicated in gene dysregulation and may contribute to the etiology of neurological diseases. While long-read sequencing facilitates the complete identification of complex MEIs and improves detection within repetitive sequences, the direct detection of low-frequency somatic MEIs in bulk tissues remains constrained by sequencing artifacts and a poor signal-to-noise ratio.

Here, we propose that the precise arrangement of ME segments is not only essential for predicting functional consequences but also critical for distinguishing true MEIs from technical artifacts, such as PCR chimeras that randomly link sequences. We present a novel two-step deep learning framework: an initial module that performs single-base-resolution annotation of ME segments within long sequencing reads, followed by a second network that classifies the insertion as a true or false MEI based on the structural arrangement of those segmented labels.

Trained on over 3 million labelled sequencing reads annotated from 145 individuals of diverse genetic backgrounds, our method achieves an average precision exceeding 0.99 across all ME subtypes for both segmentation and classification, despite relying on only a single supporting read. This high accuracy, combined with a minimal requirement for supporting reads, makes it ideal for discovering somatic mutations in bulk sequencing datasets. Thus, our approach provides a powerful, high-resolution computational tool to advance the comprehensive profiling of mobile element insertions, and has the potential to provide further insights into the functional and pathological implications of somatic retrotranspositions.

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26-P032 *26 Aug 2026*

An improved atlas-guided parcellation framework for generating individualized functionally homogeneous brain atlas

Junchen Zhou ***(Presenter)***[1,2], *Siqi Yang*[1,2], *Wenxia Li*[3,4], *Jiao Li*[3,4], *Wei Liao*[3,4] *Changsong Zhou*[1,2,5]

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Abstract

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Brain atlases are essential for decoding the architecture of the human brain, yet substantial inter-individual variability demands more refined individualized parcellation strategies. Current approaches, such as atlas-guided parcellation (AGP), rely on uniform region-growing algorithms that overlook intrinsic functional heterogeneity across brain regions. To address this limitation, we introduce an improved AGP (IAGP) framework that iteratively prioritizes expansion from the most functionally homogeneous parcels. We demonstrate that IAGP not only enhances individual identifiability based on atlas-derived topology, but also yields parcels with improved functional homogeneity. Furthermore, IAGP converges more rapidly and shows greater robustness with shorter scan durations, underscoring its practical utility in clinical settings. When applied to an autism spectrum disorder cohort, the IAGP framework exhibits heightened sensitivity to disorder-specific functional

alterations. We further confirmed the generalizability of IAGP by testing it on an independent dataset, at a distinct parcellation granularity, and with an alternative atlas. Together, our findings suggest that IAGP offers a robust and generalizable framework for individualized brain mapping, thereby facilitating progress in precision neuroscience.

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26-P051 *26 Aug 2026*

Human iPSC-Derived Co-culture Model of Neurons and Astrocytes Reveals Functional Tripartite Synapses and Alzheimer's Disease-Associated Astrocytic Phenotypes

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Abstract

Interactions between neurons and astrocytes are essential for synaptic function and brain homeostasis, yet most human induced pluripotent stem cell (iPSC)-based disease models rely on monocultures that incompletely recapitulate cellular interactions within the brain. Here, we established a human iPSC-derived neuron–astrocyte co-culture system to investigate neuron–glia interactions and their contribution to Alzheimer's disease (AD)-associated phenotypes.

Cortical neurons were generated using dual SMAD inhibition, whereas astrocytes were differentiated through embryoid body and neurosphere formation. Co-culture promoted morphological and functional maturation of both cell types, including increased astrocytic branching, enhanced neuronal activity, and increased synapse density. Immunoelectron microscopy demonstrated the formation of tripartite synapses comprising presynaptic terminals, postsynaptic structures, and astrocytic processes. Furthermore, inhibition of excitatory amino acid transporters 1 and 2 increased neuronal hyperexcitability, supporting functional glutamate regulation by astrocytes within the co-culture system.

Using familial AD iPSCs carrying the amyloid precursor protein (APP) V717L mutation, we identified an AD-associated astrogliosis-like phenotype characterized by astrocytic hypertrophy and increased glial fibrillary acidic protein expression. Notably, treatment with 17β-estradiol attenuated these astrocytic abnormalities. These disease-associated phenotypes were not fully captured in neuronal monocultures, highlighting the importance of neuron–astrocyte interactions in modeling AD pathology.

Together, these findings demonstrate that human iPSC-derived neuron–astrocyte co-cultures recapitulate functional tripartite synapses and reveal disease-relevant astrocytic phenotypes in AD. This platform provides a valuable human model for investigating neuron–glia interactions and evaluating therapeutic interventions for neurodegenerative disorders.

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Neurotransmission and Neuroplasticity

24-P039 *24 Aug 2026*

Optimizing the Speech Processing of Cochlear Implants with Artificial Neural Networks

*Xiaohan Bao **(Presenter)**[1], Yueying Wang[2], Zihang Xu[3], Yi Wang[1], Nicholas A Lesica[4], Jan WH Schnupp[1,2,3]*

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Abstract

*These authors have equal contributions to this work

Studying the real-time processing of sound in mammalian auditory systems is expensive and technically difficult. Recent advancement in machine learning has demonstrated successful simulation of sound-elicited spike activities in midbrains with artificial neural networks (ANNs). In light of that, the design of cochlear implants (CIs) may have the opportunity of making up for mismatched hearing experience and compromised auditory functions. Following the pioneering work (i.e., ICNet) in gerbils, we will record spike activities in rat inferior colliculus (IC) to various inputs, including artificial and naturalistic sounds, presented acoustically or electrically. The ANN parameters will be trained to achieve best predictability from stimuli to spike activities. Next, we will specifically investigate the capacity in speech processing of rat ICNet models. Differentiating aspirated and unaspirated consonants (e.g., /t/ in stop vs. top) represents a major challenge for listening in adverse scenarios. Study1: we will present the pairs of speech tokens to acoustic- and CI-based ICNets under various levels of noise masking. The ICNet outputs will be compared with neural recordings experimentally derived from anesthetized animals of different species (gerbils, shrews) and contrasted with the behavioral performance using animal and human psychophysics. Study2: we will fit the parameters of CI processors with different targets on spike activities, such as (a) similarities between acoustic- and CI-based ICNets; (b) dissimilarity in the temporal envelope between different tokens; (c) strength of phase-locking to vowel frequency. Once being narrowed down, the most preferable parameters will be evaluated with behavior outcomes. Summary: this project will be the first of its kind where artificial intelligence (AI) and neurophysiology techniques, hand-in-hand, fine-tune the performance of medical devices that are globally deployed already. It is expected to establish a framework for AI-empowered medical innovations while motivating the development of data science (i.e., refining ICNet structure) for societal benefit.

24-P040 *24 Aug 2026*

mGluR5-Mediated Astrocytic Calcium Signaling Regulates EAAT2 Expression and Novel Object Recognition Memory

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Abstract

Astrocytic Ca^{2+}signals can couple neuronal activity to metabolic output, yet the mechanisms linking $Ca^{2+}$to cognition-depended metabolic support remain unclear. We identify metabotropic glutamate receptor 5 (mGluR5) in hippocampal astrocytes as a key driver of Ca^{2+} activity that links behavior-evoked glutamate to excitatory amino acid transporter 2 (EAAT2) regulation and lactate production. Fiber photometry shows that mGluR5 is required for both tonic and behavior-evoked astrocytic Ca^{2+}activity in hippocampus CA1. During recognition behavior, mGluR5-dependent Ca^{2+}responses track elevated extracellular glutamate and promote EAAT2 membrane trafficking. This pathway increases lactate output, coupling glutamate clearance machinery to metabolic support. Disrupting the cascade by mGluR5 knockdown or Ca^{2+}suppression reduces lactate and impairs recognition memory, whereas restoring Ca^{2+}dynamics with STIM1 overexpression or chemogenetic Gq activation elevates EAAT2 and lactate. These findings establish mGluR5-mediated astrocytic calcium signaling as a central hub that integrates glutamate sensing, EAAT2 regulation, and metabolic output to support hippocampal-dependent recognition memory.

This work was funded by the General Research Fund (GRF) of the Research Grants Council of Hong Kong (11103721, 11102820, and 11100018), Health@InnoHK funding support from the Innovation Technology Commission of the Hong Kong

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24-P041 *24 Aug 2026*

The Effects of α-Synuclein Mutation on Synaptic Transmission

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Abstract

Parkinson's disease (PD) is one of the major neurodegenerative diseases affecting millions worldwide, with a substantial and growing global burden. Yet, the pathogenic mechanisms of PD remain incompletely understood. One established genetic contributor is the mutation of α-synuclein (αSyn). αSyn is a small protein encoded by the SNCA gene found abundantly at the presynaptic terminal, where it plays an important role in synaptic vesicle trafficking and neurotransmitter release. In particular, the αSyn A53T mutation is associated with an aggressive hereditary, early-onset form of PD and is thought to accelerate pathological aggregation and compromise neurotransmission. However, the detailed pathogenic mechanisms linking this mutation to synaptic dysfunction remain elusive. Here, we overexpressed αSyn A53T in primary hippocampal neurons to examine its effects on synaptic transmission. Using real-time imaging of the lipophilic dye FM4-64 during electrical field stimulation, we found that neurons overexpressing αSyn A53T exhibited altered amounts of released FM4-64 during stimulation, indicating disrupted synaptic vesicle dynamics. Together, our findings suggest that the αSyn A53T mutation perturbs synaptic transmission, offering mechanistic insights into how αSyn-linked pathology may contribute to neurodegeneration in PD.

24-P050 *24 Aug 2026*

Unique dynamics and distinct pools of spontaneously recycled inhibitory synaptic vesicles revealed by real-time three- dimensional single-vesicle tracking

Chungwon Park ***(Presenter)***[1], *Sangyong Jung* [2], *Hyokeun Park* [1,3]

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Abstract

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Activity-independent spontaneous neurotransmission differently operates from activity-evoked neurotransmission. Previous studies unveiled peculiar features of spontaneous neurotransmission such as a distinct set of vesicle fusion machinery proteins and spatially segregated release sites in excitatory glutamatergic synapses. However, the understanding of dynamics and exocytosis of spontaneous synaptic vesicles remains insufficient, especially in inhibitory GABAergic synapses. In this study, individual GABAergic synaptic vesicles were spontaneously labeled with quantum dot-conjugated antibodies against vesicular GABA transporter luminal domain in the presence of tetrodotoxin and three-dimensionally tracked in real time. The results demonstrated that spontaneously recycled GABAergic synaptic vesicles were distinguished from activity-dependently recycled ones in terms of dynamics and exocytosis. And around one-third of the spontaneously recycled vesicles underwent evoked release under sustained electrical stimulation, showing dynamically unique features and predominant use of untethered vesicles. Intriguingly, tethered vesicles showed a prolonged final dwelling close to fusion sites immediately before fusion, compared to untethered vesicles. But their final dwelling was significantly shortened under the knockdown of Synaptotagmin-2 (Syt2), implying an inhibitory role of Syt2 in spontaneous fusion of tethered vesicles. Our results suggest the existence of two dynamically and spatiotemporally distinct pools of spontaneously recycled GABAergic synaptic vesicles, revealing the subset of spontaneous GABAergic synaptic vesicles available to maintain inhibitory neurotransmission against synaptic depletion under sustained activity.

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24-P054 *24 Aug 2026*

Input-sequence-dependent regulation of spike-timing-dependent plasticity in mouse hippocampal CA1 neurons ex vivo

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Abstract

Spike-timing-dependent plasticity (STDP) links the relative timing of pre- and postsynaptic activity to long-term changes in synaptic strength and provides a cellular framework for learning, memory and circuit refinement. However, synapses in vivo are rarely activated in isolation. Instead, converging inputs arrive in temporally structured sequences and may interact through local dendritic, receptor-dependent and neuromodulatory signals. Here, I investigated how activation of one excitatory input influences STDP at a second input onto the same hippocampal CA1 pyramidal neuron.

Using whole-cell current-clamp recordings from acute mouse hippocampal slices, I applied a two-input pre1-post-pre2 triplet paradigm to Schaffer collateral inputs, in which two independent presynaptic pathways were activated at distinct timings around a postsynaptic action potential. Under conventional pair-based conditions, post-before-pre pairing at the second input induced t- LTD. Strikingly, when this same post-before-pre input was preceded by activation of another excitatory input, its plasticity outcome was converted from t-LTD to t-LTP. This demonstrates that STDP polarity is determined not only by pairwise spike timing but also by recent input history.

Pharmacological dissection showed that this sequence-dependent plasticity depends on NMDAR signalling but cannot be fully explained by classical postsynaptic NMDAR-dependent coincidence detection. Blockade of NMDAR channel function, glycine/D-serine co-agonist-site signalling, and metabotropic glutamatergic pathways disrupted the plasticity outcome, while D-serine manipulation shifted established LTD toward baseline. Genetic deletion of presynaptic GluN1 did not abolish triplet-induced polarity reversal, whereas astrocytic Grin1 deletion disrupted timing-dependent depression, suggesting that glycine-site-dependent neuron–glia signalling may contribute to the permissive state required for this form of associative plasticity.

Together, these findings reveal an input-sequence-dependent heterosynaptic interaction that expands the classical STDP rule in hippocampal CA1 neurons. This mechanism may allow individual neurons to integrate temporally clustered synaptic events across an extended associative window, providing a cellular substrate through which hippocampal circuits encode ordered patterns of experience.

25-P031 *25 Aug 2026*

Granule Cell–Specific LKB1 Deficiency Drives Progressive Cerebellar Dysfunction via Synaptic Remodeling of Parallel Fiber Boutons

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Abstract

The cerebellum plays a pivotal role in motor coordination and learning by integrating two types of inputs into Purkinje cells (PCs)): parallel fibers (PFs), the axons of granule cells (GCs), and climbing fibers. The serine/threonine kinase Liver Kinase B1 (LKB1) has been shown to regulate GC migration and cerebellar cortical folding; however, its role in PF synapse formation and maintenance remains unclear. In this study, we generated conditional knockout mice (LKB1 cKO) with GC-specific LKB1 depletion during the postnatal period. These mice showed an age-dependent reduction in locomotor activity, suggesting

progressive cerebellar dysfunction. Morphological analysis revealed reduced cerebellar cross-sectional area and molecular layer thickness in older (20-30 weeks) LKB1 cKO mice, with atrophy initiating in the posterior lobules. Additionally, immunolabeling of anti-Iba1 antibody indicated increased density of microglia in the molecular layer of LKB1 cKO mice.

To consider the PF-PC synapse degeneration, we performed the scanning electron microscopy (SEM) of sagittal cerebellar sections, enabling large-field and high-resolution synaptic analysis. While the density of PF-PC synapses remained unchanged, presynaptic terminal size increased in the LKB1 cKO mice, with reduced correlation between the mitochondria area and the terminal size. However, three-dimensional reconstruction using serial block-face SEM revealed no significant differences in the volume of PF presynaptic boutons (BTs) and their mitochondria between control and LKB1 cKO mice. In contrast, the surface area of BTs was significantly reduced in LKB1 cKO mice. Furthermore, whereas a single BT typically forms a synapse with one PC spine in control mice, BTs in LKB1 cKO mice frequently formed multiple synapses. These results suggest that LKB1 is essential for maintaining synaptic structural integrity and specificity of PF boutons, and its loss may impair the precise wiring of cerebellar circuits, potentially leading to motor dysfunction.

This study was supported by JSPS KAKENHI and ABiS.

25-P032 *25 Aug 2026*

Fear Memory Induced by the Motor Efferent Copy of Avoiding Behavior

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Abstract

Classical James-Lange theory of emotion proposed that emotions occur as a result of physiological reactions to events, that is, our retrospective interpretation of physical responses to environmental stimuli results in emotions. This theory is so fascinating, however, has been difficult to prove. Here, we demonstrate that selective optogenetic activation of the motor command for innate avoidance behavior originating from the motor layers of superior colliculus can form fear memory in the passive avoidance test through its efference copy pathway to the amygdala via the posterior thalamic nucleus triangular in mice. We propose that such immediate activation of the amygdala by the efference copy of motor commands, rather than peripheral feedback of physiological reactions, can induce fearful memory as updates of James-Lange theory of emotion.

25-P033 *25 Aug 2026*

C1qtfn4 is a locally translated mRNA that encodes the secretory factor CTRP4 for synapse formation of hippocampal neurons

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Presenter: *Xuejun Li*

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Abstract

The complicated neuronal morphology of dendritic arborization and elongated axon demands huge amount of newly synthesized proteins. Local mRNA translation near synapses is also crucial to rapidly adjust the synaptic proteomes in response to stimulation during synaptic plasticity. Previous transcriptomic studies have identified thousands of different mRNAs in dendrites and axons. The key question of whether different mRNAs are transported to distinct sub-dendritic compartments remains largely unexplored. Our unpublished transcriptomic data identified C1qtnf4 as one of the novel mRNAs enriched in the synaptoneurosome. We found that C1qtnf4 mRNA is specifically localized at dendritic spines of hippocampal neurons in response to chemical long-term potentiation (cLTP) and becomes spatially close to the dendritic micro-secretory organelles at the base of dendritic spines. C1qtnf4 encodes the secreted protein CTRP4, which is highly expressed in the brain, yet its neuronal function is poorly understood. Our results show that CTRP4 is locally translated near dendritic spines, and its depletion leads to fewer mushroom spines and excitatory synapses. Our findings therefore

demonstrate C1qtnf4 as a synaptically localized mRNA that is translated near the dendritic micro-secretory system organelles to promote synapse development in hippocampal neurons.

25-P034 *25 Aug 2026*

Presynaptic Release Deficits and Reduced Inhibitory Synapse Density in Autism-Like VRK3-KO Mice

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social interaction and behavior, though its underlying causes remain unclear. Vaccinia-related kinase 3 (VRK3), a serine/threonine kinase, is known to be involved in cellular development and proliferation. Mice lacking VRK3 (VRK3-KO) display autism-like behaviors, such as reduced social interaction, but the molecular basis for this phenotype is not well understood. In this study, we show that VRK3 is present at both pre- and postsynaptic terminals of hippocampal neurons, with a marked preference for inhibitory presynaptic terminals. Loss of VRK3 disrupts synaptic vesicle release and the secretion of neurotransmitters, including glutamate and GABA, in primary hippocampal neurons. Notably, this disruption selectively lowers the density of inhibitory synapses, while excitatory synapse density remains unchanged. In 12-week-old VRK3-KO mice, a significant decrease in inhibitory synapse density is observed, along with a pronounced loss of inhibitory presynaptic terminals in the CA1 region, whereas excitatory synapses show only a slight reduction. These results suggest that deficits in presynaptic neurotransmitter release and reduced inhibitory synapse density may contribute to the autism-like behaviors seen in VRK3-KO mice, highlighting the importance of presynaptic dysfunction in ASD.

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26-P033 *26 Aug 2026*

Granule Cell Activity Shapes Presynaptic Signaling to Purkinje Cells during OKR Learning

Hojeong Lee ***(Presenter)***[1,2], *Sang Jeong Kim*[1,2], *Yong-seok Lee*[1,2]

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Abstract

Long-term depression (LTD) at parallel fiber-Purkinje cell (PF-PC) synapses is a fundamental mechanism underlying cerebellar motor learning and optokinetic response (OKR) learning. Although postsynaptic plasticity in PCs have been majorly studied, the contribution of granule cells (GC) to learning-dependent synaptic regulation remains less understood. In particular, it is still unclear how presynaptic activity at the level of GCs and PFs shapes PF-PC transmission during motor learning. To address this question, we used patch-clamp recordings combined with GC manipulation to examine presynaptic changes after OKR learning. Our results show that OKR training induces significant modifications in PF-PC transmission and GC activity which is required for proper expression of learning-related behavioral adaptation. These findings indicate that GCs are not merely passive relays of input, but active contributors to the regulation of cerebellar synaptic plasticity. Together, our data suggest that GC transmission plays an important role in shaping presynaptic inputs to PCs during cerebellar motor learning and in supporting the behavioral expression of adaptation.

26-P034 *26 Aug 2026*

Neuronal-specific Roles of PRMT8 in Excitatory / Inhibitory Balance during Associative Fear Learning

*Beth Wing Lam So **(Presenter)**[1,2], Lian Huang[1], Xiaoqian Hu[1], Qiyu Zheng[1,2], Ryan Ka Yan Chan[3], Kwok On Lai[4], Kenneth Kin Yip Wong[2,3], Cora Sau Wan Lai[1,2]*

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Abstract

Protein arginine methylation is a major post-translational modification in synaptic proteins. Among the arginine methyltransferase (PRMT) family, PRMT8 is the only member with brain-specific expression. In vitro studies have shown the localization of PRMT8 in dendritic spines of pyramidal neurons (PNs), and parvalbumin-positive interneurons (PVINs). However, the roles of PRMT8 in synaptic plasticity and excitatory/inhibitory (E-I) balance remained poorly understood in vivo. Here, we show that the mRNA expression of Prmt8 is neuronal-specific. Reduction of Prmt8 expression is associated with a spectrum of neuropsychiatric disorders, including autism. Using a total knockout mouse model of Prmt8 (Prmt8KOF), we found that the loss of PRMT8 led to a male-specific auditory-cued fear learning deficit. While the developmental cortical dendritic spine plasticity remained normal in Prmt8KOF males, they displayed a significant impairment in fear learning-induced dendritic spine formation of layer 5 PNs in the auditory cortex. This impairment was thin spine-specific, and correlated with the freezing behaviour during fear recall. Photometric recordings of PNs and PVINs further revealed a disruption of E-I during fear acquisition, and before the onset of freezing in Prmt8KOF males. Further electrophysiological and mRNA-seq results revealed a significant reduction in membrane excitability of PVINs via reduction in expression of ion channel-related genes, and weakened PVIN-to-PN synaptic strength, after the loss of PRMT8. Selective chemogenetic activation of auditory cortical PVINs in Prmt8KOF rescued fear learning behavior, ameliorated synaptic deficits, restored E-I balance during learning, and broadly reversed knockout-induced transcriptomic alterations in gene clusters linked to PVIN firing properties, PN plasticity, and PV–PN synaptic strength. Collectively, our results demonstrate the divergent roles of PRMT8 in both PNs and PVINs, which are important in maintaining E-I and proper auditory-cued fear learning.

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26-P035 *26 Aug 2026*

Spatially restricted BDNF-TrkB signaling drives postsynaptic differentiation at neuromuscular synapses

*Jinkai Zhang **(Presenter)**[1], Chi Wai Lee[1]*

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Abstract

Efficient transmission at the neuromuscular junctions (NMJs) depends on the formation of high-density acetylcholine receptor (AChR) clusters at postsynaptic membranes. While agrin-Lrp4-MuSK signaling is central to this process, emerging evidence implicates the involvement of brain-derived neurotrophic factor (BDNF) and its receptor TrkB in NMJ development. Intriguingly, the spatial pattern of BDNF stimulation is known to cause diverse presynaptic and postsynaptic effects: local gradients promote axonal outgrowth, growth cone turning, and synaptic maturation, whereas global application suppresses agrin synthesis and AChR clustering. In this study, we examined the spatiotemporal regulation of postsynaptic differentiation by BDNF-TrkB signaling using polystyrene beads coated with recombinant BDNF proteins in cultured Xenopus muscle cells. BDNF beads were effective to induce robust AChR clustering, which could be attenuated by global BDNF application or TrkB inhibition, highlighting the requirement for spatially restricted BDNF-TrkB signaling. Unlike agrin-induced AChR clustering, the postsynaptic effects of BDNF were independent of Lrp4. Next, we used live-cell imaging of ERK-KTR (kinase translocation reporter) biosensor that revealed spatially enriched activated ERK signals at BDNF bead-muscle contacts, accompanied by elevated phosphorylated nuclear-excluded ERK signals in the cytoplasm of bead-contacted cells. Additionally, pharmacological inhibition of MAPK/ERK suppressed postsynaptic differentiation induced by BDNF beads, but not agrin beads. At developing NMJs, blockade of MAPK/ERK signaling also impaired nerve-induced AChR cluster formation. Together, this study reveals a distinct mechanism in which localized BDNF-TrkB signaling promotes

postsynaptic differentiation, contrasting with global BDNF actions and operating independently of agrin-Lrp4-MuSK signaling, during vertebrate NMJ development.

Sensory and Motor Systems

24-P051 *24 Aug 2026*

A Novel Sequential Dexterous Forelimb Task Reveals Learning-Dependent Refinement of Motor Cortical Population s

*Yinan Zheng **(Presenter)**, Zhikun WANG[2], Jiajia HUANG[2], Ya KE[2], Wing-Ho YUNG[1]*

Presenter: *Yinan Zheng*

Abstract

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Complex motor behaviors require the precise coordination of multiple movement components organized into rapid sequential actions with defined transitions. Disruptions in sequential motor control are common in neurological disorders such as Parkinson's disease and stroke, even when basic motor abilities remain preserved. However, the neural mechanisms underlying the learning and execution of complex movement sequences remain incompletely understood. To address this question, we developed a novel dexterous forelimb task in which mice learn to pull a lever along fixed trajectories composed of multi-phase sequential movements with defined turning points. The task incorporates gradual shaping, beginning with simple straight pulls followed by progressive introduction of turning phases. Over training, mice exhibited robust motor learning, with success rates approaching 100% and cue-to-reward response times decreasing to approximately 1 second. Kinematic analysis revealed progressive refinement of movement execution, characterized by smoother and more consistent trajectories, reduced deviations, and optimized velocity and acceleration profiles, suggesting the emergence of coordinated and stereotyped motor strategies. To examine the neural dynamics underlying this process, we performed long-term two-photon imaging in the caudal forelimb area of the primary motor cortex (M1) during learning. Population-level analyses revealed progressive changes in cortical activity patterns across training, as neural trajectory analyses demonstrated increasingly structured temporal dynamics during expert performance. Together, our findings suggest that M1 population activity is dynamically refined during the acquisition and optimization of skilled sequential forelimb movements, providing a framework for investigating the neural mechanisms of complex motor learning.

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26-P041 *26 Aug 2026*

Quantitative Kinematic Analysis of Visuomotor Learning for Controlling Visually-Mediated Body Representations in Monkeys

*Taisei Kato **(Presenter)**[1], Taro Takane[1], Daisuke Tajima[2], Hiroki Uchida[2], Ken-Ichiro Tsutsui[1], Shinya Nakamura[1], Shunichi Kasahara[2,3]*

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Abstract

Self-body recognition may involve the integration and synchronization of sensory and motor information. Virtual reality (VR) technologies have been widely used to investigate this process, and their application to monkeys could provide valuable insights into the neural basis of self-body recognition. Recently, we developed a VR device for monkeys consisting of a screen facing the subject and a camera positioned behind it, which projects a first-person-perspective image onto the screen. In this study, using this device, we aimed to quantitatively characterize the visuomotor learning process through detailed time-series analysis of hand movements, in order to examine how monkeys acquire control over their on-screen body image through training.

Three male Japanese monkeys were trained to retrieve food rewards from wells on a board through the VR device. Training was first conducted with the left hand and was then extended to the right hand. Initially, the monkeys performed the task inefficiently, making exploratory hand movements to locate the rewards. With training, however, they gradually learned to reach the reward locations precisely. Eventually, they performed the task through the VR system at a level comparable to direct-view performance. DeepLabCut-based kinematic analysis revealed that a single food-picking movement could be segmented into four distinct phases. Based on this segmentation, we analyzed longitudinal changes in movement efficiency

and reproducibility to determine how training effects emerged in each movement phase. Training effects were most prominent in exploratory/corrective reaches and in the endpoints of ballistic reaches. Self-organizing map analysis further showed that right-hand learning started from a higher performance level and progressed faster than left-hand learning. These findings quantify the tuning process underlying visuomotor adaptation to an on-screen body image. Moreover, this intermanual transfer suggests that visuomotor learning occurs at an abstract cognitive level shared across limbs.

26-P042 *26 Aug 2026*

Pulse-Rate Dependent Integration of ITD and ILD Cues in the Mouse Auditory Midbrain

Muhammad Zeeshan ***(Presenter)***[1,2], *Yi Wang*[1], *Jan W.H. Schnupp*[1,2,3]

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Abstract

Mice are gaining importance as an animal model in auditory research given their suitability for genetic techniques, but how suitable they are for studying binaural hearing remains uncertain. Here, we investigated the integration of interaural time (ITD) and level (ILD) differences in the mouse inferior colliculus (IC) with acoustic pulse (click) trains of varying rates. Multiunit activity was recorded using 64-channel silicon electrodes. At 100 pulses per second (pps), most neurons with frequency selectivity are tuned to both ITD and ILD, predominantly exhibiting monotonic increasing tuning shape that favour the contralateral stimulus. At 900 pps, ILD tuning remained robust with similar monotonic tuning, whereas ITD tuning significantly decreased, with more neurons showing peaked tuning centered near 0 ITD. A small subset of neurons showed shifts in their tuning peaks when both cues were varying, indicating an ITD/ILD cue interaction. ITD sensitivity declined for pulse rates above 500 pps and phase-locking above 300 pps. Like other previous studies, we therefore found widespread and robust ILD sensitivity, but in addition, at low pulse rates, we also observed a fair amount of ITD sensitivity as well as synergistic interactions between ITD and ILD cues in a subset of neurons.

26-P043 *26 Aug 2026*

Regulation of Motor Learning by Apical and Basal Dendritic Inputs to M1 L5 Pyramidal Neurons

Hong-Yan Geng ***(Presenter)***[1], *Xiao-Lin Shen*[1,2,3], *Lin Cao*[1], *Li-Zhang Zeng*[2,3], *Wing-Ho Yung*[4], *Ya Ke*[5], *Yong-Xiang Wang*[1,6,7]

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Abstract

Layer 5 pyramidal neurons in the primary motor cortex (M1L5) receive inputs from the ventromedial thalamus (VM) and layer 5 of the secondary motor cortex (M2L5), but the role of their distinct dendritic compartments in dopamine-dependent motor learning remains unclear. Using fiber photometry, 6-OHDA lesions, optogenetics, chemogenetics, and the single-pellet reaching task, we found that both VM and M2L5 are recruited during skill acquisition. Local dopamine depletion in either apical or basal dendrites of M1L5 impaired learning. Optogenetic activation of the VM→apical dendrite pathway rescued deficits caused by apical dendrite lesion, whereas activation of the M2L5→basal dendrite pathway rescued deficits caused by basal dendrite lesion. This compartment-specific improvement depended on local D1 receptors in apical dendrites and D2 receptors in basal dendrites, respectively. These findings reveal that distinct long-range inputs regulate motor learning through specific dendritic compartments and dopamine receptor subtypes, offering new mechanistic insights into movement disorders such as Parkinson's disease.

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26-P044 *26 Aug 2026*

Circuit Mechanisms of Challenging Motor Performance

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Abstract

Motor performance relies on coordinated interactions between cortical and subcortical circuits, particularly when animals perform challenging motor tasks that require adaptive control. However, how specific long-range circuits support motor performance under increased task demand remains unclear. Here, we investigated the organization and functional contribution of a cortical–midbrain circuit involved in motor control. Our anatomical tracing confirmed and extended previously reported broad cortical projections from motor and sensory cortical areas to the midbrain. Using a rotarod task with constant rotation speeds of varying difficulty, we examined motor performance across different levels of task demand. Chemogenetic inhibition of either cortical input or midbrain recipient neurons within this pathway selectively impaired performance under high-demand conditions, while performance at lower speeds remained largely unaffected. Calcium photometry recordings showed demand-dependent neural dynamics, ranging from minimal responses under low-demand conditions to sustained activation during highly demanding performance. Together, these findings reveal a cortical–midbrain circuit that is selectively recruited to support motor performance during challenging tasks.

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26-P045 *26 Aug 2026*

Spinal cord interneuronal population activities coordinate muscle activities through a low-dimensional communication subspace

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Abstract

The spinal cord integrates complex supraspinal commands to coordinate muscle activities for stable movement. To reduce the computation complexity and enable flexible motor control, the spinal cord is thought to generate voluntary movement by recruiting neuromotor modules, known as muscle synergies, encoded by spinal premotor interneurons. Recent advances in large-scale neural population recordings suggest that the low-dimensional neural manifold constructed by projecting activities of high-dimensional interconnected units onto dominant neural modes may form a fundamental neural basis for stable and efficient motor control. Despite these technical advancements, their application for stable and long-term spinal cord recordings in freely moving animals is limited. Thus, it remains unclear how spinal interneuronal populations coordinate muscle activities during natural movement.

To address these questions, we simultaneously recorded population activity from spinal interneurons using a 128-channel hyper-flexible spinal cord array and activities from multiple ipsilateral hindlimb muscles using intramuscular electrode pairs in freely walking mice. Our results showed that the spinal interneuronal population coordinates multiple muscle activities through a low-dimensional communication subspace, formed by identifying neural patterns whose projected population activities are most predictive of the recorded muscle activities. We also found that the neural-constrained muscle patterns are more stable than muscle synergies across different days.

These findings suggest that during locomotion, spinal interneuronal populations are dynamically coordinated to shape muscle synergies, allowing for flexible motor control across different spinal states.

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26-P046 *26 Aug 2026*

From Muscle synergies to Motor Units: Evidence of Synergy Degeneracy in Human Motor System

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Abstract

Muscle synergies are considered a potential control strategy implemented by the central nervous system to coordinate multiple muscles during movement execution. However, some critics of synergies emphasize that synergies should instead be implemented at the motor unit level since muscles are not the basic control units. Recent advances in high-density surface electromyography (HD-sEMG) recording and motor unit decomposition algorithms have enabled the non-invasive decoding of large populations of motor units, leading to the emergence of the concept of motor neuron synergies. Unlike traditional muscle synergies that are defined at the whole-muscle level, motor neuron synergies transcend anatomical boundaries and form functional clusters across muscles. Whether these motor neuron synergies align with conventional muscle synergies remains uncertain.

To address this question, we first conducted a simulation study incorporating simulated spike trains and physiologically realistic motor unit action potentials. Ground truth synergy structures were manually defined at both the whole-muscle and motor unit levels to evaluate the performance of traditional synergy extraction algorithms, such as non-negative matrix factorization (NMF). The results demonstrated that NMF could retrieve synergy information from this non-linear system regardless of whether the underlying structure was implemented at the whole-muscle or motor unit level. Notably, the simulations suggest that different implementation types of motor unit synergies could result in the same muscle synergies, indicating degeneracy in the motor control system.

To assess whether this synergy degeneracy generalizes to actual biological systems, we then recruited twenty healthy subjects and recorded 64-channel HD-sEMG along with traditional single-channel EMGs to simultaneously extract motor unit activities and muscle synergies. Analysis across different hand tasks and force levels revealed that muscle synergies remained largely consistent. By tracking common motor units across tasks, we examined all possible two-trial and three-trial combinations to assess the relationship between motor unit and muscle synergies. Grouping motor unit synergies into stable and unstable clusters revealed that stable motor unit synergies consistently produced stable muscle synergies, whereas unstable motor unit synergies resulted in a broader range of muscle synergy similarities. These findings are consistent with the simulation results showing that different motor unit synergies can converge to the same muscle synergy output, thus revealing the many-to-one correspondence between motor unit synergies and muscle synergies and the synergy degeneracy in the motor system.

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26-P047 *26 Aug 2026*

Can Rodents Count? ——Unveiling Number Sense in Mice

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Abstract

The studies of number sense in different species are severely hampered by the inevitable entanglement of nonnumerical attributes inherent in nonsymbolic stimuli representing numerosity, resulting in contrasting theories of numerosity processing. Utilizing our published algorithm and associated analytical methods to generate auditory numerical stimuli that can not only minimize the impact of non-numerical magnitudes in numerosity perception but also allowed their quantification, we trained number-naïve mice with these stimuli as sound pulses representing two or three numbers and demonstrated that their numerical discrimination ability mainly relied on numerosity. This numerical processing is associated with specific activation of some subregions of auditory cortex and thalamus. Our study helps dissect the relationship between magnitude and numerosity processing, demonstrate the catagorical ability of numerosity in mice, and pointed brain regions involved in numerosity processing.

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Others

26-P036 *26 Aug 2026*

The Effect Of Neonatal 3-Methyl-4-Nitrophenol Exposure On Reproductive Function In Female Rats

*Yukihiro Maeda **(Presenter)**[1], Gen Watanabe[2], Yasuhiko Kondo[3], Rie Yanagisawa[4], Osamu Udagawa[4], Maiko Kawaguchi[1]*

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Abstract

Environmental exposure to endocrine-disrupting chemicals may contribute to infertility and altered sexual development. This study examined how neonatal exposure to 3-methyl-4-nitrophenol (MNP), a degradation product of the pesticide fenitrothion and a component of diesel exhaust, affects reproductive function. Previous studies have shown that MNP acts as an estrogen receptor agonist in birds and rodents, suggesting that it may affect brain sexual differentiation. Female Wistar-Imamichi rats were orally administered MNP (1 or 100 mg/kg/day) for 5 consecutive days starting on postnatal day 1, a critical period for brain sexual differentiation. Corn oil served as the vehicle control, while estradiol-17β (E2; 20 mg/kg) was used as the positive control. E2 was given only on postnatal day 1 via subcutaneous injection. Following treatment, vaginal opening and estrous cyclicity were monitored. At 7 weeks of age, blood samples were collected from females identified as being in estrus, after which ovariectomy was performed. Earlier vaginal opening was observed only in the E2-treated group. Partner preference and sexual behavior were assessed at 9 and 10 weeks, respectively, followed by tissue dissection at 11 weeks. All females received estradiol benzoate and progesterone prior to various testing. Partner preference was evaluated using a three-chamber apparatus containing a sexually active male and an estrus-induced female. Control females spent more time investigating opposite-sex rats, but this preference was not observed in either the MNP- or E2-treated groups. These findings suggest that neonatal MNP exposure disrupts brain sexual differentiation and alters the neural mechanisms underlying adult sociosexual behavior. The similarities between the MNP- and E2-treated groups further suggest that MNP may exert estrogenic effects during development. Although the effects on sexual behavior were minimal, uterine weights increased in the high-dose MNP and E2 groups. These results underscore concerns regarding the long-term effects of endocrine disruptors on brain development and reproductive function.

26-P037 *26 Aug 2026*

Ethical Challenges in Predicting Dementia Onset

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Abstract

Predicting dementia onset is expected to increase opportunities for prevention and early intervention while also supporting life planning, advanced care planning, and informed decision-making. However, it raises important ethical, legal, and social issues.

One major concern is whether informing individuals of their future risk of dementia truly serves their best interest. Current methods for predicting dementia onset and estimating the timing of disease development remain limited at the individual level, and evidence-based interventions for preventing dementia are still insufficient. This situation created a dilemma between the “right to know” and the “right not to know”, posing challenges for respecting patient autonomy and self-determination. Furthermore, because current approaches rely largely on probabilistic risk estimation, ethical questions remain regarding the validity of risk communication and the appropriateness of recruiting asymptomatic individuals into trial-ready cohorts and prevention trials based on estimated risk.

Amyloid PET and APOE genetic testing have been introduced to facilitate early diagnosis and risk assessment. In Japan, relevant academic societies have developed guidelines regarding disclosure and appropriate use of these tests, while systems for genetic counseling have also been established. Nevertheless, questions remain regarding the communication of test results and the ethical implementation of these technologies.

This report describes the outcomes of an expert meeting involving neuroscientists and bioethicists from different research projects. From a bioethical perspective, we examined informed consent practices based on the 'right to know' and the 'right not to know' concerning genetic testing for dementia. From the standpoint of clinical neurology, we reviewed the current status of amyloid PET, using Japanese multidisciplinary appropriate use guidelines as a case example, and discussed ethical challenges associated with dementia prediction in trial-ready cohort research.

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26-P038 *26 Aug 2026*

Unified Geometric Rules Predict Mammalian Connectomes Across Multiple Species

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Abstract

The cortical connectivity supports rich cognitive functions of the brain, yet its underlying organizational principles remain largely unclear. Many previous studies primarily focused on the analysis of the native cortical sheet in the three-dimensional space, leaving open the question of whether alternative representation of the cortex might reveal novel organizational principles. Here, by analyzing the connectivity of flattened cortices of mouse, marmoset, macaque and human using polar coordinates, we uncover unified geometric rules of large-scale cortical organization: (1) Projection angles and distances are largely statistically independent; (2) Projection angles nearly follow a uniform angle rule (UAR); (3) Projection distances nearly follow an exponential distance rule (EDR), inherited from the EDR previously observed in the original three-dimensional cortical sheet. By integrating UAR and EDR in the two-dimensional cortical plane, we develop a single-parameter generative model that simulates connections at the microscopic neuronal level while accurately predicting macroscopic inter-areal connectomes across all four species. Notably, the same model also recapitulates intra-areal projections as an emergent property, thereby unifying inter- and intra-areal connectivity within a common framework. Analysis of the model parameter further reveals a conserved cross-species scaling law. Together, these findings establish UAR and EDR as fundamental geometric features of connectome organization, which provide a concise and unified framework for cross-species connectome characterization and prediction.