2026

March 24th to 28th
Rusutsu Ski Resort
Hokkaido, Japan

ORGANIZERS

Dr. Yoshiyuki Kubota
National Institute for Physiological Sciences

Dr. Yimin Zou
UC San Diego

Dr. Yi Zuo |
UC Santa Cruz

Dr. Daniel Choquet
French National Centre for Scientific Researchs

Dr. Mark Dell'Acqua
University of Colorado Anschutz Medical Campusss

NeuroWinter Summit

From Synapse to Behavior

NeuroWinterSummit.org

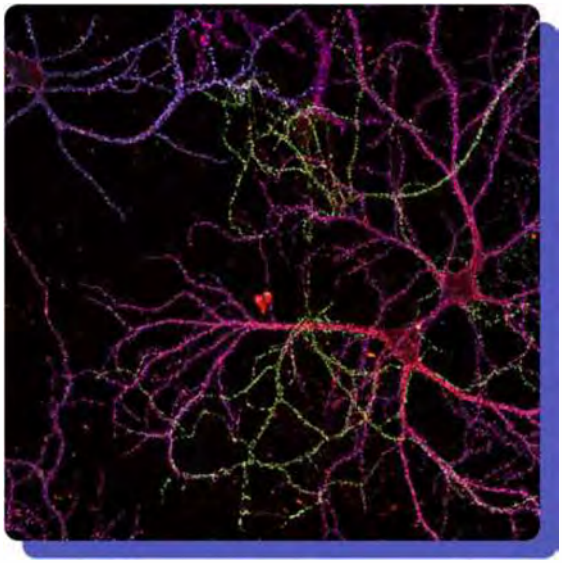
INDEX

Neuro Winter Summit

From Synapse to Behavior
March 24-28, 2026

About the Summit

Breakthroughs in neuroscience research thrive on dynamic communication and collaboration. We are excited to introduce the NeuroWinterSummit, a new annual forum set in the enchanting winter wonderland of Hokkaido.



This unique venue allows us to sidestep the crowded summer and fall conference schedules. The summit will gather leading researchers to explore groundbreaking discoveries across synaptic mechanisms and complex behaviors in health and disease, as well as the latest technologies advancing our field.

Expect engaging presentations from distinguished speakers, concise talks from submitted abstracts, and interactive poster sessions. With ample free time for stimulating discussions in a relaxed atmosphere, this summit promises to be a remarkable opportunity to connect, learn, and inspire one another!

A number of short talk presentations will be selected from abstracts giving the opportunity to trainees, young investigators and last minute breakthroughs to present their work in oral form.

Venue

Convention Hall No. 18,
4th floor North Wing,
Rusutsu Resort Hotel & Convention

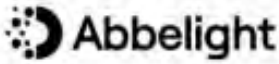
Image source: *Rusutsu Resort Hokkaido Japan*

News

Mar 14, 2025
The official website has been launched. NEW

SPONSORS

We are very thankful to the sponsors listed below that helped making possible the first Japanese Neuro Winter Summit



First NeuroWinter Summit

From synapse to behavior

Rusutsu, Hokkaido, Japan. March 24th-28th 2026

Tuesday March 24th	
14:00 - 18:00	**Arrival and Check in, hotel front desk and reception desk at North wing front lobby**
18:00 - 20:00	**Welcome event at Crescent hall on the 2nd floor in the North Wing**
Wednesday March 25th	
Organizers and Companies talks. Chair Yi Zuo at Convention hall 18 on 4th floor in the North wing	
07:30 - 07:50	**Yi Zuo** *(University of California, Santa Cruz, CA, USA)*
	Unraveling the Synaptic Basis of Motor learning
07:50 - 08:00	**Quantum Design Japan**
	TBD
08:00 - 08:10	**RWD Life Science CO., LTD**
	TBD
08:10 - 08:30	**Mark Dell'Acqua** *(University of Colorado, Anschutz Medical Campus, Aurora, CO, USA)*
	L-type Ca2+ channels and AKAP-PKA signaling in heterosynaptic regulation of excitatory and inhibitory balance
08:30 - 08:40	**Florida Lifetime Imaging LLC.**
	TBD
08:40 - 08:50	**VOXA**
	TBD
08:50 - 09:10	**Yimin Zou** *(University of California, San Diego, CA, USA)*
	"Planar cell polarity proteins in glutamatergic synapse formation and function"
9:10 - 9:20	**Vizgen**
	TBD
9:20 - 9:30	**Abbelight**
	TBD
9:30 - 9:40	**MaxWell Biosystems**
	TBD
9:40 - 10:00	**Daniel Choquet** (*CNRS-Université de Bordeaux, France*)
	Linking glutamatergic synapse dynamic nanoscale organization, function, plasticity and memory mechanisms
15:00 - 16:00	**Posters, Room 3, 5, 7, 18 and Foyer**

	Circuits 1 (Room A). Chair Nathalie Rochefort		**Synapse 1 (Room B). Chair Laurent Groc**
16:00 - 16:20	**Greg Stuart** *(Department of Physiology, Monash University, Australia)*	16:00 - 16:20	**Giordano Lippi** *(The Scripps Research Institute, San Diego, CA, USA)*
	Interhemispheric communication in binocular visual cortex		MicroRNA mechanisms of plasticity
16:20 - 16:40	**Nathalie Rochefort** *(University of Edinburgh, Edinburgh UK)*	16:20 - 16:40	**Marcelo A Wood** *(University of California Irvine, CA, USA)*
	Movie-trained transformer reveals novel response properties to dynamic stimuli in mouse visual cortex		Investigating the interface of epigenetics and metabolism underlying synaptic plasticity and memory in the adult and aging brain
16:40 - 17:00	**Ron Yu** *(Department of Neurosciences, Case Western Reserve University, Cleveland, OH, USA)*	16:40 - 17:00	**Joris de Wit** *(VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium)*
	Basal Forebrain Cholinergic Input Mediates Adaptive Attention Allocation to Enhance Olfactory Discrimination		Proteomics Approaches to Dissect Synapse Composition in Neural Circuits
17:00 - 17:20	**Kuan Hong Wang** *(University of Rochester Medical Center, Rochester, New York, USA)*	17:00 - 17:20	**Laurent Groc** *(CNRS-Bordeaux University, Bordeaux, France)*
	Unique Adolescent Plasticity of Frontal Dopaminergic Circuits: From Cellular Mechanisms to Therapeutic Potential		Membrane NMDA receptor surface interactome sets physiological and pathological neuronal functions
17:20 - 17:40	**Lucy Palmer** *(Florey Institute of Neuroscience and Mental Health,*	17:20 - 17:40	**Peter Scheiffele** *(University of Basel, Switzerland)*
	Cortical circuit dynamics during learning and memory		Molecular Mechanisms of Cortical Wiring and Plasticity
17:40 - 18:00	**Short Break, Foyer**		
	Circuits 2 (Room A). Chair Lucy Palmer		**Method 1 (Room B). Chair Ryohei Yasuda**
18:00 - 18:20	**Hwai-Jong Cheng** *(Institute of Molecular Biology, Academia Sinica, Taipei Taiwan)*	18:00 - 18:20	**Takeshi Imai** *(Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan)*
	Integration of progenitor cells from adult brain into mature hippocampal circuits		Dendritic compartment-specific spine formation in layer 5 neurons underlies cortical circuit maturation during adolescence

18:20 - 18:40	**Mazen Kheirbek** *(University of California San Francisco, San Francisco, USA)*	18:20 - 18:40	**Takayasu Mikuni** *(Department of Cellular Neuropathology, Brain Research Institute, Niigata University, Japan)*
	Representations of stimulus features in the ventral hippocampus		Single-cell synaptome mapping of different protein subpopulations in the brain
18:40 - 18:50	**Houhui Xia** *(University of Rochester, USA)*	18:40 - 18:50	**David Stroebel** *(Ecole Normale, CNRs, Paris, France)*
	Protein Phosphatase-1 and 2A in Health and Neurodevelopmental Disorders		Molecular Evolution of iGluR Functions
18:50 - 19:10	**Yasunori Hayashi** *(Graduate School of Medicine, Kyoto University, Kyoto, Japan)*	18:50 - 19:10	**Ryohei Yasuda** *(Max Planck Florida Institute for Neuroscience, Jupiter, FL USA)*
	Transformation of a locally activated hippocampal code for space to a cortical contextual engram		Decoding Synaptic Signaling Dynamics Underlying Plasticity

Thursday March 26th			
	Circuits 3 (Room A). Chair Alexei Semyanov		**Synapse 2 (Room B). Chair Aki Kusumi**
07:30 - 07:50	**Masanori Murayama** (RIKEN Center for Brain Science, Wako-city, Japan)	07:30 - 07:50	**Angela M. Getz** *(CNCR, Vrije Universiteit Amsterdam, Netherlands)*
	Large-scale Ca2+ imaging reveals segregated cortical functional networks during unconsciousness		A pipeline for single molecule imaging of endogenous synaptic proteins in brain tissue
07:50 - 08:10	**Yoko Yazaki-Sugiyama** *(Okinawa Institute of Science and Technology Graduate University, Onna-son, Japan)*	07:50 - 08:10	**Katharine Smith** *(University of Colorado School of Medicine, Aurora, CO, USA)*
	Developmental transient auditory to motor projections for zebra finch song learnin		illuminating inhibitory synaptic function in health and disease
08:10 - 08:30	**Alexey Semyanov** *(College of Medicine, Jiaxing University, Jiaxing City, China)*	08:10 - 08:30	**Matthew Dalva** *(Tulane Brain Institute, Department of Cell and Molecular Biology, Tulane University; New Orleans, LA, USA)*
	Four phases and a temporal threshold of population calcium response in cortical astrocytes during locomotion.		VLK drives extracellular phosphorylation of EphB2 to govern the EphB2-NMDAR interaction and injury-induced pain
08:30 - 08:50	**Chia-Chien Eric Chen** *(Duke Kunshan University, Behavioral Science, Suzhou, China)*	08:30 - 08:50	**Aki Kusumi** *(Okinawa Institute of Science and Technology Graduate University (OIST), Okinawa, Japan)*
	Probiotic Intervention Restores Microglial Surveillance and Synaptic Architecture in the Aging Cortex		Postsynaptic receptor turnover on PSD protein condensates revealed by single-molecule imaging
08:50 - 09:10	**Kei M Igarashi** *(Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine USA)*	08:50 - 09:00	**Saahil Acharya** *(Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan)*
	Circuit mechanisms of item memory and its disruption in Alzheimer's disease		SynGAP forms condensates from nanomolar concentrations, recruiting PSD95 and key synaptic receptors
09:10 - 09:30	**Yu-Wei Wu** *(Academia Sinica)*	09:00 - 09:10	**Risa Yamada** *(Kyoto University, Kyoto, Japan)*
	Mixed selectivity and low-dimensional dynamics in STN couple movement and licking		Mesoscale Simulation of Phosphorylation-Dependent Reorganization of Postsynaptic Density Condensates
15:00 - 16:00	**Posters, Room 3, 5, 7, 18 and Foyer**		
	Degeneration 1 (Room A). Chair Aaron Gitler		**Synapse 3 (Room B). Chair Fred Meunier**
16:00 - 16:20	**Julia TCW** *(Boston University, MA, USA)*	16:00 - 16:20	**Nils Brose** *(Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany)*
	Apoe4-driven splicing defects disrupt neurite projection in excitatory neurons		Dynamic Control of Presynaptic Function in Health and Disease
16:20 - 16:40	**Aaron D. Gitler** *(Department of Genetics, Stanford University, CA, USA)*	16:20 - 16:40	**Frederic A Meunier** *(Queensland Brain Institute, The University of Queensland, St Lucia, Queensland, Australia)*
	An emergent disease-associated motor neuron state precedes cell death in a mouse model of ALS		Phospholipase A1 isoform DDHD2 controls memory formation and long-term potentiation
16:40 - 17:00	**Kim Green** *(Department of Neurobiology and Behavior, University of California, Irvine, USA)*	16:40 - 17:00	**Dmitri Rusakov** *(Queen Square Institute of Neurology, University College London, London, United Kingdom)*
	Development of new mouse models of Alzheimer's disease that combine humanized A□, Tau, and APOE4 knock-in alleles.		Glutamate Spillover is Common in the Living Brain and May Help Memory Recall
17:00 - 17:20	**Fen-Biao Gao** *(University of Massachusetts Chan Medical School)*	17:00 - 17:20	**Kirill Volynski** *(UCL Queen Square Institute of Neurology, London, UK)*
	Neural Mechanisms Underlying a Novel Link Between Aging and Poly(GR) Toxicity in C9ORF72-ALS/FTD		Modelling the impact of vesicular release site heterogeneity within active zones on presynaptic information processing
17:20 - 17:30	**Sungho Hong** *(Institute for Basic Science, Korea)*	17:20 - 17:30	**Ken Kunugitani** *(Kyoto University Graduate School of Medicine)*
	Disinhibitory circuit mechanisms of climbing fiber-instructed cerebellar learning		CaMKII Activation Drives Phase Separation with AMPA Receptor Regulatory Protein Shisa
17:30 - 17:50	**Short Break, Foyer**		
	Degeneration 2 (Room A). Chair Monica Sousa		**Synapse 4 (Room B). Chair Pierre Paoletti**
17:50 - 18:10	**Monica M Sousa** *(i3S, University of Porto, Porto, Portugal)*	17:50 - 18:10	**Terunaga Nakagawa** *(Department of Molecular Physiology and Biophysics, Vanderbilt University, School of Medicine, TN, USA)*
	From Scar to Repair: Defining the Cellular and Molecular Roadmap for Mammalian Spinal Cord Regeneration		AMPA receptor structure and function
18:10 - 18:30	**Robert A. Sweet** *(University of Pittsburgh, PA, USA)*	18:10 - 18:30	**Ingo Greger** *(MRC-University of Cambridge)*
	Rethinking MAP2 as a Target for Recovery in Neuropsychiatric Illness		Linking AMPA receptor organisation with LTP
18:30 - 18:50	**Dylan A. McCreedy** *(Texas A&M University College Station, TX USA)*	18:30 - 18:50	**Pierre Paoletti** *(Institute of Biology ENS (IBENS), INSERM, CNRS, Paris, France)*
	Mature neutrophils promote resolution of inflammation and long-term recovery after spinal cord injury		Excitatory glycine receptors: atypical NMDA receptors in brain signaling
18:50 - 19:10	**Hui-Chen Lu** *(Indiana University Bloomington, Bloomington IN, USA)*	18:50 - 19:10	**Rob Meijers** *(Head of Neuroscience, Institute for Protein Innovation, Boston, USA)*
	NAD + Reduction in Glutamatergic Neurons Triggers Metabolic Reprogramming, Neuroinflammation, and Neurodegeneration		Developing systematic antibody panels for neuronal receptor hubs
19:30 - 21:30	**Sake & Buffet at Crescent hall on the 2nd floor in the North Wing**		

Friday March 27th			
	Development (Room A). Chair Simon Hippenmeyer		**Synapse 5 (Room B). Chair Yoshiyuki Kubota**
			Sponsored by Emergence of Brain Functions from the Dynamic Connectome
07:30 - 07:50	**Carlos Portera-Cailliau** *(David Geffen School of Medicine at the University of California, Los Angeles, CA USA)*	07:30 - 07:50	**Elva Diaz** *(Department of Pharmacology, University of California, Davis, CA USA)*
	Translatome Profiling of Inhibitory and Excitatory Neurons of Fragile X Mice Identifies a Novel Therapeutic Target		Regulation of AMPAR recycling and endosomal trafficking by the transmembrane auxiliary subunit SynDIG4/PRRT1
07:50 - 08:10	**Simon Hippenmeyer** *(Institute of Science and Technology Austria)*	07:50 - 08:10	**Karen Zito** *(Center for Neuroscience, University of California, Davis, CA 95618, USA.)*
	Mechanisms Generating Cell-Type Diversity		From snowflakes to synapses: how environmental cues shape Ephexin5-mediated synaptic plasticity
08:10 - 08:30	**Ai Nakashima** *(Graduate School of Pharmaceutical Sciences, University of Tokyo, Japan)*	08:10 - 08:30	**Jason Shepherd** *(University of Utah)*
	Decoding spontaneous activity patterns for olfactory receptor-specific glomerular segregation		Virus-like Intercellular Synaptic Plasticity
08:30 - 08:50	**Shen-Ju Chou** *(Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan)*	08:30 - 08:50	**Ken Mackie** *(Indiana University Bloomington, USA)*
	Specifying neuronal regional properties and forming boundaries between cortical regions by transcription factor gradients		Roles for endocannabinoids and the impact of exogenous cannabinoids on the developing brain
08:50 - 09:10	**Tomomi Shimogori** *(Brain Development at the RIKEN Center for Brain Science)*	08:50 - 09:10	**Peter Penzes** *(Northwestern University Feinberg School of Medicine, Department of Neuroscience, Chicago, USA)*
	Cell Type Evolution and Species-Specific Brain Functions Revealed from the Gene Expression Map of the Marmoset Developing Brain		Regulation of Brain Circuits and Behavior by Synaptic Soluble Ectodomains
09:10-09:20	**Silvia Turchetto** *(DANDRITE, Aarhus University, Aarhus, Denmark)*	09:10-09:20	**Takumi Sakano** *(The University of Tokyo, Tokyo)*
	Local Regulation of Protein Degradation At Neuronal Synapses		Ultrastructural analysis of synaptic vesicle rearrangement underlying mechanical pressure–mediated facilitation
09:20-09:40	**Christophe Leterrier** *(Institute for Neurophysiopathology, NeuroCyto lab, CNRS-Aix Marseille University, Marseille, France)*	09:20-09:40	**Yoshiyuki Kubota** *(National Institute for Physiological Sciences, Okazaki, Japan)*
	The axonal cytoskeleton down to the nanoscale		Converging Perisynaptic Astrocytic Processes onto Active Dendrites after Motor Learning
15:00 - 16:00	**Posters, Room 3, 5, 7, 18 and Foyer**		
	Degeneration 3 (Room A). Chair Brett J. Hilton		**Method 2 (Room B). Chair Valentin Naegerl**
16:00 - 16:20	**Andrea Tedeschi** *(The Ohio State University Wexner Medical Center, OH, USA)*	16:00 - 16:20	**Radu Aricescu** *(LMB, Cambridge, UK)*
	In vivo programming of adult pericytes aids axon regeneration by providing cellular bridges for SCI repair		The Structural Landscape of a Synaptic GABA A Receptor Capture Complex
16:20 - 16:40	**Brett J. Hilton** *(University of British Columbia, Vancouver, British Columbia, Canada)*	16:20 - 16:40	**Haining Zhong** *(Oregon Health & Science University, OR, USA)*
	Targeting neuronal maturation to promote axon regeneration following spinal cord injury		In vivo imaging of second messenger signaling underlying circuit control
16:40 - 17:00	**Timothy Faw** *(University of Maryland, Baltimore, USA)*	16:40 - 17:00	**Valentin Nägerl** *(University of Göttingen, Germany)*
	Harnessing Apolipoprotein E to Improve Recovery after Spinal Cord Injury		Nanoscale imaging of the extracellular space in amyloid brain tissue in vivo
17:00 - 17:20	**Tuan V. Bui** *(Center for Neural Dynamics, Department of Biology, University of Ottawa, Ottawa, Canada)*	17:00 - 17:20	**Tadashi Yamazaki** *(The University of Electro-Communications, Tokyo, Japan)*
	dI3 neurons form spinal circuits for motor adaptation and recovery		Large-scale microscopic-level brain simulation on a supercomputer
17:20 - 17:40	**Short Break, Foyer**		
	Circuits 4 (Room A). Chair Ruediger Klein		**EM (Room B). Chair Shigeki Watanabe**
17:40 - 17:50	**Tomohisa Hosokawa** *(Kyoto University, Kyoto, Japan)*	17:40 - 17:50	**Takaaki Miyazaki** *(National Institutes of Natural Sciences, Japan)*
	CaMKII Condensates Driven by Excitatory Stimulation Function as Synaptic		Synaptic-level organization of reciprocal cortico-cortical circuits in the
17:50 - 18:10	**Tianyi Mao** *(Oregon Health & Science University, OR, USA)*	17:50 - 18:10	**Kea Joo Lee** *(Neural Circuits Research Group, Korea Brain Research Institute, Daegu, South Korea)*
	Neuronal architecture of the mouse insular cortex underlying its diverse functions		Synaptic Ultrastructural Alterations in Human Focal Cortical Dysplasia: Insights from Volume Electron Microscopy
18:10 - 18:30	**Ruediger Klein** *(Max-Planck Inst for Biological Intelligence, Munich, Germany)*	18:10 - 18:30	**Moritz Helmstaedter** *(Max Planck Institute for Brain Research)*
	Central amygdala circuits controlling biting, feeding, and drinking		Cerebral Cortex Connectomics
18:30 - 18:50	**Jun Ding** *(Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA USA)*	18:30 - 18:50	**Shigeki Watanabe** *(Johns Hopkins University, Baltimore, MD, USA)*
	Remodeling of Corticostriatal Axonal Boutons During Motor Learning		Membrane mechanics dictate axonal morphology and function
19:10- 21:10	**Gala dinner at Crescent hall on the 2nd floor in the North Wing** (Sponsored by Abberior Instruments)		
	Concluding remarks will begin at 19:10. Poster Award presentation will be held at 20:45		
Saturday March 28th			
Departure			

All Speakers							
Last Name	**First Name**	**Title**	**Email**	**Type (20'/10')**	**Day**	**Time**	**Page**
Abbelight		TBD		Sponsor talk	Wednesday March 25th	09:20 - 09:30	
Acharya	Florida Lifetim	SynGAP forms condensates from nanomolar concentrations, recruiting PSD95 and key synaptic receptors	saahil@oist.jp	Short talks	Thursday March 26th	09:30–09:40	35
Aricescu	MaxWell Biosy	The Structural Landscape of a Synaptic GABA A Receptor Capture Complex	radu@mrc-lmb.cam.ac.uk	Invited speaker	Friday March 27th	16:00 - 16:20	36
Brose	Quantum Desi	Dynamic Control of Presynaptic Function in Health and Disease	brose@mpinat.mpg.de	Invited speaker	Thursday March 26th	16:00 - 16:20	ND
Bui	RWD Life Scier	dI3 neurons form spinal circuits for motor adaptation and recovery	tuan.bui@uottawa.ca	Invited speaker	Friday March 27th	17:00 - 17:20	37
Chen	Vizgen	Probiotic Intervention Restores Microglial Surveillance and Synaptic Architecture in the Aging Cortex	chiachien.chen@dukekunshan.edu.cn	Invited speaker	Thursday March 26th	09:10 - 09:30	38
Chen	VOXA	COMET: Cortex-wide Observational Miniature Epifluorescence Technique enables imaging of large single-neuron populations	lychen@pku.edu.cn	Invited speaker	Wednesday March 25th	18:20 - 18:40	39
Cheng	Hwai-Jong	Integration of progenitor cells from adult brain into mature hippocampal circuits	hjcheng@as.edu.tw	Invited speaker	Wednesday March 25th	18:00 - 18:20	40
Choquet	Daniel	Linking glutamatergic synapse dynamic nanoscale organization, function, plasticity and memory mechanisms	daniel.choquet@u-bordeaux.fr	Organizer talk	Wednesday March 25th	09:40 - 10:00	41
Chou	Shen-Ju	Specifying neuronal regional properties and forming boundaries between cortical regions by transcription factor	schou@gate.sinica.edu.tw	Invited speaker	Friday March 27th	08:30 - 08:50	42
Dalva	Matthew	VLK drives extracellular phosphorylation of EphB2 to govern the EphB2-NMDAR interaction and injury-induced pain	mdalva@tulane.edu	Invited speaker	Thursday March 26th	08:30 - 08:50	43
Dell'Acqua	Mark	L-type Ca2+ channels and AKAP-PKA signaling in heterosynaptic regulation of excitatory and inhibitory balance	mark.dellacqua@cuanschutz.edu	Organizer talk	Wednesday March 25th	08:10 - 08:30	44
deWit	Joris	Proteomics Approaches to Dissect Synapse Composition in Neural Circuits	joris.dewit@kuleuven.be	Invited speaker	Wednesday March 25th	16:40 - 17:00	45
Diaz	Elva	Regulation of AMPAR recycling and endosomal trafficking by the transmembrane auxiliary subunit SynDIG4/PRRT1	ediaz@ucdavis.edu	Invited speaker	Friday March 27th	07:30 - 07:50	46
Ding	Jun	Remodeling of Corticostriatal Axonal Boutons During Motor Learning	junding12@gmail.com	Invited speaker	Friday March 27th	18:40 - 19:00	47
Faw	Timothy	Harnessing Apolipoprotein E to Improve Recovery after Spinal Cord Injury	TFaw@som.umaryland.edu	Invited speaker	Friday March 27th	16:40 - 17:00	48
Florida Lifetime Imaging		TBD		Sponsor talk	Wednesday March 25th	08:30 - 08:40	
Gao	Fen-Biao	Neural Mechanisms Underlying a Novel Link Between Aging and Poly(GR) Toxicity in C9ORF72-ALS/FTD	fenbiao@gmail.com	Invited speaker	Thursday March 26th	17:20 - 17:40	49
Getz	Angela M.	A pipeline for single molecule imaging of endogenous synaptic proteins in brain tissue	a.m.getz@vu.nl	Invited speaker	Thursday March 26th	07:30 - 07:50	50
Gitler	Aaron D.	An emergent disease-associated motor neuron state precedes cell death in a mouse model of ALS	agitler@stanford.edu	Invited speaker	Thursday March 26th	16:20 - 16:40	52

Green	Kim	Development of new mouse models of Alzheimer's disease that combine humanized A□, Tau, and APOE4 knock-in alleles.	kngreen@uci.edu	Invited speaker	Thursday March 26th	17:00 - 17:20	53
Greger	Ingo	AMPA receptor structure	ig@mrc-lmb.cam.ac.uk	Invited speaker	Thursday March 26th	18:20 - 18:40	54
Groc	Laurent	Membrane NMDA receptor surface interactome sets physiological and pathological neuronal functions	laurent.groc@u-bordeaux.fr	Invited speaker	Wednesday March 25th	17:00 - 17:20	ND
Hayashi	Yasunori	Transformation of a locally activated hippocampal code for space to a cortical contextual engram	yhayashi-tky@umin.ac.jp	Invited speaker	Wednesday March 25th	18:40 - 19:00	55
Helmstaedter	Moritz	Cerebral Cortex Connectomics	moritz.helmstaedter@brain.mpg.de	Invited speaker	Friday March 27th	18:20 - 18:40	ND
Hilton	Brett J.	Targeting neuronal maturation to promote axon regeneration following spinal cord injury	bhilton@icord.org	Invited speaker	Friday March 27th	16:20 - 16:40	57
Hippenmeyer	Simon	Mechanisms Generating Cell-Type Diversity	simon.hippenmeyer@ist.ac.at	Invited speaker	Friday March 27th	07:50 - 08:10	58
Hong	Sungho	Disinhibitory circuit mechanisms of climbing fiber-instructed cerebellar learning	sunghohong@ibs.re.kr	Short talks	Thursday March 26th	09:30 - 09:40	59
Hosokawa	Tomohisa	CaMKII Condensates Driven by Excitatory Stimulation Function as Synaptic Tags for Protein Accumulation	hosokawa.tomohisa.5s@kyoto-u.ac.jp	Short talks	Friday March 27th	17:40–17:50	60
Igarashi	Kei M	Circuit mechanisms of item memory and its disruption in Alzheimer's disease	kei.igarashi@uci.edu	Invited speaker	Thursday March 26th	16:40 - 17:00	61
Imai	Takeshi	Dendritic compartment-specific spine formation in layer 5 neurons underlies cortical circuit maturation during	imai.takeshi.457@m.kyushu-u.ac.jp	Invited speaker	Wednesday March 25th	18:00 - 18:20	62
Kheirbek	Mazen	Representations of stimulus features in the ventral hippocampus	Mazen.Kheirbek@ucsf.edu	Invited speaker	Wednesday March 25th	18:20 - 18:40	66
Klein	Ruediger	Central amygdala circuits controlling biting, feeding, and drinking	rklein@neuro.mpg.de	Invited speaker	Friday March 27th	18:20 - 18:40	68
Kubota	Yoshiyuki	Converging Perisynaptic Astrocytic Processes onto Active Dendrites after Motor Learning	yoshiy@nips.ac.jp	Organizer talk	Friday March 27th	09:20 - 09:40	69
Kunugitani	Ken	CaMKII Activation Drives Phase Separation with AMPA Receptor Regulatory Protein Shisa	kunuken846@gmail.com	Short talks	Thursday March 26th	09:30 - 09:40	71
Kusumi	Aki	Postsynaptic receptor turnover on PSD protein condensates revealed by single-molecule imaging	akihiro.kusumi@oist.jp	Invited speaker	Thursday March 26th	08:50 - 09:10	72
Lee	Kea Joo	Synaptic Ultrastructural Alterations in Human Focal Cortical Dysplasia: Insights from Volume Electron Microscopy	relaylee@gmail.com	Invited speaker	Friday March 27th	18:00 - 18:20	73
Lee	Wei-Chung	Circuit Motifs of Behavior	wei-chung_lee@hms.harvard.ed	Invited speaker	Wednesday March 25th	17:20 - 17:40	ND
Leterrier	Christophe	The axonal cytoskeleton down to the nanoscale	christophe.leterrier@univ-amu.fr	Invited speaker	Friday March 27th	09:20 - 09:40	74
Lippi	Giordano	MicroRNA mechanisms of plasticity	glippi@scripps.edu	Invited speaker	Wednesday March 25th	16:00 - 16:20	75
Lu	Hui-Chen	NAD + Reduction in Glutamatergic Neurons Triggers Metabolic Reprogramming, Neuroinflammation, and Neurodegeneration	hclu@iu.edu	Invited speaker	Thursday March 26th	19:00 - 19:20	

Mackie	Ken	Roles for endocannabinoids and the impact of exogenous cannabinoids on the developing brain	kmackie@iu.edu	Invited speaker	Friday March 27th	08:30 - 08:50	76
Mao	Tianyi	Neuronal architecture of the mouse insular cortex underlying its diverse functions	mao@ohsu.edu	Invited speaker	Friday March 27th	18:00 - 18:20	79
MaxWell Biosystems		TBD		Sponsor talk	Wednesday March 25th	09:30 - 09:40	
McCreedy	Dylan A.	Mature neutrophils promote resolution of inflammation and long-term recovery after spinal cord injury	dmccreedy@bio.tamu.edu	Invited speaker	Thursday March 26th	18:40 - 19:00	80
Meijers	Rob	Developing systematic antibody panels for neuronal receptor hubs	rob.meijers@proteininnovation.org	Invited speaker	Thursday March 26th	19:00 - 19:20	81
Meunier	Frederic A	Phospholipase A1 isoform DDHD2 controls memory formation and long-term potentiation	Frederic Meunier <f.meunier@uq.edu.au>	Invited speaker	Thursday March 26th	16:20 - 16:40	82
Mikuni	Takayasu	Single-cell synaptome mapping of different protein subpopulations in the brain	tmikuni@bri.niigata-u.ac.jp	Invited speaker	Friday March 27th	16:40 - 17:00	83
Miyazaki	Takaaki	Synaptic-level organization of reciprocal cortico-cortical circuits in the marmoset prefrontal cortex revealed by large-volume	tmz@nips.ac.jp	Short talks	Friday March 27th	17:40–17:50	84
Murayama	Masanori	Large-scale Ca2+ imaging reveals segregated cortical functional networks during unconsciousness	masanori.murayama@riken.jp	Invited speaker	Thursday March 26th	07:30 - 07:50	85
Nägerl	Valentin	Nanoscale imaging of the extracellular space in amyloid brain tissue in vivo	valentin.nagerl@med.uni-goettingen.de	Invited speaker	Friday March 27th	17:00 - 17:20	87
Nakagawa	Terunaga	AMPA receptor structure and function	terunaga.nakagawa@vander	Invited speaker	Thursday March 26th	18:00 - 18:20	88
Nakashima	Ai	Decoding spontaneous activity patterns for olfactory receptor-specific glomerular segregation	anaka0911@g.ecc.u-tokyo.ac.jp	Invited speaker	Friday March 27th	08:10 - 08:30	89
Palmer	Lucy	Cortical circuit dynamics during learning and memory	lucy.palmer@florey.edu.au	Invited speaker	Wednesday March 25th	18:50 – 19:10	92
Paoletti	Pierre	Excitatory glycine receptors: atypical NMDA receptors in brain signaling	pierre.paoletti@ens.psl.eu	Invited speaker	Thursday March 26th	18:40 - 19:00	93
Penzes	Peter	Regulation of Brain Circuits and Behavior by Synaptic Soluble Ectodomains	p-penzes@northwestern.edu	Invited speaker	Friday March 27th	08:50 - 09:10	94
Portera-Cailliau	Carlos	Translatome Profiling of Inhibitory and Excitatory Neurons of Fragile X Mice Identifies a Novel Therapeutic Target	CPCailliau@mednet.ucla.edu	Invited speaker	Friday March 27th	07:30 - 07:50	96
Quantum Design Japan		TBD		Sponsor talk	Wednesday March 25th	07:50-08:00	
Rochefort	Nathalie	Movie-trained transformer reveals novel response properties to dynamic stimuli in mouse visual cortex	N.Rochefort@ed.ac.uk	Invited speaker	Wednesday March 25th	16:20 - 16:40	97
Rusakov	Dmitri	Glutamate Spillover is Common in the Living Brain and May Help Memory Recall	d.rusakov@ucl.ac.uk	Invited speaker	Thursday March 26th	16:40 - 17:00	98
RWD Life Science		TBD		Sponsor talk	Wednesday March 25th	08:00 - 08:10	
Sakano	Takumi		sakanotakuminosaka@g.ecc.u-tokyo.ac.jp	Invited speaker	Friday March 27th	09:10 - 09:20	101

Scheiffele	Peter	Molecular Mechanisms of Cortical Wiring and Plasticity	peter.scheiffele@unibas.ch		Wednesday March 25th	17:20 - 17:40	103
Semyanov	Alexey	Four phases and a temporal threshold of population calcium response in cortical astrocytes during locomotion.	alexeysemyanov@gmail.com	Invited speaker	Thursday March 26th	08:50 - 09:10	104
Shepherd	Jason	Virus-like Intercellular Synaptic Plasticity	Jason.Shepherd@neuro.utah.edu	Invited speaker	Friday March 27th	08:10 - 08:30	107
Shimogori	Tomomi	Cell Type Evolution and Species-Specific Brain Functions Revealed from the Gene Expression Map of the Marmoset	tomomi.shimogori@riken.jp	Invited speaker	Friday March 27th	08:50 - 09:10	
Smith	Katharine	illuminating inhibitory synaptic function in health and disease	katharine.r.smith@cuanschutz.edu	Invited speaker	Thursday March 26th	07:50 - 08:10	109
Sousa	Monica M	From Scar to Repair: Defining the Cellular and Molecular Roadmap for Mammalian Spinal Cord Regeneration	msousa@i3s.up.pt	Invited speaker	Thursday March 26th	18:00 - 18:20	110
Stroebel	David	Molecular Evolution of iGluR Functions	david.stroebel@ens.fr	Invited speaker	Friday March 27th	17:20 - 17:30	
Stuart	Greg	Interhemispheric communication in binocular visual cortex	Greg.Stuart@monash.edu	Short talks	Wednesday March 25th	16:00 - 16:20	111
Sweet	Robert A.	Rethinking MAP2 as a Target for Recovery in Neuropsychiatric Illness	sweetra@upmc.edu	Invited speaker	Thursday March 26th	18:20 - 18:40	114
TCW	Julia	Apoe4-driven splicing defects disrupt neurite projection in excitatory neurons	juliatcw@bu.edu	Invited speaker	Thursday March 26th	16:00 - 16:20	115
Tedeschi	Andrea	In vivo programming of adult pericytes aids axon regeneration by providing cellular bridges for SCI repair	Andrea.Tedeschi@osumc.edu	Invited speaker	Friday March 27th	16:00 - 16:20	116
Turchetto	Silvia	Local Regulation of Protein Degradation At Neuronal Synapses	silvia.turchetto@dandrite.au.dk	Invited speaker	Friday March 27th	09:10 - 09:20	
Vizgen		TBD		Sponsor talk	Wednesday March 25th	09:10 - 09:20	
Volynski	Kirill	Dissection of multiple Synaptotagmin 7 functions with quantal analysis.	k.volynski@ucl.ac.uk	Short talks	Thursday March 26th	17:00 - 17:20	119
VOXA		TBD		Sponsor talk	Wednesday March 25th	08:40 - 08:50	
Wang	Kuan Hong	Unique Adolescent Plasticity of Frontal Dopaminergic Circuits: From Cellular Mechanisms to Therapeutic Potential	kuanhong_Wang@urmc.rochester.edu	Invited speaker	Wednesday March 25th	17:00 - 17:20	120
Watanabe	Shigeki	Membrane mechanics dictate axonal morphology and function	shigeki.watanabe@jhmi.edu	Invited speaker	Friday March 27th	18:40 - 19:00	121
Wood	Marcelo A	Investigating the interface of epigenetics and metabolism underlying synaptic plasticity and memory in the adult and	mwood@uci.edu	Invited speaker	Wednesday March 25th	16:20 - 16:40	
Wu	Yu-Wei	Mixed selectivity and low-dimensional dynamics in STN couple movement and licking	wuyuwei@as.edu.tw	Invited speaker	Thursday March 26th	08:10 - 08:30	122
Xia	Houhui	Protein Phosphatase-1 and 2A in Health and Neurodevelopmental Disorders	houhui_xia@urmc.rochester.edu	Invited speaker	Friday March 27th	17:20 - 17:30	
Yamada	Risa	Mesoscale Simulation of Phosphorylation-Dependent Reorganization of Postsynaptic Density Condensates	yamada.risa.57w@st.kyoto-u.ac.jp	Short talks	Thursday March 26th	09:20 - 09:30	123

Yamazaki	Tadashi	Large-scale microscopic-level brain simulation on a supercomputer	contact25@numericalbrain.org	Short talks	Wednesday March 25th	18:50 – 19:10	124
Yasuda	Ryohei	Decoding Synaptic Signaling Dynamics Underlying Plasticity	ryohei.yasuda@mpfi.org	Invited speaker	Wednesday March 25th	18:40 - 19:00	125
Yazaki-Sugiyama	Yoko	Developmental transient auditory to motor projections for zebra finch song learnin	yazaki-sugiyama@oist.jp	Invited speaker	Thursday March 26th	08:30 - 08:50	
Yu	Ron	Basal Forebrain Cholinergic Input Mediates Adaptive Attention Allocation to Enhance Olfactory Discrimination	congrong.yu@case.edu	Invited speaker	Wednesday March 25th	16:40 - 17:00	
Zhong	Haining	In vivo imaging of second messenger signaling underlying circuit control	zhong@ohsu.edu	Invited speaker	Friday March 27th	16:20 - 16:40	
Zito	Karen	From snowflakes to synapses: how environmental cues shape Ephexin5-mediated synaptic plasticity	kzito@ucdavis.edu	Invited speaker	Friday March 27th	07:50 - 08:10	128
Zou	Yimin	Planar cell polarity proteins in glutamatergic synapse formation and function	yzou@ucsd.edu	Invited speaker	Wednesday March 25th	08:50 - 09:10	129
Zuo	Yi	Unraveling the Synaptic Basis of Motor Learning	yizuo@ucsc.edu	Organizer talk	Wednesday March 25th	07:30 - 07:50	130

Poster list

Poster number	First Name	Family Name	Institution	Poster or short talk
1	Xiaoyi	Zhan	Duke Kunshan University	Poster only
2	Silvia	Turchetto	DANDRITE	short talk
3	Michael	Maher	Johnson & Johnson Innovative Medicine	Poster only
4	Houhui	Xia	University of Rochester	short talk
5	Gyu Hyun	Kim	Korea Brain Research Institute	Poster only
6	Jawon	Gim	Korea Brain Research Institute	Poster only
7	Na-young	Seo	Korea Brain Research Institute	Poster only
8	Sungho	Hong	Institute for Basic Science	short talk
9	Nilton	Kamiji	Hamamatsu University School of Medicine	Poster only
10	Takaaki	Miyazaki	National Institutes of Natural Sciences	short talk
11	Chih wei	Fu	National Institutes of Natural Sciences	Poster only
12	Takumi	Sakano	The University of Tokyo	short talk
13	Masafumi	Tsuboi	The University of Tokyo	Poster only
14	Hana	Samejima	The University of Tokyo	Poster only
15	Tetsuhiko	Kashima	The University of Tokyo	Poster only
16	Yasuko	Isoe	MCB, Harvard University, USA	Poster only
17	Masaaki	Sato	Kyoto Institute of Technology	Poster only
18	Takuya	Kaneko	Nagoya University	Poster only
19	Takahito	Higashi	National Medical Defense College	Poster only
20	Ken	Kunugitani	Kyoto University	short talk
21	Risa	Yamada	Kyoto University	short talk
22	Tomohisa	Hosokawa	Kyoto University	short talk
23	Masashi	Kawamura	The Garduate School of Pharmaceutical Sciences	Poster only
24	Lexin	Gitler	Shanghai American School, Stanford University (High School	Poster only
25	Florent	Haiss	Institut Pasteur	Poster only
26	David	Stroebel	CNRS	short talk
27	Viviana	Villicaña-Muñoz	Institut Interdisciplinaire de Neurosciences	Poster only
28	Yuji	Konyuba	JEOL	Poster only
29	Tomoyuki	Mano	Okinawa Institute of Science and Technology	Poster only
30	Aleksandra	Gavrilova	Okinawa Institute of Science and Technology	Poster only
31	Saahil	Acharya	Okinawa Institute of Science and Technology	short talk
32	Shanshan	Li	Florey Institute of Neuroscience, Australia	Poster only
33	Kye	Kudo	University of Queensland	Poster only
34	Shoi	Shi	University of Tsukuba	Poster only
35	Shinnosuke	Nomura	University of Tsukuba	Poster only
36	Naoki	Kato	Waseda University	Poster only
37	BOXIAO	ZHAO	Waseda University	Poster only
38	Tomoya	Uchida	Waseda University	Poster only
39	Nicky	Scheefhals	Radboud university medical center	Poster only

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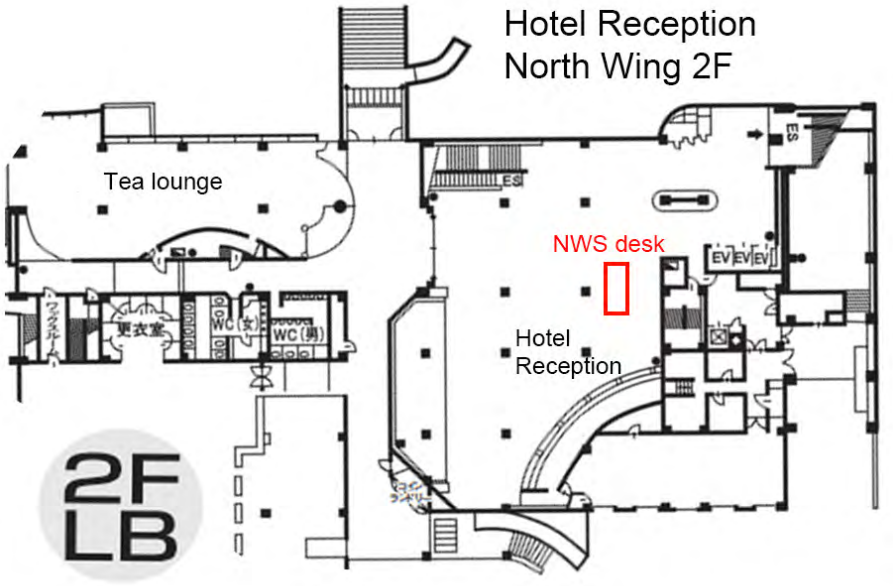
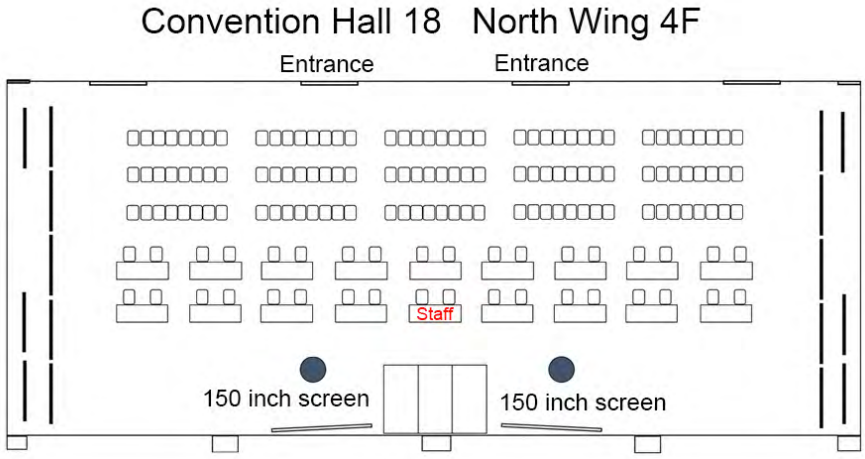
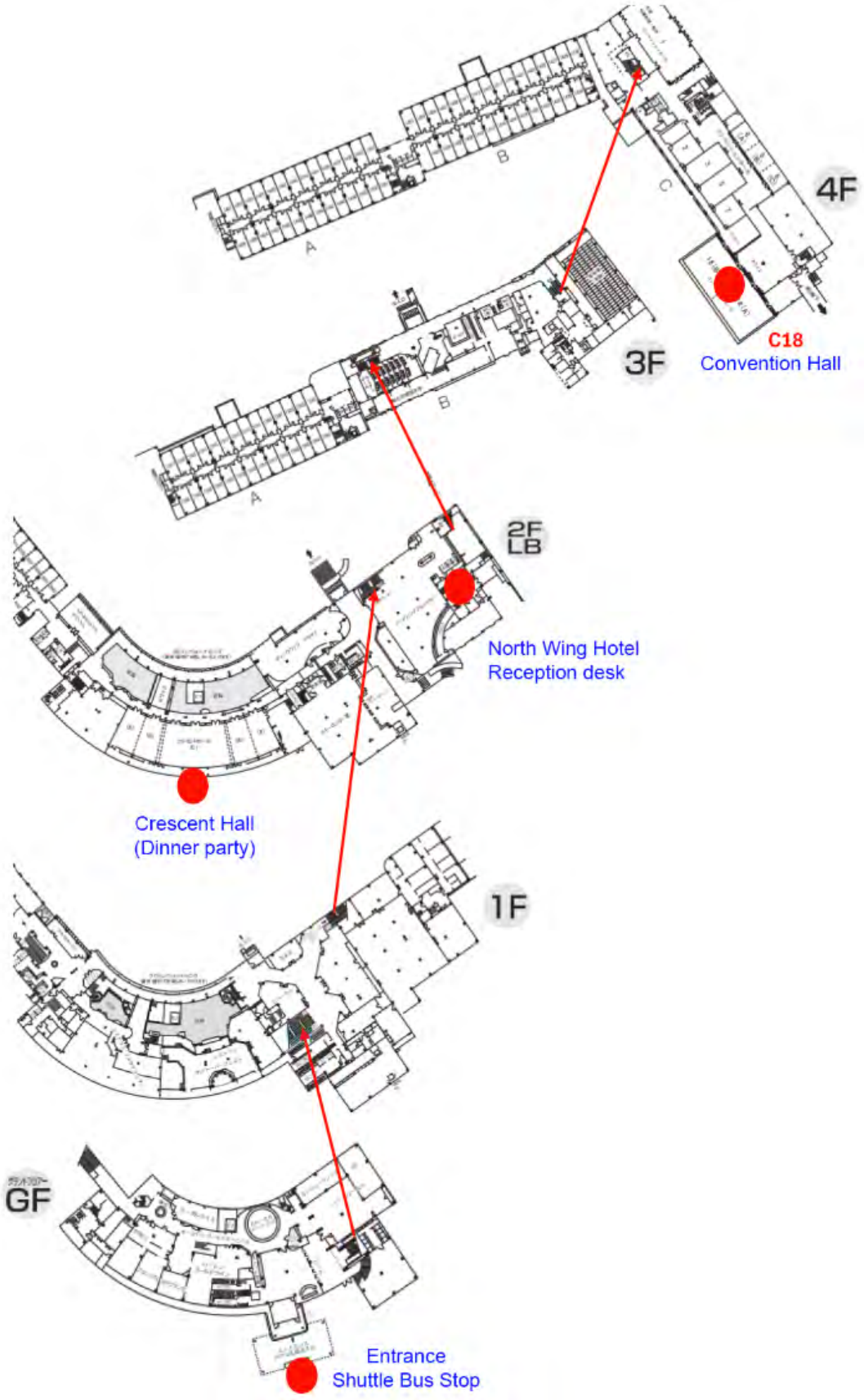
Poster list

Poster number	First Name	Family Name	Institution	Poster or short talk
31	Saahil	Acharya	Okinawa Institute of Science and Technology	short talk
11	Chih wei	Fu	National Institutes of Natural Sciences	Poster only
30	Aleksandra	Gavrilova	Okinawa Institute of Science and Technology	Poster only
6	Jawon	Gim	Korea Brain Research Institute	Poster only
24	Lexin	Gitler	Shanghai American School, Stanford University (High School	Poster only
25	Florent	Haiss	Institut Pasteur	Poster only
19	Takahito	Higashi	National Medical Defense College	Poster only
8	Sungho	Hong	Institute for Basic Science	short talk
22	Tomohisa	Hosokawa	Kyoto University	short talk
16	Yasuko	Isoe	MCB, Harvard University, USA	Poster only
9	Nilton	Kamiji	Hamamatsu University School of Medicine	Poster only
18	Takuya	Kaneko	Nagoya University	Poster only
15	Tetsuhiko	Kashima	The University of Tokyo	Poster only
36	Naoki	Kato	Waseda University	Poster only
23	Masashi	Kawamura	The Garduate School of Pharmaceutical Sciences	Poster only
5	Gyu Hyun	Kim	Korea Brain Research Institute	Poster only
28	Yuji	Konyuba	JEOL	Poster only
33	Kye	Kudo	University of Queensland	Poster only
20	Ken	Kunugitani	Kyoto University	short talk
32	Shanshan	Li	Florey Institute of Neuroscience, Australia	Poster only
3	Michael	Maher	Johnson & Johnson Innovative Medicine	Poster only
29	Tomoyuki	Mano	Okinawa Institute of Science and Technology	Poster only
10	Takaaki	Miyazaki	National Institutes of Natural Sciences	short talk
35	Shinnosuke	Nomura	University of Tsukuba	Poster only
12	Takumi	Sakano	The University of Tokyo	short talk
14	Hana	Samejima	The University of Tokyo	Poster only
17	Masaaki	Sato	Kyoto Institute of Technology	Poster only
39	Nicky	Scheefhals	Radboud university medical center	Poster only
7	Na-young	Seo	Korea Brain Research Institute	Poster only
34	Shoi	Shi	University of Tsukuba	Poster only
26	David	Stroebel	CNRS	short talk
13	Masafumi	Tsuboi	The University of Tokyo	Poster only
2	Silvia	Turchetto	DANDRITE	short talk
38	Tomoya	Uchida	Waseda University	Poster only
27	Viviana	Villicaña-Muñoz	Institut Interdisciplinaire de Neurosciences	Poster only
4	Houhui	Xia	University of Rochester	short talk
21	Risa	Yamada	Kyoto University	short talk
1	Xiaoyi	Zhan	Duke Kunshan University	Poster only
37	BOXIAO	ZHAO	Waseda University	Poster only

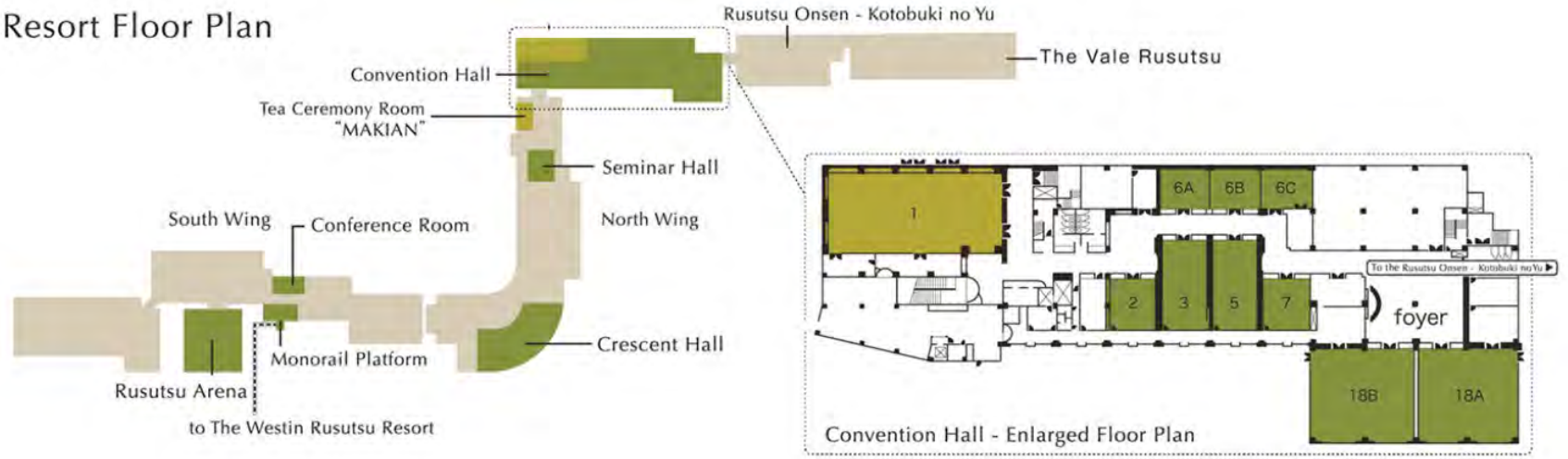




NeuroWinterSummit desk is located North Wing Lobby (24-25th) on the 2F

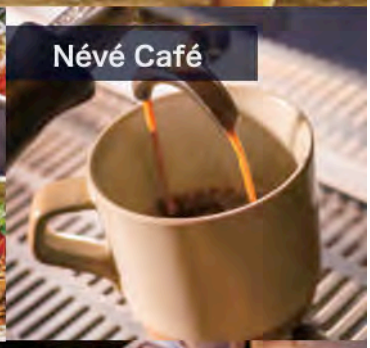

4F
C18
Convention Hall
3F
2F
LB
North Wing Hotel
Reception desk
Crescent Hall
(Dinner party)
1F
GF
Entrance
Shuttle Bus Stop

Resort Floor Plan

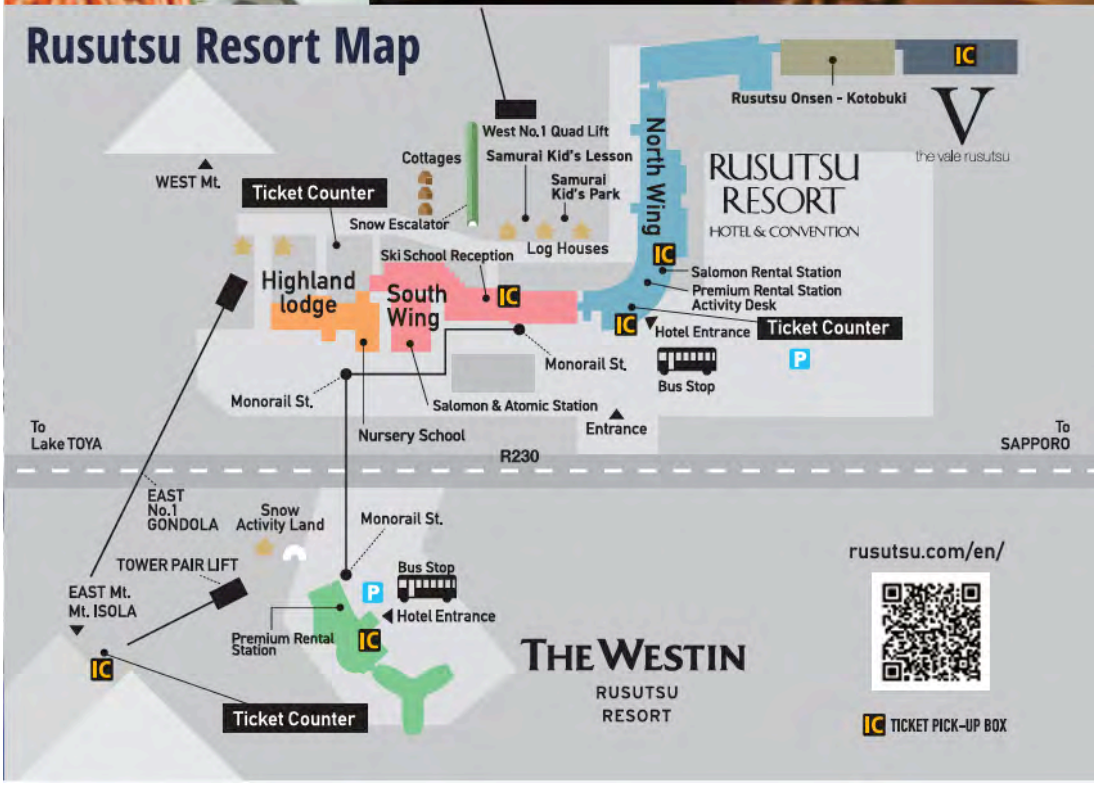


Conference room, Posters, Company Tables, 4th floor in the North Wing

Dining



Rusutsu Resort Map



Ski mountain information

Spring Season : 16/03/2026(Mon.) – 31/03/2026(Tue.)

	Adult (Ages 19-64)	Senior (Ages 65+)	Youth (Ages 13-18)	Child (Ages 4-12)
25 Hour Ticket	34,700 JPY (33,100 JPY)	28,900 JPY (27,700 JPY)	28,900 JPY (27,700 JPY)	17,400 JPY (16,600 JPY)
Spring Season Top Up 5 Hour	5,300 JPY (5,300 JPY)	4,300 JPY (4,300 JPY)	4,300 JPY (4,300 JPY)	2,400 JPY (2,400 JPY)

*Prices in parentheses '( )' are for online purchases
*The 25 hour and Top up 5 hour can be used in one hour increments. Please do not share 1 lift ticket with more than one person.
*Top up 5 hour can only be recharged by those who have purchased a 25 hour ticket (including advance tickets). New IC cards cannot be used to purchase Top up 5 hour.

	Adult (Ages 19-64)	Senior (Ages 65+)	Youth (Ages 13-18)	Child (Ages 4-12)
1 Day Ticket (Spring Season)	9,500 JPY (9,500 JPY)	6,800 JPY (6,800 JPY)	6,800 JPY (6,800 JPY)	4,000 JPY (4,000 JPY)
Point Ticket (1 Point)	800 JPY	700 JPY	700 JPY	500 JPY

*1 Day Ticket (Early Season 1 and 2) sale at only the ticket office.

Remarks

· The lifts are free of charge for children ages 3 and younger.
· The closing time is subject to change, depending on the time of the year and other circumstances.
· Night ski operation schedule Mid-Dec/2025 – 30/03/2026 (Mon.).The hours for night skiing are 16:00 to 20:00 (last lift ride: 19:45). ※Opening dates may be subject to change depending on seasonal snow conditions.
· For prices of tickets for 6 or more days, please contact our General Reservation Center.
· Other matters subject to general operational conditions.

Proof of age

· When purchasing tickets, you will be required to present an ID (e.g. passport, driving licence, health insurance card, student ID card, etc.) that verifies your age. When purchasing online, you will be asked to upload a photo of an ID document that confirms your age. The age will be verified in accordance with the passport. If the documents are incomplete, the purchase may be cancelled.
· When you pass through the gates of the gondolas and lifts, a light will come on to confirm your ticket type. At that time, the lift attendant may ask you to show proof of age. If it is found that you are not of the eligible age, you will be refused access to the lifts as a misuse of your ticket.

Regarding Hourly Tickets

[5 Hour Ticket]
· The 5 hour ticket is valid for a continuous period of time from the first time you pass through the ticket gate (5 hour ticket cannot be used on multiple days)

[25 Hour Ticket · Top Up 5 Hour]
· The 25 hour ticket and Top up 5 hour can be used in one hour increments. Tickets are valid across all dates during the current season. The first time you pass through the IC gate, one hour is automatically deducted from the ticket. The user can then pass through muliple gates until one hour has passed. If the user passed through another after 1-hour has passed an additional hour will be deducted.
· The remaining time is displayed in one hour increments on the gate monitor when you pass through the gate.
· Top up 5 hour can only be recharged by those who have purchased a 25 hour ticket (including advance tickets). New IC cards cannot be used to purchase Top up 5 hour.
· To add a Top up 5 hour through online purchase, user registration is required when purchasing either the 25 hour ticket online (including advance tickets). After completing user login, you will then be able to select the 5-hour top-up option.
· Only IC cards that have been used to purchase a 25 hour ticket can be used with a Top up 5 hour at the lift ticket counter (including advance tickets). Please note other lift ticket types will not be accepted.

*How to use the 25 hour ticket >

Point Tickets (requires reward points)

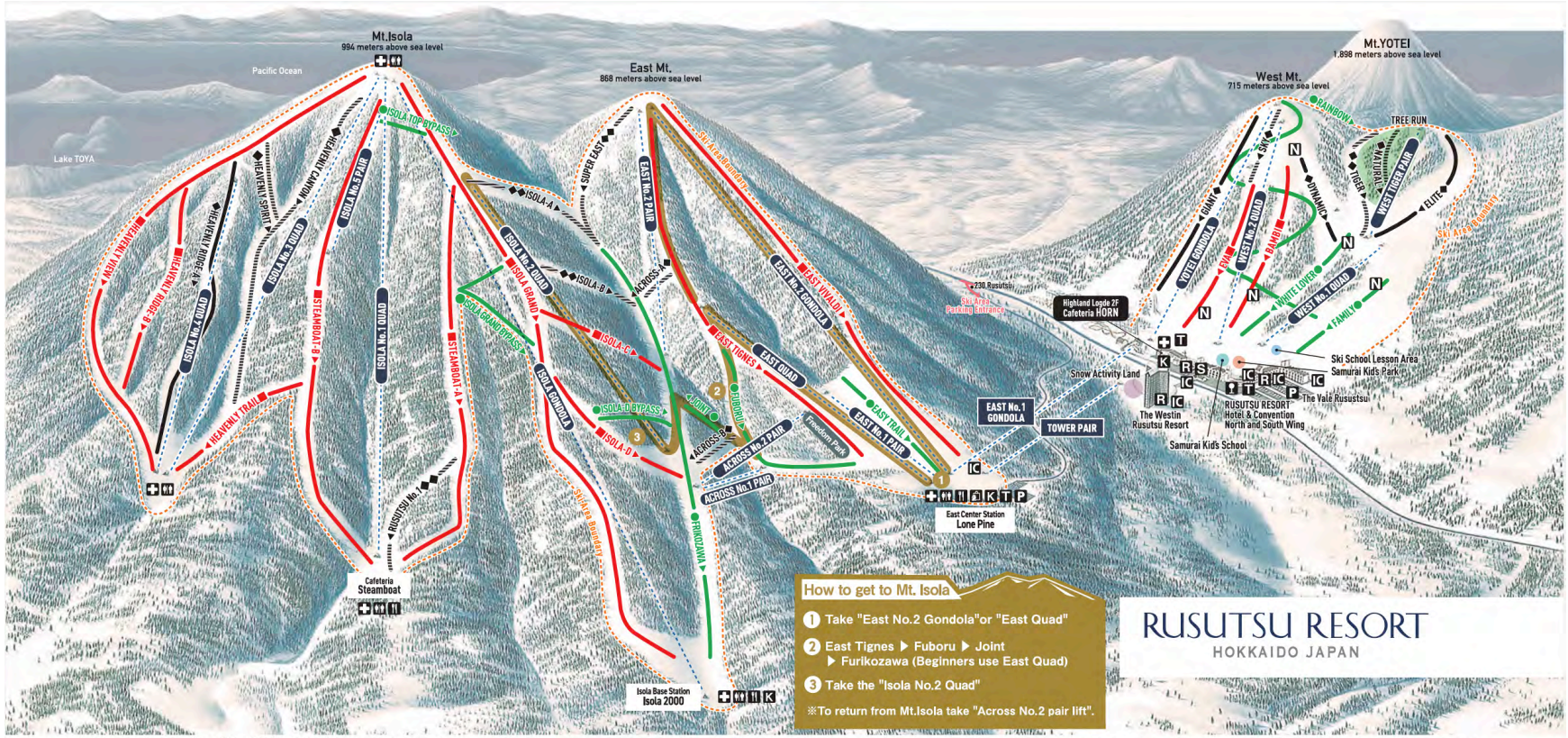
· Pair Lift, West No.1 Quad Lift : 1 Point
· Quad Lift : 2 Points
· Gondola : 3 Points

*Number of points required depends on which lift / gondola will be used.
*East No.1 Gondola, Tower Pair Lift, Across No.1 Pair Lift, and Across No.2 Pair Lift are free of charge.

Payment Method

Credit / Debit Card
American Express / VISA / MasterCard / JCB / Diners Club / DISCOVER / China Union Pay /
E-money
Edy / QUICPay / iD / WAON / nanaco / Kitaca / Suica / PASMO / toICa / manaca / ICOCA / SUGOCA / nimoca / hayakaken /
QR Code Payment
PayPay / d-payment / auPay / merpay / Rakuten Pay / Ginko Pay / WeChatPay / AliPay /

*Online purchases can only be made via credit card.



RUSUTSU RESORT **Tel.+81-136-46-3111**

◆◆EXPERT ◆ADVANCED ■INTERMEDIATE ●BEGINNER ⟋⟋UNGROOMED TRAIL SKI PATROL S SKI&SNOWBOARD SCHOOL R SKI&SNOWBOARD RENTAL T TICKET SALES REST ROOM RESTAURANT SHOP K K-LOUNGE BUS STOP P PARKING N NIGHT SKIING AREA (Subject to change) IC TICKET PICK-UP BOX

HOKKAIDO **No.1**

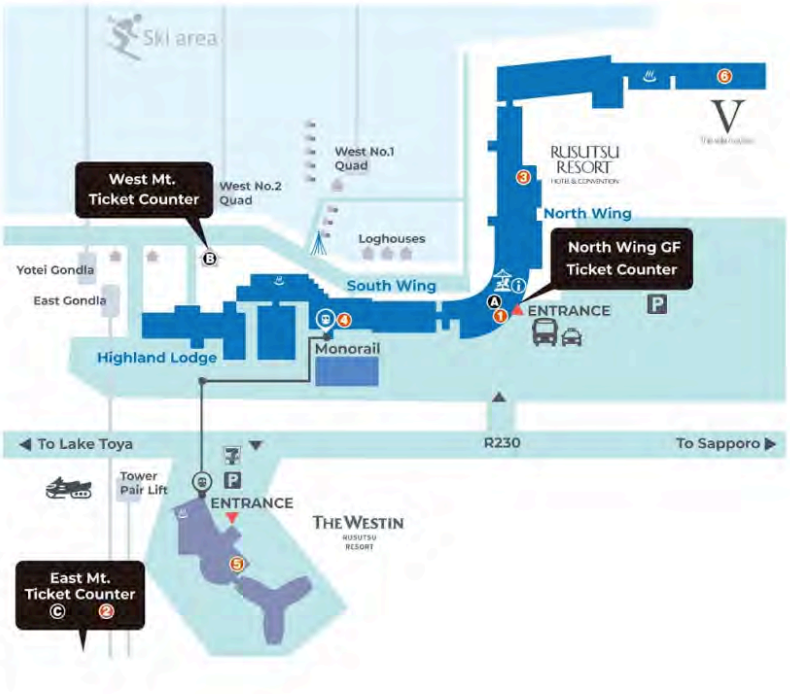
- No.1 for number of trails — 37 trails
- No.1 for total trail length — 42 km
- No.1 for max lift capacity — 30,728 people per hour
- Gondolas : 4 / Quad lifts : 7 / Pair Lifts : 7

- Beginner 30% / Intermediate 40% / Advance 30%
- Max Inclines — 40 degrees (Super East)
- Longest Trail — 3.5 km (ISOLA GRAND)
- AVERAGE SNOWFALL — 2.95 m / 13 m

LIVE LIFT & TRAIL INFORMATION

LIFT TICKET

GONDOLA / LIFT TICKET OFFICE



Gondola / Lift Ticket Office

A. Center Ticket Counter
(North Wing GF)
Operating Hours／8:15 – 16:45

B. West Ticket Counter
(In front of Highland Lodge)
Operating Hours／8:15 – 19:30
(During night-time operation)

C. East Ticket Counter
(East Center Station)
Operating Hours／8:15 – Last boarding times for the East Quad Lift

* For items B and C, the business hours vary depending on the condition of the Lift Status.

To the Lift Status >

Pick-up Boxes

①Center Ticket Counter
(North Wing GF)

②East Ticket Counter
(East Center Station)

③North Wing 2F
(In front of Névé Café)

④South Wing 1F
(In front of Cricket)

⑤Westin 1F
(In front of rentals-station)

⑥The Vale Rusutsu 1F
(next to front desk)

How to purchase lift tickets online

Pick-up box System

STEP 1 Click on the "Buy now" button to purchase your ticket. When making a purchase a QR code will be instantly sent via email.

STEP 2 Please scan the QR code at the ticket machine via on a smart phone screen or print off the QR code and scan it at the pick-up-box.

STEP 3 Please collect your IC card.

STEP 4 Go to the IC gate, scan your ticket and access the lifts.

BUY PASS

Charging Method

STEP 1 Click "BUY PASS" or scan the QR code on the back of your IC card to access the purchase page.

STEP 2 Select your ticket and enter the WTP code on the back of your IC card. Then, load your ticket with a credit card.
(The WTP code will appear automatically once you scan the QR code)

STEP 3 You will receive a thank-you email that confirms that loading is complete.

STEP 4 Go to the IC gate, scan your ticket and access the lifts.

BUY PASS

PICK-UP BOXES

At Rusutsu Resort, we have introduced automatic lift ticket machines (pick-up boxes). Purchase your tickets in advance using a credit card via our official website.

For the online webshop – customers with existing IC cards can re-charge lift tickets online, while we will also introduce a pick-up box system for new customers who do not have an IC card. First, purchase your lift ticket online to receive a QR code, next scan the QR code at the pick-up box in the resort to be issued a lift ticket on an IC card.

Bus information

All the shuttle buses between Rusutsu resort hotel and the airport must be booked online 7 days before your travel date.

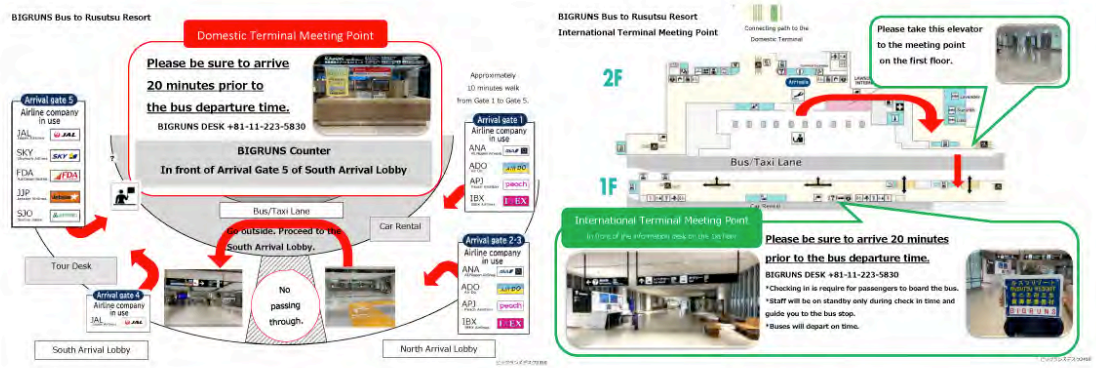
https://rusutsu.com/en/access-shuttle-bus-niseko/

Home > Access – New Chitose Airport ⇔ Rusutsu Shuttle Buses (BIGRUNS BUS)

The Bigruns bus offers convenient access from New Chitose Airport to Rusutsu Resort.

Approximate Time	120minutes
Operating period	29/11/2025(Sat.) – 31/03/2026(Tue.) *Please note that on 29/11/2025(Sat.), only one-way departures from the airport will be available, and on 31/03/2026(Tue.), only one-way departures from Rusutsu will be available.
Fare (tax included)	・Standard：5,500 JPY (one way / per seat) ・Online reservation：5,000 JPY (one way / per seat, advance payment by credit card required) *The same fare applies to adults and children. *Children aged 4 and above require a reserved seat. *Children aged 3 and under may travel free of charge if seated on a parent's lap.
Cancellation Policy	・Day before the reserved service：40% of the fare ・Day of the reserved service (before departure)：50% of the fare ・No-show or cancellation after departure on the day of the reserved service：100% of the fare
Reservation	・Please check the timetable and select your preferred bus departure time. ・Online reserve by clicking the "RESERVATION" button no later than 24:00, 7 days before your travel date.

Meeting point: New Chitose Airport



From New Chitose Airport

29/11/2025(Sat.) – 30/03/2026(Mon.)

	Location	1101	*1103	1105	*1107	*1109	1111	*1113	1115
Departure	International terminal	–	11:05	12:20	13:05	14:05	15:05	16:50	–
	Domestic terminal	10:15	11:15	12:30	13:15	14:15	15:15	17:00	19:00
Arrival	Rusutsu Resort Hotel & Convention	12:15	13:15	14:30	15:15	16:15	17:15	19:00	21:00
	The Westin Rusutsu Resort	12:25	13:25	14:40	15:25	16:25	17:25	19:10	21:10
	The Vale Rusutsu	12:35	13:35	14:50	15:35	16:35	17:35	19:20	21:20

・「*」Services marked with an asterisk will operate from 20/12/2025(Sat.).
・There is a break of approximately 10 minutes on all journeys.

[Transfer Time]
・Arrival at Domestic Terminal → Meeting and departure from Domestic Terminal : 45 minutes or more
・Arrival at International Terminal → Meeting and departure from International Terminal : 90 minutes or more
・Arrival at International Terminal → Meeting and departure from Domestic Terminal : 120 minutes or more
*Buses 1101 and 1115 do not stop at the International Terminal.

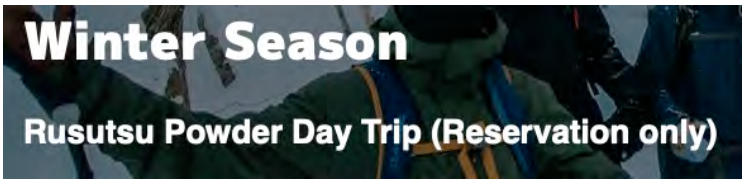
From Rusutsu Resort

30/11/2025(Sun.) – 31/03/2026(Tue.)

	Location	1102	*1104	1106	1108	*1110	1112	*1114
Departure	The Vale Rusutsu	8:40	9:40	11:10	12:40	13:40	15:40	17:20
	The Westin Rusutsu Resort	8:50	9:50	11:20	12:50	13:50	15:50	17:30
	Rusutsu Resort Hotel & Convention	9:00	10:00	11:30	13:00	14:00	16:00	17:40
Arrival	Domestic terminal	11:00	12:00	13:30	15:00	16:00	18:00	19:40
	International terminal	11:10	12:10	13:40	15:10	16:10	18:10	19:50

・「*」Services marked with an asterisk will operate from 21/12/2025(Sun.).
・Direct bus service (no stops)

[Transfer Time]
・Connecting to a domestic flight : 50 minutes or more
・Connecting to an international flight : 90 minutes or more



Online reserve by clicking the “RESERVATION” button no later than 15:00, 1 day before your travel date.

・Only online reservations and advance payment are available.

Meeting point

In front of Hirafu Welcome Center

9-31, Niseko Hirafu 1-jo 3-chome, Kutchan-cho

A convenient 1-day trip from Niseko to Rusutsu Resort.

Approximate Time	45 minutes
Operating period	03/01/2026(Sat.) – 28/02/2026(Sat.)
Fare (tax included)	Round trip 9,000 JPY *Bus only. Lift tickets are not included. *If you do not have a lift ticket, please purchase online. *The same fare applies to adults and children. *Please reserve a seat for guests aged 4 and over. *No fare is charged for children aged 3 or younger who do not need a seat.
Cancellation Policy	・Day before the reserved service：40% of the fare ・Day of the reserved service (before departure)：50% of the fare ・No-show or cancellation after departure on the day of the reserved service：100% of the fare
Capacity	40 people, per day
Reservation	・Online reserve by clicking the “RESERVATION” button no later than 15:00, 1 day before your travel date. ・Only online reservations and advance payment are available.

From Niseko

	Location	
Departure	Hirafu Welcome Center	8:30
Arrival	Rusutsu Resort East Mt.	9:15

*No break on the way.

From Rusutsu Resort

	Location	
Departure	Rusutsu Resort East Mt.	16:30
Arrival	Hirafu Welcome Center	17:15

*No break on the way.

Approximate Time 120minutes

Reservation
- Online reserve by clicking the "RESERVATION" button no later than 15:00 on the previous day before your travel date.
- Only online reservations are available.
- Please check the important information at the link below before making a reservation.

From Sapporo

29/11/2025(Sat.) – 31/03/2026(Tue.)

	Location	3101
Departure	Kamori Building 3, Sapporo	8:00
Arrival	Rusutsu Resort Hotel & Convention The Westin Rusutsu Resort The Vale Rusutsu	10:00 10:10 10:20

- There is a break of about 10 minutes at Nakayama Touge.

From Rusutsu Resort

29/11/2025(Sat.) – 31/03/2026(Tue.)

	Location	3102
Departure	The Vale Rusutsu The Westin Rusutsu Resort Rusutsu Resort Hotel & Convention	16:40 16:50 17:00
Arrival	Kamori Building 3, Sapporo	19:00

SynGAP forms condensates from nanomolar concentrations, recruiting PSD95 and key synaptic receptors

Saahil Acharya[1], Taka A. Tsunoyama[1], Irina Meshcheryakova[1], Christian Hoffmann[2], Perez Gerard Aguilar[2], , Aya Nakamura-Norimoto[1], Amine Aladag[1], Tara Mastro[3], Ward G. Walkup IV[3], Takahiro K. Fujiwara[4], Mary B. Kennedy[3], Dragomir Milovanovic[2], and Akihiro Kusumi[1,4]

[1]Membrane Cooperativity Unit, Okinawa Institute of Science and Technology Graduate University, Onna-son, Okinawa 904-0495, Japan;
[2]Laboratory of Molecular Neuroscience, German Center for Neurodegenerative Diseases (DZNE), 10117 Berlin, Germany;
[3]Division of Biology and Biological Engineering, California Institute of Technology, Pasadena 91125, California, U.S.A;
[4]Institute for Integrated Cell-Material Sciences (WPI-iCeMS), Kyoto University, Kyoto 606-8501, Japan.

Synapse formation lies at the core of neuronal circuit development and plasticity. In mature postsynapses, a dense protein assembly adjacent to the post-synaptic plasma membrane, known as the post synaptic density (PSD), orchestrates synaptic funciton. Recent work suggests that condensation of key PSD proteins via liquid-liquid phase separation constitutes the structural basis of the PSD[1]. However, how such assemblies are initially nucleated at concentrations far below those found in mature spines, such as during nascent synapse formation, remains unknown.

Using in-vitro microscope observations of purified proteins combined with live-cell single-molecule and confocal imaging, we found that SynGAP forms nanoscale clusters containing a median of 13 molecules at 10-nM-order concentrations, and micron-scale condensates at sub-micromolar concentrations.

SynGAP condensation requires its large intrinsically disordered region (IDR) and coiled-coil domain, suggesting that the coiled-coil-induced IDR trimers act as minimal multivalent units for homophilic interactions for inducing condensation. CaMKII-mediated phosphorylation moderately suppresses SynGAP condensation while enhancing condensate liquidity.

PSD95 does not undergo nanoscale clustering or micron-scale condensation under comparable conditions, but it is recruited to SynGAP condensates through specific PDZ binding to the C-terminal PDZ-binding motif of the SynGAPα1 isoform. SynGAP[PSD95] condensates recruit and immobilize postsynaptic transmembrane proteins, Neuroligin1 and AMPAR-TARP2 complexes, with residency times dependent on the oligomerization states of transmembrane proteins, highlighting the importance of multivalent binding at various stages of PSD assembly.

Collectively, these findings suggest that SynGAP nano- and micron-scale assemblies may act as key nucleation hubs for PSD formation at very early stages of synaptogenesis, when concentrations of PSD constituent proteins are far below the levels found in mature spines.

References:
1. Hayashi et. al., (2021) *J Neurosci.* 41(5):834–844

The Structural Landscape Of A Synaptic GABAa Receptor Capture Complex

Vikram Babu Kasaragod1, Tokiwa Yamasaki2, Andrija Sente1, Eva Kaulich1, Steven W. Hardwick3, Dimitri Y. Chirgadze3, Michisuke Yuzaki2,4 and A. Radu Aricescu1,4

1 MRC Laboratory of Molecular Biology, Cambridge, UK;

2 Department of Physiology, Keio University School of Medicine, Tokyo, Japan;

3 Department of Biochemistry, University of Cambridge, Cambridge, UK;

4 Human Biology–Microbiome–Quantum Research Center (Bio2Q), Keio University, Tokyo, Japan

Multiple proteins and post-translational modifications are thought to regulate the 'capture' and retention of neurotransmitter receptors at diverse synapse types. However, their mechanisms of operation and the impact of synaptic anchoring on receptor function remain enigmatic. We report a series of single-particle cryogenic electron microscopy (cryo-EM) structures of the full-length human GABAA receptor α1β3γ2, a synaptic pentameric ligand-gated ion channel, bound to the tetraspan GARLH4 and the transmembrane region of the adhesion molecule Neuroligin2. These proteins form a vertebrate-specific receptor capture complex stabilized by gamma subunit palmitoylation, cholesterol and specific phospholipids. We show that these molecular assemblies are highly dynamic, enabling unrestrained conformational transitions during GABAA receptor gating. We identify key molecular signatures for the selective capture of synaptic versus extrasynaptic GABAA receptor subtypes and report the structure of a noncanonical receptor subtype bound to two anchoring complexes, which may represent the seed for higher-order, mesophasic organisation of GABAA receptor clusters observed at inhibitory synapses by cryogenic electron tomography. Moreover, we show why diazepam (Valium) triggers the downregulation of synaptic GABAA receptor levels, a process linked to the development of tolerance, dependence and withdrawal, commonly associated to benzodiazepine medication. Our findings define the dynamic organisational framework of prototypical inhibitory neurotransmitter receptor complexes and enable an understanding of GABAergic signalling mechanisms in closer to physiological assemblies. Furthermore, our description of novel binding sites for lipids and lipid modifications opens new avenues for the specific pharmacological modulation of synaptic GABAA receptors, a protein family of fundamental clinical importance.

Di3 Neurons Form Spinal Circuits For Motor Adaptation And Recovery

Tuan V. Bui

Center for Neural Dynamics, Department of Biology, University of Ottawa, Ottawa, Canada

Spinal circuits are critical to many movements we make. Yet the span of their contributions to motor control is underappreciated. We reveal here that spinal circuits centered on a population of spinal neurons named dI3 neurons, are central to capable of generating rapid motor adaptations in response to perturbations. Using an array of electrophysiology, circuit mapping, closed-loop stimulation and behavioural tests, our findings reveal a spinal comparator module centered on these neurons. Furthermore, we show that dI3 neurons play a central role in the recovery of locomotor movements. Together, our findings reveal spinal circuits that are central to achieving particular motor goals in the intact animal, as well as restoring lost motor function due to trauma to the spinal cord.

Probiotic Intervention Restores Microglial Surveillance And Synaptic Architecture in the Aging Cortex

Chia-Chien Eric Chen1,2, Hyo Gun Lee1, Ju Lu2,3, Yi Zuo2

1. Behavioral Science and Neurobiology, Duke Kunshan University. Suzhou, Jiangsu Province, China.

2. Molecular Cell & Developmental Biology, University of California Santa Cruz. Santa Cruz, California, USA.

3. Biology, Lehigh University. Bethlehem, Pennsylvania.

Aging is a major risk factor for cognitive decline and neurodegenerative disease, marked by reduced cortical plasticity and impaired brain adaptability. To investigate the cellular basis of these changes, we compared young (2–3 months) and aged (>18 months) C57BL/6J mice using complementary approaches in vivo and in fixed tissue. Two-photon in vivo imaging revealed that microglia in aged cortex exhibited reduced process dynamics and surveillance, while fixed-tissue immunohistochemistry confirmed a loss of youthful, highly ramified morphology. Golgi staining further demonstrated structural alterations in neuronal architecture within the barrel cortex. Importantly, chronic probiotic supplementation not only restored microglial morphology and motility but also improved synaptic and morphological features of neurons, with rejuvenation observed across multiple cortical areas. These cellular changes were accompanied by enhanced performance in cognitive assays, supporting a functional impact of treatment. Taken together, convergent evidence from in vivo longitudinal imaging and fixed-tissue morphometry demonstrates that aging is characterized by microglial de-ramification and neuronal decline, and that targeted interventions such as probiotics can promote cognitive resilience by restoring microglia–neuron interactions and synaptic integrity across the cortex.

Comet: Cortex-wide Observational Miniature Epifluorescence Technique Enables Imaging Of Large Single-neuron Populations In Freely Moving Mice

Liangyi Chen

National Biomedical Imaging Center, State Key Laboratory of Membrane Biology, Institute of Molecular Medicine, Peking-Tsinghua Center for Life Sciences, College of Future Technology, Peking University, Beijing, China

To understand how neuronal networks integrate sensory input, process information, and drive behavior, recording single-cell activity across the entire dorsal cortex in freely moving animals is important but technically challenging. We present COMET (Cortex-wide Observational Miniature Epifluorescence Technique), a 3.75g head-mounted mesoscope coupled with a denoising and signal extraction pipeline, capable of capturing Ca2+ signals from over 15,000 individual neurons across areas up to 10-mm in diameter, without altering the natural behavior of freely behaving mice. Using an auditory trace fear conditioning paradigm, we observed changes in functional network architecture within VISa, VISam and RSPagl regions after the first shock, followed by shifts in neuronal firing rates within the comparator and integrator groups after the second shock, culminating in widespread cortical activation at the fourth cue. Thus, COMET enables decoding of multi-stage cross-scale neural representations underlying complex behaviors, paving the way for explorations of distributed cortical computations in naturalistic settings.

Integration of progenitor cells from adult brain into mature hippocampal circuits

Hwai-jong Cheng

Director and Distinguished Research Fellow

Institute of Molecular Biology

Academia Sinica, Taiwan

In adult mammalian hippocampus, neurogenesis is prominent in the subgranular zone of dentate gyrus (DG). These adult-born neurons are functionally integrated into the existing mature hippocampal circuitry. Abnormalities in adult hippocampal neurogenesis (AHN) are implicated in neurological disorders related to learning, memory, and emotion. AHN is less efficient with aging. Our lab has been studying how aging processes change AHN in mice. We developed an efficient method to culture neurospheres from adult and aged neural progenitors in DG, and keep them as adult hippocampal neural progenitor cells (ahNPCs). Single cell RNA (sc-RNA) sequencing analysis was performed on ahNPCs to identify intrinsic factors that might regulate aging changes of these progenitor cells. We transplanted ahNPCs into mouse DG in vivo to explore how these ectopic cells differentiate and integrate in the mature hippocampus. Spatial transcriptomic analysis was used to demonstrate transplanted ahNPCs exhibit same expression profile as neighboring endogenous granule cells. Our ultimate goal is to investigate whether the cultured ahNPCs can be utilized for treating neurological disorders.

Linking Glutamatergic Synapse Dynamic Nanoscale Organization, Function, Plasticity And Memory Mechanisms

Daniel Choquet1

1 Interdisciplinary Institute for Neuroscience, UMR 5297 CNRS-Université de Bordeaux, 33000, France

The spatio-temporal organization of neurotransmitter receptors in the postsynaptic membrane is a fundamental determinant of synaptic transmission and thus information processing by the brain. Ionotropic AMPA glutamate receptors (AMPAR) mediate fast excitatory synaptic transmission in the central nervous system. Using a combination of high resolution single molecule superresolution imaging and tracking techniques, we have established that AMPARs are not all stable in the synapse as thought initially, but in large part undergo continuous entry and exit to and from the post-synaptic density through lateral diffusion. The other fraction of AMPAR are highly concentrated inside synapses into a few clusters of around seventy nanometers. These results have opened the new possibility that glutamatergic synaptic transmission is controlled by the regulation at the nanometer scale of the position and composition of these highly concentrated nanodomains. The dynamic exchange of AMPAR within the PSD and between synaptic and extrasynaptic sites is highly regulated by neuronal activity. Using methods to exogenously control AMPAR surface diffusion, we have demonstrated that AMPAR activity-dependent diffusion-trapping from extrasynaptic to synaptic sites directly controls the establishment of long term synaptic plasticity. We have also demonstrated that AMPAR conformation strongly impacts their mobility, desensitized receptors being more mobile than naïve ones. This property likely explains how post-synaptic AMPAR receptor mobility can regulate short term synaptic plasticity, a feature previously ascribed to pre-synaptic mechanisms. We will also present a series of new experiments that decipher the respective contributions of transmitter release, AMPAR desensitization and surface diffusion in the control of high frequency dependent short term plasticity. Our data indicate that AMPAR surface diffusion is not only important for the expression of synaptic potentiation but also for frequency dependent information processing by synapses.

Specifying Neuronal Regional Properties And Forming Boundaries Between Cortical Regions By Transcription Factor Gradients

Shen-Ju Chou,

Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan

The mammalian cerebral cortex is a remarkably complex organ responsible for the perception of sensory stimuli, the execution of motor actions, learning, cognition, and consciousness. To carry out these complicated functions, it is compartmentalized into multiple functional units or cortical regions, including the newly evolved neocortex and evolutionarily older paleocortex and archicortex. Each region has unique cytoarchitectures, patterns of gene expression, and distinct sets of input and output projections to perform specialized functions. As many neurological disorders assault specific types of neurons in particular brain regions, understanding the mechanisms controlling cortical regional specification will contribute to the understanding of cortical dysfunction in disease states. We study how cortical neurons acquire region-specific properties and how boundaries between cortical regions are established during development. We found that COUP-TFI, an orphan receptor expressed in a high-caudal-lateral-to-low-rostral-medial gradient in cortical progenitors, determines the size and relative position of multiple cortical regions, and the sensory areas in the neocortex. Additionally, COUP-TFI determines the integrity of the borders between abutting cortical regions. For example, by inducing protocadherin 19 expression, COUP-TFI establishes a sharp boundary between the neocortex and the medial entorhinal cortex. Our findings suggest that the expression gradients of COUP-TFI and other patterning transcription factors in the cortical progenitors play an instructive role in cortical regional specification.

Vlk Drives Extracellular Phosphorylation Of Ephb2 To Govern The Ephb2-nmdar Interaction And Injury-induced Pain

Kolluru D. Srikanth1,2†, Hajira Elahi3, 4,10†, Praveen Chander1,2†, Halley R. Washburn2,5†, Shayne Hassler3,6, Juliet M. Mwirigi3, 4, Moeno Kume3, 4, Jessica Loucks3, Rohita Arjarapu3, Rachel Hodge2, Lucy He3,4, Khadijah Mazhar3,4, Stephanie I. Shiers3, 4, Ishwarya Sankaranarayanan3, 4, Hediye Erdjument-Bromage9, Thomas A. Neubert9, Patrick M. Dougherty10, Zachary T. Campbell7, Raehum Paik7,8, Theodore J. Price3, 4 *, Matthew B. Dalva1,2*

1Tulane Brain Institute, Department of Cell and Molecular Biology, Tulane University; New Orleans, LA 70118, USA. 2Jefferson Synaptic Biology Center, Department of Neuroscience, Thomas Jefferson University, Philadelphia, PA 19107 3Department of Neuroscience, The University of Texas at Dallas; Richardson, TX 75080, USA. 4Center for Advanced Pain Studies, University of Texas at Dallas; Richardson, TX 75080, USA. 5Department of Molecular Biology, Princeton University; Princeton, NJ 08544, USA. 6College of Medicine, University of Houston; Houston, TX 77004, USA. 7Department of Anesthesiology, University of Wisconsin-Madison; Madison, WI 53792, USA. 8Department of Genetics, University of Texas Health Science Center at San Antonio; San Antonio, TX 78229, USA. 9 Department of Neuroscience and Physiology and Neuroscience Institute, NYU Grossman School of Medicine, New York, NY, 10016, USA 10Department of Pain Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, 77030, USA

Phosphorylation of hundreds of protein extracellular domains is mediated by two kinase families, yet the significance of these kinases is underexplored. Here, we find that the presynaptic release of the tyrosine directed-ectokinase, Vertebrate Lonesome Kinase (VLK/Pkdcc), is necessary and sufficient for the direct extracellular interaction between EphB2 and GluN1 at synapses, for phosphorylation of the ectodomain of EphB2, and for injury-induced pain. Pkdcc is an essential gene in the nervous system, and VLK is found in synaptic vesicles, and is released from neurons in a SNARE-dependent fashion. VLK is expressed by sensory neurons where presynaptic sensory neuron specific knockout renders mice resistant to post-surgical pain, without changing proprioception. VLK defines an extracellular mechanism that regulates protein-protein interaction and acute pain in response to injury.

L-type Ca^{2+} channels and AKAP-PKA signaling in heterosynaptic regulation of excitatory and inhibitory balance

Jennifer L. Sanderson[1], Katlin M. Zent[1], Sara Gookin[1], Katharine R Smith[1] and Mark L. Dell'Acqua[1]

[1]Department of Pharmacology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA 80045

The use-dependent strengthening of glutamatergic excitatory synapses is essential for neuronal circuit dynamics underlying complex brain functions, such as hippocampal-dependent spatial learning and memory. However, increasing excitation, such as through the induction of long-term potentiation (LTP), if left unchecked can lead to synaptic saturation, neuronal hyperexcitability, and circuit instability. Thus, LTP is countered by homeostatic and heterosynaptic mechanisms that coordinately increase the strength of dendritic GABAergic inhibitory synapses to maintain a careful balance of excitation and inhibition (i.e. E/I balance). Recently we discovered an unappreciated role for L-type voltage-gated Ca^{2+} channels (LTCCs) in heterosynaptic potentiation of $GABA_A$ receptor ($GABA_AR$) responses during induction of homeostatic plasticity in hippocampal neurons. We found that LTCCs act downstream of NMDARs to mediate potentiation of $GABA_AR$ mIPSC responses in coordination with AMPAR mEPSC responses via pathways controlled by local PKA signaling organized by the scaffold protein A-kinase anchoring protein (AKAP) 79/150. Although AKAP79/150 and LTCCs are present in dendritic spines where they play established roles in regulating AMPARs during excitatory plasticity, both are also found along the dendrite shaft plasma membrane where they could be localized near inhibitory synapses. Accordingly, employing structured-illumination microscopy (SIM) we observed that AKAP150 is clustered into nano-domains in peri-synaptic regions of dendritic inhibitory synapses. Localization of AKAP79/150 near both excitatory and inhibitory synapses ideally positions this scaffold for a role in relaying heterosynaptic signals. Indeed, using neurons cultured from ΔPKA knockin mice carrying a mutation that disrupts PKA anchoring to AKAP150, we found that AKAP-PKA signaling promotes LTCC-mediated signal transduction from excitatory to inhibitory synapses during homeostatic plasticity to control dendritic inhibitory postsynaptic nano-architecture imaged with SIM and synaptic strength recorded as mIPSCs. Electrophysiological recording of evoked EPSCs and IPSCs from acute brain slices prepared from ΔPKA mice uncovered similar roles for AKAP-PKA signaling and LTCCs in heterosynaptic potentiation of $GABA_AR$-mediated dendritic inhibition (i.e. iLTP) in response to LTP induction at stratum radiatum CA1 excitatory synapses *ex vivo*. Thus, the LTCC-AKAP-PKA signaling complex plays a previously unappreciated key role in heterosynaptic control of E/I balance.

Proteomics Approaches to Dissect Synapse Composition in Neural Circuits

Dan Dascenco[1,2], Anastasia Malloupoulou[1,2], Jeroen Vandensteen[1,2], Blanca Lorente-Echeverría[1,2], Pedro Magalhães[1,3], Elke Leysen[1,2], Artemis Koumoundourou[1,2] and Joris de Wit[1,2]

[1] VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium;
[2] Department of Neurosciences, KU Leuven, Leuven, Belgium;
[3] VIB-KU Leuven Center for Brain & Disease Research Technologies, Proteomics Unit, Leuven, Belgium

Neural circuits are composed of different types of neurons and the specific patterns of synaptic connectivity between them. The highly heterogeneous nature of neuronal cell types and their connections presents a major challenge to the characterization of neural circuits at the molecular level. Progress in addressing this challenge has come from transcriptomic profiling techniques, which enabled the characterization of the molecular composition of specific cell types within circuits. While single-cell transcriptomics have been instrumental in mapping cell-type diversity in the brain, these approaches are poorly suited to capture the diversity and molecular identity of synapses. In this talk, I will present our recent efforts to map synapse composition and diversity in neural circuits, using synaptic proximity biotinylation approaches coupled with mass spectrometry. We analyze the postsynaptic proteome of CA1 hippocampal pyramidal neurons and characterize the specific molecular composition of their proximal and distal inputs. As CA1 pyramidal neurons are especially vulnerable in Alzheimer's disease (AD), we use these approaches to map their postsynaptic protein composition in *App*$^{NL-G-F}$ mice modeling amyloid-beta pathology and detect early and progressive synaptic changes in AD. Taken together, these proteomics approaches enable the dissection of synapse composition in intact neural circuits in health and disease, and should be broadly applicable to other brain regions and neuron types.

Regulation Of Ampar Recycling And Endosomal Trafficking By The Transmembrane Auxiliary Subunit Syndig4/prrt1

Elva Diaz

Department of Pharmacology, University of California, Davis

A key neural mechanism of learning and memory is thought to be activity-dependent changes in AMPA-type glutamate receptor (AMPAR) levels at synapses. Changes in synaptic AMPAR content are driven by long-term potentiation (LTP) and depression (LTD) of synaptic strength. Increases in synaptic strength are mediated by the recruitment of GluA1-containing AMPARs from nearby reserve pools and stabilization at synapses. Previously, we identified SynDIG4 (Synapse Differentiation Induced Gene 4; SD4), also known as PRRT1 (Proline-rich transmembrane protein), as an auxiliary factor of GluA1-containing AMPARs necessary for maintaining extra-synaptic pools of that are targeted to synapses during LTP and required for higher order cognitive function such as learning and memory. However, how SD4 establishes and maintains these pools is unclear. Previous studies suggested that endocytic machinery is important for maintaining a pool of mobile surface AMPARs, and that proteins associated with such cellular machinery are critical for proper protein trafficking and internalization. Here we show that SD4 governs GluA1-AMPAR trafficking through recycling endosomes (RE) whereby loss of SD4 causes intracellular accumulation of GluA1-AMPARs in Rab4-positive RE and an apparent disruption in trafficking between Rab4-Rab11 compartments. Furthermore, SD4 harbors a functional YxxΦ endocytic motif that binds the μ2 subunit of the AP-2 adaptor complex. Disruption of this sorting motif leads to accumulation of SD4 at the plasma membrane of heterologous cells and hippocampal neurons. We propose that SD4 acts as a cargo selection device to maintain a mobile pool of GluA1-AMPARs within intracellular endosomes through AP-2-mediated internalization that is essential for synaptic targeting during synaptic plasticity.

Remodeling Of Corticostriatal Axonal Boutons During Motor Learning

Jun Ding

Department of Neurosurgery, Stanford University School of Medicine

Abstract:

Motor skill learning induces long-lasting synaptic plasticity at not only at dendritic spines, but also at the outputs of motor cortical neurons to the striatum. However, little is known about corticostriatal axon activity and structural plasticity during learning in the adult brain. Here, using longitudinal in vivo two-photon imaging, we tracked thousands of corticostriatal axonal boutons in the dorsolateral striatum of awake mice. We found that learning a new motor skill dynamically regulates these boutons. The activities of motor corticostriatal axonal boutons exhibited selectivity for rewarded movements (RM) and un-rewarded movements (UM). Strikingly, boutons on the same axonal branches showed diverse responses during behavior. Motor learning significantly increased the proportion of RM boutons and reduced the heterogeneity of bouton activities. Moreover, motor learning-induced profound structural dynamism in boutons. By combining structural and functional imaging, we identified that newly formed axonal boutons are more likely to exhibit selectivity for RM and are stabilized during motor learning, while UM boutons are selectively eliminated. These findings reveal a novel form of plasticity in corticostriatal axons, showing that motor learning drives dynamic bouton reorganization to support motor skill acquisition and execution

Harnessing Apolipoprotein E to Improve Recovery after Spinal Cord Injury

Timothy D. Faw[1,2,3], Emily M. Abbott[4], Eujin Chung[5], Sanoe Rapozo[5], Paola Abad[6], Brianna R. Cellini[5], Nina Zhang[5], Haichen Wang[7], Ping Fan[8], Ellora Haukenfrers[9], Khooshbu K. Patel[9], Vaibhav Jain[9], Stephanie Arvai[9], Ivan Spasojevic[8], Simon Gregory[9], Warren Grill[4], Daniel T. Laskowitz[7]

[1]Department of Orthopaedic Surgery, Duke University, Durham, NC, USA; [2]Department of Physical Medicine and Rehabilitation Science, University of Maryland, Baltimore, Baltimore, MD, USA; [3]University of Maryland – Medicine Institute on Neuroscience Discovery, University of Maryland, Baltimore, Baltimore, MD, USA; [4]Department of Biomedical Engineering, Duke University, Durham, NC, USA; [5]Psychology & Neuroscience, [6]Biology, Trinity College of Arts and Sciences, Duke University, Durham, NC, USA; [7]Department of Neurology, Duke University, Durham, NC, USA; [8]Department of Medicine, Duke University, Durham, NC, USA; [9]Department of Neurosurgery, Duke University, Durham, NC, USA

Abstract:

Spinal cord injury (SCI), the second leading cause of paralysis in the U.S., affects more than 27 million people worldwide with far-reaching effects on physical, emotional, and financial wellbeing. Despite research progress, there are still no FDA-approved therapeutics that alter the trajectory of SCI recovery; thus, the need for acute therapeutics that can reduce damage and improve function remains critical. Apolipoprotein E (APOE, gene; ApoE, protein) has emerged as a major genetic determinant of outcomes from neurotrauma, including SCI. Since apoE is too large to cross blood-nervous system barriers, we developed peptides that mimic apoE's neuroprotective and anti-inflammatory properties to improve function after acute brain injury. The purpose of these experiments was to optimize delivery and test the efficacy of the lead candidate apoE-mimetic peptide, CN-105, to improve outcomes from SCI.

Pharmacokinetic analysis of a single CN-105 dose (5.0 mg/kg) 45 minutes after moderate SCI (75 kdyn + 1 sec dwell) at T9 revealed that CN-105 accesses the injury epicenter within 5 minutes and has delayed elimination compared to plasma (spinal cord half-life = 52 minutes, ; plasma halflife = 25 minutes). Single-nuclei RNA-sequencing revealed distinct pharmacodynamic effects of repeated CN-105 treatment (5.0 mg/kg) on neurons and immune cells (microglia, macrophages) at the injury site 4 hours and 7 days following SCI indicating upregulation of anti-inflammatory and pro-reparative genes with downregulation of pro-inflammatory and oxidative stress genes. Functionally, CN-105 treatment (2.0 mg/kg) for the first 3-days after SCI improved locomotor recovery over 35 days in mice, with greatest effects observed 21 days post-injury. Similarly, CN-105 treatment for seven days improved bladder outcomes (increased bladder capacity, decreased non-voiding contractions) in rats with SCI.

Together, these data identify apoE-mimetic peptides, specifically CN-105, as potential novel therapeutics for acute SCI that warrant further development.

Neural Mechanisms Underlying A Novel Link Between Aging And Poly(gr) Toxicity In C9orf72-als/ftd

Fen-Biao Gao, PhD

Frontotemporal Dementia Research Center, RNA Therapeutics Institute, University of Massachusetts Chan Medical School, Worcester, USA

Frontotemporal dementia (FTD) is one of the major neurodegenerative diseases and the most common presenile dementia before age of 60 without any effective treatment. FTD is caused by progressive focal atrophy of the prefrontal and anterior temporal cortex, leading to changes in personality and social behaviors, loss of empathy and language production, and other cognitive impairments. FTD shares extensive genetic and pathological overlaps with the motor neuron disease amyotrophic lateral sclerosis (ALS). In particular, GGGGCC (G4C2) repeat expansion in the first intron of C9ORF72 is the most common genetic cause of both ALS and FTD. Both sense and antisense repeats-containing RNAs can be translated into different dipeptide repeat (DPR) proteins including poly(GR). We previously established a Drosophila model of C9ORF72-ALS/FTD in which poly(GR) is specially expressed only in neurons of adult flies, bypassing its toxic effects during neural development (Yuva-Aydemir et al., Nat. Commun. 2019). Using this model, we perform an RNA-seq analysis and identified a number of misregulated genes (Lee et al., Neuron 2023). In this talk, I will describe how one of the most downregulated genes affects poly(GR) neurotoxicity and its unexpected link to the molecular regulation of aging.

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A Pipeline For Single Molecule Imaging Of Endogenous Synaptic Proteins In Brain Tissue

Authors: Maxime Malivert1,2, Magali Mondin2, Chiara Galizia3, Bram A.A.J.W. Willems1, Dario Crippa1, Cécile Lemoigne3, Matthieu Sainlos3, Daniel Choquet2,3, Mathieu Ducros2, Angela M. Getz1,2,3

1 – Functional Genomics Department (FGA), Center for Neurogenomics and Cognitive Research (CNCR), Vrije Universiteit Amsterdam, The Netherlands. 2 – Bordeaux Imaging Center (BIC), CNRS UAR 3420, INSERM US 4, Université de Bordeaux, France. 3 – Interdisciplinary Institute for Neuroscience (IINS) CNRS UMR 5297, Université de Bordeaux, France. Presenter: Angela M. Getz (Assistant Professor, Group Leader, CNCR, Vrije Universiteit Amsterdam, NL)

Abstract:

The number and dynamic nanoscale organization of synaptic AMPA receptors defines synaptic transmission efficacy and is regulated by a variety of activity-dependent plasticity mechanisms. Visualizing these receptor trafficking and clustering processes at high-resolution – at the level of endogenous receptors in intact synaptic networks – is a key remaining challenge to understand how organizational diversity defines synapse-type-specific function, how this is remodelled during bona fide synaptic plasticity, and how these processes are disrupted in synaptopathies. A major technical hurdle has been the development of effective molecular labeling strategies and imaging technologies. We have recently reported a new molecular toolkit for high-resolution imaging of endogenous GluA2-containing AMPA receptors in integrated slice models. This is based on genetic knock-in of the biotin acceptor peptide tag, molecular strategies for target-specific biotin ligase expression, and small high-affinity imaging probes based on avidin family biotin binding proteins. Here, we have further engineered and optimized avidin-based imaging probes to develop superresolution imaging of endogenous AMPAR nanoscale organization and live diffusion-trapping processes. To achieve high-speed nanometric scale localization precision for imaging inside brain slices, we implemented single molecule localization microscopy (SMLM) techniques, including DNA-PAINT and single-particle tracking, with lattice light-sheet microscopy (LLSM). We developed an active image optimization (AIO) method and implemented adaptive optics (AO) with LLSM. Controlled PSF shaping with the deformable mirror of our AO-LLSM allows 3D reconstructions that capture the entire dendritic spine profile in a single acquisition. These advanced imaging techniques with improved spatiotemporal resolution will allow more precise exploration of the molecular mechanisms underlying synaptic diversity and plasticity in integrated networks.

Keywords:

AMPA Receptors, Advanced labeling techniques, Lattice light-sheet microscopy, Superresolution microscopy, Synapse diversity

How Altered Dendritic Spine Morphology Promotes Hyperexcitability in Focal Cortical Dysplasia

Jawon Gim[1], Na Young Seo[1], Gyu Hyun Kim[1], Kea Joo Lee[1] and Joon Ho Choi[2]

[1] Neural Circuits Research Group, Korea Brain Research Institute, Daegu, Republic of Korea; [2] Sensory and Motor System Research Group, Korea Brain Research Institute, Daegu, Republic of Korea

Focal cortical dysplasia (FCD) is a major cause of drug-resistant epilepsy in children and is characterized by pronounced structural and functional abnormalities in the cortex. Previous 3D volume electron microscopy (vEM) analysis revealed that neurons within the epileptogenic region exhibit marked alterations in microarchitecture compared with those in the control region, including reductions in spine density and changes in spine geometry. In this study, computational modeling was used to evaluate how dendritic spine alterations identified in vEM data contribute to hyperexcitability associated with epileptogenesis. The models incorporated EM-derived spine morphologies rather than idealized geometries, enabling a biologically realistic representation of spine-to-dendrite structure and avoiding oversimplified assumptions. By directly embedding morphological variability into the model, we were able to examine how specific structural deviations influence synaptic integration and excitability at the single-cell level. The results demonstrate that alterations in excitatory microstructure alone are sufficient to increase neuronal excitability, broadening current understanding of the cellular mechanisms underlying epilepsy development.

An Emergent Disease-associated Motor Neuron State Precedes Cell Death In A Mouse Model Of Als

Aaron D. Gitler

Stanford University

The spinal cord is a fascinating structure that is responsible for coordinating movement in vertebrates. Spinal motor neurons control muscle activity by transmitting signals from the spinal cord to diverse peripheral targets. In this study, we profiled 43,890 single-nucleus transcriptomes from the adult mouse spinal cord using fluorescence-activated nuclei sorting to enrich for motor neuron nuclei. We identified 16 sympathetic motor neuron clusters, which are distinguishable by spatial localization and expression of neuromodulatory signaling genes. We found surprising skeletal motor neuron heterogeneity in the adult spinal cord, including transcriptional differences that correlate with electrophysiologically and spatially distinct motor pools. We also provide evidence for a novel transcriptional subpopulation of skeletal motor neuron (γ*). Collectively, these data provide a single-cell transcriptional atlas (http://spinalcordatlas.org) for investigating the organizing molecular logic of adult motor neuron diversity, as well as the cellular and molecular basis of motor neuron function in health and disease. To uncover molecular determinants of motor neuron degeneration and selective vulnerability in amyotrophic lateral sclerosis (ALS), we generated longitudinal single-nucleus transcriptomes and chromatin accessibility profiles of spinal motor neurons from the SOD1-G93A ALS mouse model. Vulnerable alpha motor neurons showed thousands of molecular changes, marking a transition into a novel cell state we named ‘disease-associated motor neurons’ (DAMNs). We identified transcription factor regulatory networks that govern how healthy cells transition to become DAMNs as well as those linked to vulnerable and resistant motor neuron subtypes. Using spatial transcriptomics, we found reactive glia located near motor neurons early in disease, suggesting early signaling events between motor neurons and glia. Finally, we found that genomic regions in alpha motor neurons that were differentially accessible with disease in mice are enriched for single nucleotide polymorphisms associated with human ALS, providing evidence that the genetic underpinnings of motor neuron vulnerability are conserved.

Microglial Replacement In A Sandhoff Disease Mouse Model Reveals Myeloid-derived B-hexosaminidase Is Necessary For Neuronal Health

Kim Green, Ph.D.

Department of Neurobiology and Behavior, University of California, Irvine, USA

Lysosomal storage disorders (LSDs) are a large disease class involving lysosomal dysfunction, often resulting in neurodegeneration. Sandhoff disease (SD) is an LSD caused by a deficiency in the β subunit of the β-hexosaminidase enzyme (Hexb). Although Hexb expression in the brain is specific to microglia, SD primarily affects neurons leading to the question of why a microglial expressed gene and enzyme manifests in a primarily neuronal phenotype, leading to neurodegeneration and death.

To investigate how a microglial gene is involved in neuronal homeostasis, we show that β-hexosaminidase is secreted by microglia and integrated into the lysosomal compartment of neurons. To assess therapeutic relevance, we treat the Hexb-/- SD mouse model with bone marrow transplant and colony stimulating factor 1 receptor inhibition, which broadly replaces Hexb-/- microglia with Hexb-sufficient cells. Microglial replacement reverses apoptotic gene signatures, improves behavior, restores β-hexosaminidase enzymatic activity and Hexb expression, prevents substrate buildup, and normalizes neuronal lysosomal phenotypes, underscoring the critical role of myeloid-derived β-hexosaminidase in maintaining neuronal health and establishing microglial replacement as a potential LSD therapy.

These results show that microglia produce lysosomal enzymes which are secreted and taken up by neurons, and necessary for their lysosomal function. Disruptions in HEXB production result in substrate accumulation in neurons resulting in neurodegeneration and death, while providing HEXB sufficient myeloid cells prevents these phenotypes, underlining a critical function of microglia in the healthy brain – neuronal support through the supply of critical lysosomal enzymes.

Molecular Diversity Of Ampa Receptors In Synaptic Transmission

And Plasticity

Ingo H Greger,

Neurobiology Division, MRC LMB, Cambridge, CB2 0QH, UK

AMPA-type glutamate receptors (AMPARs) mediate the majority of fast excitatory neurotransmission throughout the brain, and chiefly contribute to synaptic plasticity mechanisms. AMPARs are uniquely diverse, they assemble into tetramers from four subunits (GluA1-4) in various combinations, and are further associated with an array of diverse auxiliary subunits. Auxiliary subunit type and stoichiometry varies greatly and shapes receptor trafficking, synaptic localisation, and channel gating. Amongst them transmembrane AMPA receptor regulatory proteins (TARPs) are the most diverse and widely distributed.

In this talk I will provide an overview of AMPAR-auxiliary subunit organisation based on cryo-EM structure and on functional analysis, I will discuss how receptor organisation impacts synaptic transmission and plasticity, and will present data on the structural organisation of native AMPAR complexes.

Transformation of a locally activated hippocampal code for space to a cortical contextual engram

Yasunori Hayashi

Graduate School of Medicine, Kyoto University, Kyoto, Japan

Abstraction of information that flows from lower-level mnemonic regions to higher-level cortical areas is critical for the formation of the generalized representations that comprise long-term memories. However, where and how this computation takes place remains elusive. Here, we demonstrate that the locally activated, discretized representation of space generated in the hippocampus during a spatial navigation task converges to give rise to a neuron representing contextual information in the anterior cingulate cortex (ACC), through activity during offline periods. The formation of this contextual representation requires repeated experience, which leads to a transition from multiple sparsely distributed receptive fields, to broad continuous spatial tuning, stabilizing in a time frame indicative of memory consolidation. These context-representing neurons preferentially express c-Fos, identifying them as functional members of a cortical memory engram. Critically, we find that hippocampal sharp-wave ripples (SWRs) during offline periods drive this process, providing the physiological bridge that converges discretized spatial codes into generalized representations. Our study demonstrates how memory engram cells represent the external world and how they emerge through the SWR-mediated convergence of lower-level hippocampal spatial information into higher-order cortical representations.

Morphological remodeling of cholinergic axon terminals in the neocortex of BMP4 cKO mice

Takahito Higashi[1], Horie Sawa[1], Akinori Y. Sato[2], Takeuchi F. Ryosuke[2], Fumitaka Osakada[2], Shigeo Okabe[3,4], Yasushi Kobayashi[1], Kiyomasa Nishii[1]

[1] National Defense Medical College, Tokorozawa, Japan
[2] Nagoya University, Nagoya, Japan
[3] The University of Tokyo, Tokyo, Japan
[4] Institute of Physical and Chemical Research (RIKEN), Wako, Japan

Cholinergic projections from the basal forebrain innervate extensively to the neocortex and elaborate local collateral branches to establish circuit connectivity. The basal forebrain–neocortex cholinergic neural circuit regulates higher brain functions, including plasticity, arousal, and attention. Its disruption contributes to cognitive decline. However, the mechanisms governing cholinergic axonal ramification remain unclear. Bone morphogenetic protein 4 (BMP4), a classically identified morphogen, also functions postnatally. Using cholinergic neuron-specific BMP4 conditional knockout (BMP4 cKO) mice, we previously found that BMP4 secreted by axons suppressed cholinergic axon ramification and bouton formation. Here, to determine how the genetic perturbation influences neocortical function, we analyzed the morphology of the cholinergic axonal terminals in these mice.

Coronal brain sections from BMP4 cKO and control (BMP4 fl/fl) mice were immunostained for vesicular acetylcholine transporters (VAChT) to visualize cholinergic terminals, and F-actin clusters were labeled with phalloidin conjugated to a fluorescent dye. High-resolution confocal imaging was performed to quantify the density and morphology of VAChT-positive terminals across the neocortex. BMP4 cKO mice exhibited altered terminal architecture with a marked increase in VAChT-positive terminal morphology. Cholinergic terminals in cKO mice showed a higher proportion of protrusive type and more complex morphologies. Furthermore, VAChT-positive terminals lacking contacts with F-actin clusters increased.

These findings suggest that axon-derived BMP4 acts as a local brake on the cholinergic bouton formation, constraining terminal growth and thereby contributing to proper maturation of cholinergic circuits. We are extending these structural analyses with electron microscopy and further establishing wide-field calcium imaging to assess consequences for neocortical network function. Our study will reveal mechanisms of BMP4 signaling in the basal forebrain-neocortex and the contribution of the cholinergic neural circuit to cortical physiology.

(1857/2300 words)

Title: Targeting Neuronal Maturation To Promote Axon Regeneration Following Spinal Cord Injury

Brett J. Hilton1, 2, 3

1: Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada

2: International Collaboration on Repair Discoveries, University of British Columbia, Vancouver, British Columbia, Canada

3: Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada

Abstract: Axons of neurons in the mature mammalian central nervous system (CNS) fail to regenerate following spinal cord injury, limiting functional recovery. Remarkably, newly born or immature neurons have an immense capacity for axon growth and regeneration. Thus, neurons lose the ability to regenerate their CNS axons as they mature. Our research efforts focus on understanding how neurons lose the ability to regenerate as they mature. We and others have discovered that a major factor governing regenerative ability is chromatin accessibility, which determines whether neurons can elicit the expression of genes required for axon outgrowth. Downstream of gene expression, intracellular processes such as Calcium-dependent vesicle release regulate axon growth. Targeting chromatin accessibility or these downstream intracellular processes can enable axon regeneration in the mature mammalian spinal cord.

Mechanisms Generating Cell-type Diversity

Simon Hippenmeyer1

1 Institute of Science and Technology Austria (ISTA, Klosterneuburg, Austria

The concerted production of the correct number and diversity of neurons and glia by neural stem cells is essential for intricate neural circuit assembly. In the developing cerebral cortex, radial glia progenitors (RGPs) are responsible for producing all neocortical neurons and certain glia lineages. Clonal analysis by exploiting the single cell resolution of the genetic MADM (Mosaic Analysis with Double Markers) technology revealed an inaugural quantitative framework of RGP behavior in the developing neocortex. However, the cellular and molecular mechanisms controlling RGP lineage progression and the emergence of cortical projection neuron diversity, remains unknown. To this end we use quantitative MADM-based experimental paradigms at single RGP resolution to define the cell-autonomous functions of candidate genes and signaling pathways controlling RGP-mediated neuron and glia genesis. Ultimately, our results shall translate into a deeper understanding of brain function and why human brain development is so sensitive to the disruption of particular signaling pathways in pathological neurodevelopmental and psychiatric disorders.

Disinhibitory circuit mechanisms of climbing fiber-instructed cerebellar learning

Sungho Hong[1], Changjoo Park[2,3], Zhen Y. Yang[4], Abedulraheem Nashef [4], Jawon Gim[3,5], Ke Zhang[6], Laurence Cathala[4], Kea Joo Lee[5], Jason M. Christie[4], and Jinseop S. Kim[2,3]

[1]Center for Memory and Glioscience, Institute for Basic Science, Daejeon, South Korea; [2]Department of Biological Sciences, Sungkyunkwan University, Suwon, South Korea; [3]Laboratory of Computational Neuroscience, [5]Neural Circuits Research Group, Korea Brain Research Institute, Daegu, South Korea; [4]Dept. of Physiology and Biophysics, University of Colorado, Aurora, USA; [6]Max Planck Florida Institute for Neuroscience, Jupiter, USA

The cerebellum is crucial for maintaining movement precision by adapting movement coordination to various demands arising from constantly changing environmental parameters. Recent studies have shown that cerebellum-dependent motor adaptation is not achieved by simple error correction but can be modulated in a context-dependent way, stemming from context-dependent plasticity in the cerebellar neural circuit. However, its circuit-level underpinnings remain poorly understood. We present our finding that the disinhibitory motif in the cerebellar connectome underlies the modulation of cerebellar neural plasticity, focusing on a connectome-constrained computational network model. By analyzing electron microscopy data of a cerebellar cortical sample, we discovered that the climbing fibers (CFs), the powerful inputs that trigger synaptic plasticity in the network output neurons, Purkinje cells (PCs), also target a specific interneuron subtype (MLI2) that inhibits PC-targeting interneurons (MLI1), creating serial disinhibition. Our computational model based on the connectome data, together with *in vivo* calcium imaging experiments, showed that MLI2s integrate multiple CFs, causing their increased activation and larger CF-evoked calcium responses in PCs with CF synchrony, the role of which has been debated for decades. Crucially, experiments demonstrated that disrupting disinhibition impairs CF-instructed motor learning. We will also discuss how this mechanism interplays with the parallel fiber inputs delivering sensorimotor information to all the neurons. Our work demonstrates the circuit-level mechanisms allowing the cerebellum to modulate plasticity and learning adaptively for optimal behavioral changes in a given context.

CaMKII Condensates Driven by Excitatory Stimulation Function as Synaptic Tags for Protein Accumulation

Tomohisa Hosokawa[1], and Yasunori Hayashi[1]

[1] Graduate School of Medicine, Kyoto University, Kyoto, Japan

The establishment of late-phase long-term potentiation (LTP) requires the specific accumulation of proteins at stimulated synapses, a phenomenon described by the "synaptic tagging and capture hypothesis." While the requirements for a synaptic tag—local formation, independence from protein synthesis, and the ability to capture diverse synaptic proteins—are well-defined, its molecular identity has remained elusive. In this study, we propose that condensates formed by CaMKII via liquid-liquid phase separation (LLPS) constitute the physical entity of the synaptic tag. It is known that the interaction interface (T-site) exposed on activated CaMKII drives LLPS. We hypothesized that this T-site functions as a binding platform for diverse synaptic proteins and performed a comprehensive search for a generic binding motif (CaMKII Binding Motif: CBM) using AlphaFold3-based structural prediction. Biochemical and cell biological analyses of identified candidate sequences revealed that many indeed bind to CaMKII via the T-site and drive LLPS both *in vitro* and in cells. This ability to form condensates exhibited a continuous spectrum dependent on GluN2B presence and binding affinity. In neurons, proteins containing a CBM translocated to and accumulated at synapses in an excitatory stimulation-dependent manner. Furthermore, while dominant-negative inhibition by CBM overexpression suppressed structural LTP, the formation of CaMKII condensates was sufficient to stabilize synaptic proteins, including AMPA receptors. These results demonstrate that CaMKII activated within stimulated synapses functions as a "synaptic tag" by capturing and stabilizing a wide variety of proteins via LLPS, thereby facilitating structural LTP and leading to synaptic potentiation.

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Circuit Mechanisms Of Item Memory And Its Disruption In Alzheimer's disease

Kei M Igarashi

Chancellor's Fellow Associate Professor, Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine, www.igarashilab.org

Memory has multiple components: "what" memory (item/object), "when" memory (time) and "where" memory (space). Research in the past decades revealed neurons involved in spatial memory, including place cells in the hippocampus and grid cells in the medial entorhinal cortex (MEC). However, circuit mechanisms of memory about item and time remain largely unclear. Our lab focuses on identifying neural circuits for item memory, and how these circuits become impaired in the disease of memory – Alzheimer's disease. We previously reported the encoding of item-outcome associative memory in the lateral entorhinal cortex (LEC) (Igarashi et al., Nature, 2014), and this encoding is controlled by dopamine signals from the ventral tegmental area (Lee et al., Nature, 2021). We recently found that neuronal populations of both the LEC (layer 5/6) and their major target, the medial prefrontal cortex, formed an internal map of pre-learned and novel items, classified into dichotomic rewarded vs. punished groups (Jun et al., Nature 2024). The formation of this internal map was mutually dependent. Our result suggests that the LEC and mPFC encodes a cognitive map of item-outcome rules.

In the second part of the talk, I will share our recent finding of dysfunctional dopamine in the LEC of Alzheimer's disease mouse models (Nakagawa et al., bioRxiv 2024), which further suggests the critical role of dopamine in Alzheimer's disease.

Seedb-live: Minimally Invasive Optical Clearing Media For Live Imaging Of The Brain

Takeshi Imai

Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Tissue clearing has been widely used for fluorescence imaging of fixed tissues, but not for live tissues due to its toxicity. Here we develop minimally invasive optical clearing media for fluorescence imaging of live mammalian tissues. Light scattering is minimized by adding spherical polymers with low osmolarity to the extracellular medium. A clearing medium containing bovine serum albumin (SeeDB-Live) is minimally invasive to live cells, allowing for structural and functional imaging of live tissues, such as spheroids, organoids, acute brain slices, and the mouse brain in vivo. SeeDB-Live minimally affects the electrophysiological properties and sensory responses of neurons. SeeDB-Live facilitates fluorescence imaging of deep cortical layers in live animals without noticeable toxicity to neurons and animal behavior. We also demonstrate its utility for epifluorescence voltage imaging in acute brain slices and in live animals in vivo. Thus, SeeDB-Live expands the scale and modalities of fluorescence imaging of live mammalian tissues.

Dissection of Neural Circuit Mechanisms Underlying Selective Vagal Reflexes

Seiichi Homma[1], Austin Seroka[2], Cecilia Moens[2], Takuya Kaneko[1]

[1]Nagoya University, Nagoya, Japan;
[2]Fred Hutchinson Cancer Center, Seattle, USA

A major mediator of brain–body communication is the vagus nerve. The vagus nerve comprises bundles of sensory and motor axons that connect the brain with a wide range of internal body parts, including the pharynx, larynx, and most visceral organs. Vagal sensory neurons convey sensory information from the body to the brain, whereas vagal motor neurons reflexively transmit motor commands back to the body to elicit essential responses such as gagging, coughing, and peristalsis. Within the brainstem, both vagal sensory and motor neurons are organized in a coarse topographic map, in which neurons innervating different peripheral parts are spatially intermingled. How precise reflexive body control is achieved despite this coarse organization remains largely unclear.

In our previous study using zebrafish, we found that vagus-mediated reflexes gradually mature during postembryonic development (Kaneko et al., 2024). In larvae at 10 days post fertilization (dpf), noxious stimulation of the pharynx reflexively induces gagging-like pharyngeal contraction by selectively activating pharynx-innervating vagal motor neurons without activating unrelated motor neurons in the vicinity. In contrast, in younger larvae at 4 dpf—shortly after hatching—the same local stimulation activates not only pharynx-contracting motor neurons but also other intermingled motor neurons in a nonspecific manner. This developmental maturation suggests experience-dependent refinement of synaptic connectivity within the vagal reflex circuit.

To elucidate the anatomical basis of this refinement, we recently identified a molecularly distinct population of interneurons in the nucleus of the solitary tract (NTS) that directly relay sensory inputs to vagal motor neurons. These *vagal reflex interneurons* (VRIs) contact both vagal sensory axons and vagal motor dendrites, constituting a three-neuron reflex circuit (sensory–interneuron–motor). VRIs are robustly activated by noxious stimulation of the pharynx, supporting their role as a core component of the gagging-like pharyngeal reflex. To test whether experience refines VRI synaptic connectivity for the independent control of the pharynx, we are developing a method that reveals the long-term history of synaptic partner changes from a single snapshot observation.

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Synchrony drives Hebbian circuit assembly: Causal mechanisms in the developing visual cortex

Tetsuhiko Kashima[1,2], Takashi Yoshida[2,3,4], Kenichi Ohki[2,3,4], and Yuji Ikegaya[1,2]

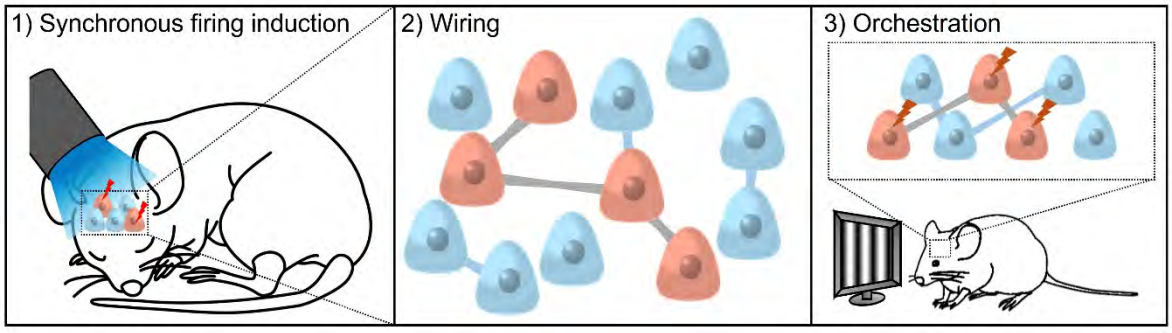
[1] Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan
[2] Institute for AI and Beyond, University of Tokyo, Tokyo, Japan
[3] Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[4] WPI-IRCN, University of Tokyo, Tokyo, Japan

The precise assembly of cortical microcircuits is fundamental to sensory processing and cognitive function. The Hebbian postulate—"cells that fire together, wire together"—is a central tenet of neuroscience, yet direct *in vivo* evidence demonstrating that synchronous firing causally instructs specific synaptic connectivity remains scarce. Specifically, it is unclear whether temporal synchrony itself, distinct from average firing rates, drives wiring in the intact spike timing and assesses the consequent circuit organization.

We performed in utero electroporation to express Channelrhodopsin-2 (ChR2) in layer 2/3 pyramidal neurons, combining this with chronic, non-invasive optogenetics. Synchronous firing was induced for one hour daily during a critical developmental window (postnatal days 9–13). Sextuple whole-cell patch-clamp recordings at three weeks of age revealed that the probability of monosynaptic excitatory connections was significantly enhanced among synchronized ChR2-positive neurons compared to non-stimulated controls or ChR2-negative neighbors.

Crucially, asynchronously elevating firing rates via chemogenetics (DREADDs) failed to recapitulate this hyper-connectivity, demonstrating that temporal coherence—rather than activity level per se—is the instructive signal for microcircuit wiring. This structural reorganization was abolished by NMDA receptor blockade, confirming reliance on LTP-like mechanisms.

Functionally, *in vivo* two-photon calcium imaging showed that these artificially wired ensembles exhibited matched orientation selectivity. We are currently analyzing spontaneous activity dynamics; preliminary data suggest that these synchronized ensembles exhibit preferential reactivation during rest, implying the establishment of stable attractor-like dynamics. Collectively, our findings provide direct experimental evidence that NMDAR-dependent synchronous activity during development causally instructs the structural and functional organization of cortical networks.



Endogenous tau aggregation suppresses neuronal activity, with early alterations in mitochondrial transport

Naoki Kato[1], Tomoya Uchida[1], Keita Matsumoto[2], Maika Itsuno[2], Masami Masuda-Suzukake[3], Masato Hasegawa[3], Hideyuki Okano[4], Hiroko Bannai[1], Sumihiro Maeda[2]

[1] Department of Electrical Engineering and Bioscience, Graduate School of Advanced Science and Engineering, Waseda University, Tokyo, Japan;
[2] Department of Physiology, School of Medicine, Keio University, Tokyo, Japan;
[3] Dementia Research Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan;
[4] Keio Regenerative Medicine Research Center, Kanagawa, Japan

Tau aggregation is a central pathological feature of Alzheimer's disease and other neurodegenerative diseases collectively known as tauopathies. In these diseases, tau accumulates abnormally within neurons and is thought to drive neuronal dysfunction long before extensive neuronal death occurs. Because neuronal activity is essential for synaptic communication and circuit stability, understanding how tau aggregation affects neuronal activity is an essential question.

Previous studies have reported inconsistent effects of tau pathology on neuronal activity, with evidence for both hyperactivity and hypoactivity. These discrepancies suggest that the relationship between tau aggregation and neuronal activity remains incompletely defined, possibly reflecting differences in cellular context, such as neuronal subtype or brain region. Consequently, how neuronal activity is affected under conditions of endogenous tau aggregation in human neurons remains unclear.

Here, we examined the effects of endogenous tau aggregation on neuronal activity and functions in human iPSC-derived excitatory neurons. We found that mitochondrial transport dynamics were altered at an early stage following tau seeding, prior to the formation of detectable fibrillar tau inclusions. These early changes occurred in the absence of detectable alterations in neuronal activity. At later stages, neurons containing mature tau aggregates exhibited a significant reduction in spontaneous neuronal activity measured by Ca^{2+} imaging. Furthermore, Ca^{2+} responses to NMDA receptor stimulation were markedly attenuated, consistent with reduced surface expression and/or functional impairment of NMDA receptors. Along with these functional deficits, Fyn kinase, which normally stabilizes NMDA receptors at dendritic spines, was mislocalized and accumulated around tau aggregates in the cell body. This redistribution likely interferes with NMDA receptor stabilization at the plasma membrane, thereby reducing the surface availability of the receptors and impairing glutamatergic signaling.

Together, these results indicate that endogenous tau aggregation in human neurons is associated with early alterations in mitochondrial transport and later suppression of neuronal activity. This study provides a human neuron–based framework for linking tau pathology to fundamental changes in neuronal activity and intracellular dynamics.

Representations of stimulus features in the ventral hippocampus

Mazen Kheirbek[1]

[1] University of California, San Francisco, San Francisco, USA

Discriminating and categorizing the meaning of environmental stimuli and responding accordingly are essential for survival. The ventral hippocampus (vHPC) controls emotional and motivated behaviors in response to environmental cues and is hypothesized to do so in part by deciphering the positive or negative quality of these cues. Yet, what features of the environment are represented in the activity patterns of ventral CA1 (vCA1) neurons and whether the positive or negative meaning of stimuli is present at this stage remain unclear. Here, using two-photon calcium imaging across six experimental paradigms, we examined which features of salient stimuli are represented by vCA1 ensembles and found that identity, sensory features, and intensity, but not valence, are robustly encoded. These results offer a reappraisal of the vCA1 function, wherein information corresponding to individual stimulus features, and not their meaning, predominates. This organizational scheme may support flexible updating of stimulus value as internal states and environmental demands change.

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Synaptoporin is required for structural integrity and functional plasticity of hippocampal mossy fiber synapses

Gyu Hyun Kim [1], Na-young Seo [1], Hyeyeon Kim [2], hyungju park [2], and Kea Joo Lee [1]

[1] Neural Circuits Group, Korea Brain Research Institute (KBRI), Deagu 14062, Republic of Korea;
[2] Neurovascular Group, Korea Brain Research Institute (KBRI), Deagu 14062, Republic of Korea

Synaptoporin (Synpr), a synaptic vesicle protein and member of the synaptophysin (Syp) family, is highly expressed in mossy fiber (MF) terminals of dentate gyrus (DG) granule cells. Despite its distinct localization, the functional role of Synpr in regulating MF synaptic structure and plasticity remains unclear. To address this, we generated Rbp4-Cre;Synpr$^{fl/fl}$ mice, enabling DG-specific Synpr deletion through Cre-dependent recombination. Confocal imaging of GFP-labeled MF boutons revealed no significant difference in bouton volume between control and Rbp4-Cre;Synpr$^{fl/fl}$ mice. However, correlative light and electron microscopy (CLEM) analysis uncovered ultrastructural alterations in Synpr-deficient MF boutons These included disrupted synaptic vesicle organization, fragmented lamellate structures, and reduced integration of postsynaptic thorny excrescences (TEs) into the bouton core. These findings indicate a loss of presynaptic integrity. To assess functional consequences of Synpr loss, we performed field excitatory postsynaptic potential (fEPSP) recordings in the CA3 region following high-frequency stimulation of the MF pathway. Synpr-deficient mice exhibit a significantly attenuated long-term potentiation (LTP) response compared to controls, suggesting impaired synaptic plasticity. Together, our results demonstrate that Synpr is essential for maintaining both the structural complexity and functional plasticity of hippocampal MF-CA3 synapses. These findings provide novel insights into the molecular mechanisms underlying MF synapse architecture, emphasizing Synpr's essential function in synaptic organization within the DG-CA3 circuit.

Central Amygdala Circuits Controlling Biting, Feeding, And Drinking

Rüdiger Klein

Max-Planck Institute for biological Intelligence, Martinsried, Germany

The central amygdala (CeA) is a brain hub for emotion and motivation that rapidly integrates salient environmental and internal stimuli to generate appropriate behavioral responses. While traditionally thought to be linked solely to defensive behavior, emerging evidence suggests that specific CeA neuronal populations play key roles in reward and consummatory behaviors, such as feeding and drinking. Since food and water are intrinsically rewarding, appetitive CeA neurons are positive valence neurons and the animals seek to promote the activation of these neurons. In vivo recordings have shown that appetitive CeA neurons respond to appetitive environmental stimuli, and to internal signals, such as the hunger hormone ghrelin. The CeA consists of genetically-defined GABAergic neuron subpopulations distributed over three anatomical subregions, capsular (CeC), lateral (CeL), and medial (CeM). Using intersectional genetics, we found that neurons driving food or water consumption are confined to the CeM. Separate CeM subpopulations exist for water only versus water or food consumption. Our results suggest that distinct CeM microcircuits evaluate liquid and solid appetitive stimuli to drive the appropriate behavioral responses.

Recently, we identified a subpopulation of neurons in the CeA expressing the transcription factor Isl1 (CeA^{Isl1}) that plays a crucial role in modulating biting behavior. In vivo calcium imaging revealed that CeA^{Isl1} neurons are robustly activated at the onset of biting across materials of varying physical properties, with distinct neuronal ensembles selectively encoding responses to the physical properties of the objects. CeA^{Isl1} neuronal activity scales positively with the hardness of the object, suggesting a role in force modulation. Optogenetic activation of CeA^{Isl1} neurons enhances biting behavior toward edible or non-edible objects, induces fictive feeding in the absence of physical targets and exerts a reinforcing effect on behavior, whereas inhibition of CeA^{Isl1} neurons impaired efficient biting of solid food by reducing jaw-closing muscle activity. These findings uncover a previously unrecognized sensorimotor function of the central amygdala in calibrating bite force and precision, linking motivational states to skilled motor output.

Converging Perisynaptic Astrocytic Processes Onto Active Dendrites after Motor Learning

Yoshiyuki Kubota

National Institute for Physiological Sciences, Okazaki, Japan;

Astrocytes play a key role in regulating synaptic transmission as part of the tripartite synapse. Each astrocyte typically occupies a distinct, non-overlapping domain. However, the plasticity of these domains—especially during learning-related synaptic remodeling—remains largely unknown. I will discuss our recent finding that after motor learning, perisynaptic astrocytic processes (PAPs) from multiple astrocytes converge onto the same short dendritic segment (<40 μm) of the apical tuft of a layer 5 pyramidal neuron in the mouse primary motor cortex.

Using two-photon imaging in Thy1-GFP mice trained for 8 days on a forelimb seed-reaching task, we first identified dendritic segments that exhibited high spine turnover (Sohn et al., Science Advances, 2022). Correlative light and electron microscopy (CLEM) using large-scale volume EM (vEM) data collected from these mice with automated tape-collecting ultramicrotome (ATUM) and scanning electron microscopy (SEM) revealed that these active dendritic segments were contacted by PAPs originating from 3–6 distinct astrocytes. Notably, these astrocytic processes extended directly and specifically toward each active dendritic segment. Despite the convergence of processes from multiple astrocytes at the level of dendritic segment, individual dendritic spines were typically contacted by PAPs from only a single astrocyte, indicating highly organized astrocyte-synapse interactions.

Our findings suggest the possibility that astrocytic processes dynamically reorganize in response to experience, contributing to synapse-specific modulation during motor learning.

In addition, I will briefly report our recent progress in developing EM image alignment method using image processing tool, FEABS (Finite-Element Assisted Brain Assembly System; https://github.com/YuelongWu/feabas) and an automated dense segmentation pipeline for large-scale EM datasets.

Reference:

Sohn J, Suzuki M, Youssef M, Hatada S, Larkum ME, Kawaguchi Y, Kubota Y (2022)

Presynaptic supervision of cortical spine dynamics in motor learning. Science Advances 8:eabm0531.

Boundary-induced Confinement By A Liquid-like Interface Drives The Spatiotemporal Clustering Of A-synuclein At The Presynapse

Kye Kudo1, Shanley F. Longfield1, Tarosi Senapati2, Nils Schoovaerts3, Patrik Verstreken3, Adekunle Bademosi1, Sean Millard2, Frédéric A. Meunier1,2*

1 Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, Australia;

2 School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, Australia;

3 VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium

Cytosolic proteins typically undergo rapid, stochastic diffusion within the cytoplasm due to thermal motion and agitation from active cellular processes, promoting the homogenous dispersal of particles in the cytoplasm. Despite this, the organization of cytosolic proteins is often highly coordinated, and their spatiotemporal clustering is critical for many cellular functions. This holds especially true at the presynaptic nerve terminal – a structure that is physically continuous with the rest of the axonal cytoplasm – where highly specialized proteins are enriched to mediate synaptic communication. Through computational simulation of the presynapse, we demonstrate that distinct biophysical mechanisms have the power to locally enrich cytosolic presynaptic proteins. Using in vivo single-molecule localization microscopy (SMLM), we first identify that synaptic vesicles (SVs) are highly mobile yet retained at the presynapse through boundary-induced confinement at a liquid-like interface. Using an RNAi screen in D. melanogaster, we identify that this SV clustering is orchestrated by a molecular network far more extensive than previously recognized. Through in vivo SMLM we find that α-Synuclein, a small cytosolic molecule, is highly mobile at the presynapse yet confined at the liquid-like boundary defined by the SV cluster. The confinement of α-synuclein at the presynapse is dramatically impaired by 1,6-hexanediol, which disrupts weak hydrophobic interactions often involved in biomolecular condensates. Missense mutations associated with familial Parkinson's Disease (PD) influence the α-synuclein clustering propensity, mobility, and 1,6-hexanediol sensitivity at the presynaptic nerve terminal. Boundary-induced confinement at a liquid-like interface drives the spatiotemporal clustering of α-Synuclein within the presynaptic vesicle cluster.

CaMKII Activation Drives Phase Separation with AMPA Receptor Regulatory Protein Shisa

Ken Kunugitani[1], Tomohisa Hosokawa[1] and Yasunori Hayashi[1]

[1] Graduate School of Medicine, Kyoto University, Kyoto, Japan

The postsynaptic density (PSD) of neurons is a highly organized assembly of postsynaptic proteins such as neurotransmitter receptors, scaffolds, and signaling molecules. This complex plays a crucial role in memory formation through its dynamic reconstruction by learning stimuli. Previously we reported that the activation of Ca2+/calmodulin-dependent protein kinase II (CaMKII), a key molecule in synaptic long-term potentiation, drives liquid-liquid phase separation (LLPS) to mediate the activity-dependent reorganization and accumulation of synaptic proteins. However, there is still a gap between CaMKII dependent protein accumulation and synaptic potentiation.

Here we conducted a comprehensive in silico analysis of the human proteome and identified potential CaMKII-binding proteins using AlphaFold3-based interface prediction. To validate these interactions, we measured binding affinities by isothermal titration calorimetry, determined structural bases by co-crystallization analysis, and evaluated incorporation into CaMKII condensates by microscopy-observation. As a result, we identified multiple CaMKII interactors involved in diverse cellular functions such as synaptic transmission, synaptogenesis, and actin regulation.

Among these newly identified candidates, we are currently focusing on Shisa, which showed a particularly strong interaction with CaMKII. Shisa is known as a membrane protein involved in the localization of AMPA receptor, a major regulator of synaptic potentiation. In this presentation, we will introduce our latest findings on CaMKII–Shisa interaction and discuss its potential role in the molecular regulation of synaptic function.

Postsynaptic Receptor Turnover On Psd Protein Condensates Revealed By Single-molecule Imaging

Akihiro Kusumi

Okinawa Institute of Science and Technology Graduate University (OIST), Okinawa, Japan

The residency time and turnover rate of neuronal receptors in the synapse is finely tuned to sustain basic synaptic activity and to enable activity-dependent synaptic plasticity, fundamental to learning and memory. However, the reported residency times (or turnover rates) of receptors in synapses remain inconsistent.

We addressed this issue for AMPA-type glutamate receptors (AMPARs) using single-molecule imaging. The distribution of AMPAR dwell lifetimes ranged broadly from 3 to 3,000 s and could be resolved into three distinct components, approximately 10-s, 100-s, and 1,000-s components, based on the locations of their distribution peaks near the decimals. The 1,000-s residency component appeared only when both GluA2 molecules in an AMPAR were bound by as-yet unidentified PDZ-domain-containing proteins located in the postsynaptic density (PSD). In contrast, Stargazin exhibited no such long-lived 1,000-s component. Both AMPARs and Stargazin displayed the 10-sec and 100-sec components, suggesting that these AMPAR components are induced by Stargazin's binding to both AMPARs and PSD95 in the PSD. These findings indicate that these transmembrane proteins and PDZ-domain proteins laterally diffuse in/on the PSD to encounter one another, and then become anchored/immobilized in the PSD upon forming complexes. Thus, the PSD exhibits two apparently contradictory properties of liquidity and immobilizing capacity.

How does the PSD achieve these dual properties? First, we found that the cytoplasmic PSD protein SynGAP is capable of forming micron-scale phase-separated liquid-hydrogel condensates through coiled-coil-mediated trimerization of its intrinsically disordered region, both in vitro (≥2 μM with 1% PEG) and in fibroblastic L cells (≥0.3 μM), concentrations far below those estimated in spine heads (≈10 μM). Second, in L cells, SynGAP assembles into nanoscale clusters containing a median of ≈13 SynGAP molecules at much lower concentrations of >10 nM. In the initial phase of synapse formation when synaptic protein concentrations are low, such SynGAP nanoclusters may form on the cytoplasmic face of dendritic or synaptic membranes before other synaptic proteins assemble and may represent nucleation sites for nascent synapses, analogous to the nanoscopic "protein islands" of focal adhesions.

SynGAP condensates recruit PSD95 as a client via the binding of the PSD95's PDZ domains to the C-terminal PDZ-binding motif of SynGAP, rather than by co-condensation. In L cells and in vitro, PSD95 alone failed to form condensates at 5 μM.

Collectively, these results suggest that the liquidity of the PSD, essential for receptor recruitment, is provided by the liquid nature of SynGAP condensates. Furthermore, since we found that receptor oligomerization enhances their anchorage on SynGAP condensates, we propose that the immobilizing capacity of SynGAP condensates arises from local reinforcement of specific molecular interactions within SynGAP condensates, conferring hydrogel-like structural stability.

Synaptic Ultrastructural Alterations In Human Focal Cortical Dysplasia: Insights From Volume Electron Microscopy

Gyu Hyun Kim1,4, Na-young Seo1,4, Yang Hoon Huh2, Ji Yeoun Lee3, Kea Joo Lee1

1Neural Circuits Group, Korea Brain Research Institute, Daegu, South Korea

2Center for Electron Microscopy Research, Korea Basic Science Institute, Cheongju, South Korea

3Pediatric Neurosurgery, Seoul National University Children's Hospital, Seoul, South Korea

4These authors contributed equally to this work.

Focal cortical dysplasia (FCD) is a developmental disorder of the cerebral cortex and a leading cause of drug-resistant epilepsy in children and young adults. A disrupted excitation-inhibition balance is a hallmark of neuronal hyperexcitability in FCD, yet the underlying synaptic ultrastructural alterations remain poorly understood. Using volume electron microscopy, we performed a detailed morphological assessment of synaptic density, size, and organelle distribution within synapses in the temporal cortical layer III of an FCD patient. Notably, the dysplastic region displayed a lower density of excitatory (asymmetric) synapses but contained extra-large excitatory synapses, which contained an increased number of synaptic vesicles. Additionally, inhibitory synapses were located further away from the nearest excitatory synapses along distal dendrites, possibly weakening the effectiveness of inhibition in the dysplastic area. There was an increase in mitochondrial density and altered mitochondrial morphology within presynaptic boutons, along with a decreased proportion of postsynaptic protrusions containing a spine apparatus. These changes suggest potential deficits in intracellular calcium handling, metabolic homeostasis, and synaptic plasticity in the epileptogenic area. Moreover, maladaptive myelination was a prominent feature in the dysplastic region. These findings collectively indicate that synaptic architectural modifications may contribute to the neuronal hyperexcitability associated with epilepsy in FCD.

Keyword: Cortex, Epilepsy, Synapse, Mitochondria, Hyperexcitability

The Axonal Cytoskeleton Down To The Nanoscale

Christophe Leterrier 1

(1) Institute for Neurophysiopathology, NeuroCyto lab, CNRS-Aix Marseille University, Marseille, France

christophe.leterrier@univ-amu.fr

The intricate arborization and molecular identity of axons is maintained for decades, but must also continuously adapt to changes in the environment and modulate the activity of neurons. Axons fulfill these paradoxical demands thanks to a unique cytoskeletal organization that ensures the coordinated transport, anchoring and assembly of axonal components. In our lab, we use super-resolution microscopy to delineate and map the nanoscale architecture of cytoskeletal structures within the axon: the periodic actin/spectrin submembrane scaffold, presynaptic actin assemblies, clathrin-coated pits, microtubule bundles. We are exploring their molecular organization and functions by combining versatile labeling approaches, correlative live-cell/super-resolution/electron microscopy and quantitative analysis that allow for high-content, nanoscale interrogation of the axonal architecture.

MicroRNA Mechanisms of Plasticity

Marwan Ghanem[1], Prakruti Nanda[2], Gerhard Schratt[2], Giordano Lippi[1]

[1] Dorris Neuroscience Center (DNC), Scripps Research, San Diego, USA
[2] ETH, Zurich, Switzerland

Distinct memory types engage specialized neural circuits with different protein synthesis demands during encoding. Hippocampal circuits require rapid dendritic translation for spatial memory consolidation, while amygdala circuits rely on presynaptic modulation for cued associations. MicroRNAs regulate synaptic protein synthesis and memory formation, yet existing tools to induce microRNA loss-of-function have very slow onset (weeks) and cause long-lasting, irreversible changes that mask short-term mechanisms. To understand when microRNAs act and in which neuronal populations, we need tools with high spatiotemporal resolution.

To address this gap, we engineered DD-T6B, an inducible and reversible peptide enabling microRNA loss-of-function with hour-scale temporal resolution. DD-T6B stabilizes within 1–3 hours in the cortex and 3–6 hours in the hippocampus. Cell-type-specific manipulations reveal that microRNA loss-of-function in CaMKIIα-expressing excitatory neurons during training impairs contextual fear memory recall, whereas identical manipulations in Dlx-expressing inhibitory neurons during cued fear conditioning have no effect. Thus, circuit-specific microRNA requirements reflect the distinct cellular mechanisms underlying different memory types.

We are currently investigating region-specific microRNA loss-of-function in regions implicated in either contextual or cued fear conditioning such as the amygdala or the hippocampus, respectively. We aim to determine whether microRNA requirements correlate with translation capacity across neuronal subtypes by functionally mapping microRNA target interactions during memory formation in the identified regions.

Roles for Endocannabinoids and the Impact of Exogenous Cannabinoids on the Developing Brain

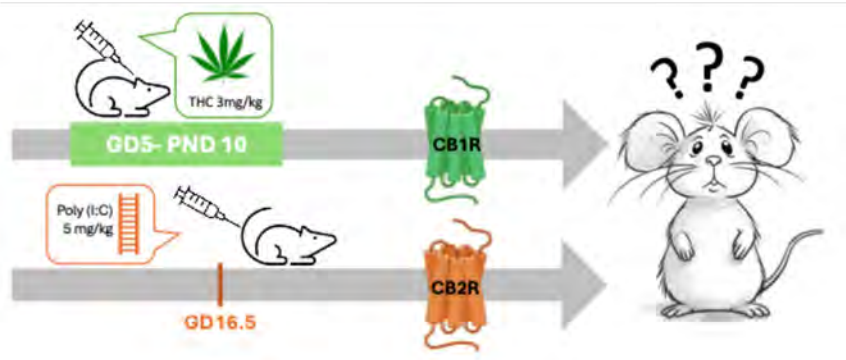
Han-Ting (Maggie) Chen[1], Hui-Chen Lu[1,2] and Ken Mackie[1,2]

[1] Gill Institute for Neuroscience, Bloomington, IN 47405;
[2] Department of Psychological and Brain Sciences, Bloomington, IN 47405

More than 250,000 infants exposed to cannabis are borne in the US each year. This exposure (perinatal cannabis exposure, PCE) is associated with adverse birth outcomes and increased risk for impaired executive function, psychosis, and depression later in life. The many children affected by prenatal cannabis exposure has stimulated clinical and preclinical research aimed at understanding cannabis's impact on the developing brain. These studies have led to an understanding of the role of the endocannabinoid system (ECS, comprised of endocannabinoids (eCBs), cannabinoid receptors and the enzymes that synthesize and degrade eCBs) in normal CNS development. In turn, this understanding highlights how THC from cannabis may detrimentally impact brain development by interfering with the ECS. A common theme emerging from our research and that from other labs is that PCE with THC (THC-PCE) leads to a hypoactive ECS in adults.

In this talk I will briefly summarize how THC from cannabis impacts the developing CNS and the role of CB1 receptors in mediating these effects. Next, I will show how another cannabinoid receptor, the CB2 receptor, is required for the adverse neurodevelopmental effects of polyI:C-induced maternal immune activation. I will then expand on our hypothesis that PCE leads to a hypoactive endocannabinoid system, finishing with recent results that found that increasing ECS activity reverses several of the behavioral deficits caused by THC-PCE.

Graphical Abstract:



Pharmacological Characterization Of Jnj-78911118, A Novel, Centrally-penetrant, Selective Glun2a Antagonist

Michael P. Maher, PhD

Johnson & Johnson Innovative Medicine

Abstract:

NMDA receptor antagonism produces rapid symptom improvement in treatment resistant depression; however, associated side-effects necessitates medical oversight during administration. We hypothesize that selective GluN2A antagonism may provide similar efficacy with an improved side effect profile. Here, we report the discovery of JNJ-78911118, a brain-penetrant, GluN2A selective antagonist. JNJ-78911118 pharmacology and MOA was characterized in vitro using fluorescence, voltage clamp, and radioligand binding assays. Target engagement was measured using ex vivo receptor autoradiography, and effects on rat prefrontal cortex (PFC) monoamine levels were measured using microdialysis. Synaptogenesis assays and patch clamp studies were used to demonstrate effects on synaptic plasticity. Cardiovascular safety and neurotoxicity were assessed in rats. We find that JNJ-78911118 is a potent and selective GluN2A antagonist that recapitulates the effect of known rapidly acting anti-depressants (RAADs) on neurotransmitter levels and synaptic plasticity. This molecule is a powerful in vivo tool that will enhance understanding of GluN2A biology.

Hierarchical processing and polarization encoding in the cephalopod visual system

Tomoyuki Mano[1], Konstantinos Tsaridis[1], Yutaka Kojima[1], Giovanni D. Masucci[1], Thi Thu Van Dinh[1], Rudi Tong[1], Vasileios Glykos[1], Lada Dolezalova[1], Keishu Asada[1], Daria Shumkova[1], Loranzie S. Rogers[2], Maxime Hamon[1], Matteo Santon[3,4], Makoto Hiroi[1], Teresa L. Iglesias[1], Nicholas W. Bellono[2], Martin J. How[3], Yukiko Goda[1], Leenoy Meshulam[5], Sam Reiter[1]

[1] Okinawa Institute of Science and Technology, Onna, Japan; [2] Harvard University, Cambridge, USA; [3] University of Bristol, Bristol, UK; [4] University of Padova, Padova, Italy; [5] Brown University, Providence, USA

Vertebrates and cephalopods have independently developed camera-type eyes — a striking example of convergent evolution. While many vertebrates detect color, cephalopods have instead evolved retinas that detect light polarization. Polarization vision is thought to confer ecological benefits in underwater environments, such as enhanced object detection and intraspecies communication. The cephalopod visual center, the optic lobe (OL), exhibits a distinctive structure with two principal divisions: the cortex, which bears morphological similarity to the vertebrate retina, and the medulla, which has a characteristic tree-like anatomical organization. However, the mechanisms by which the OL integrates luminance and polarization signals to support cephalopod behavior remain elusive, largely because *in vivo* neural recordings have been challenging to implement in these soft-bodied animals.

Here, we developed a novel head-fixation method to perform two-photon *in vivo* calcium imaging in the brain of awake juvenile squids (*S. lessoniana*). We recorded calcium responses from populations of OL cortex neurons while delivering visual stimuli that varied in intensity and polarization. Our data revealed distinct neuronal classes defined by spatiotemporal tuning and intensity–polarization specificity. These included (i) neurons selective for a single polarization orientation, (ii) additive integrators, and (iii) subtractive integrators of orthogonal polarization orientations. We also observed orientation- and direction-selective neurons in the inner granule layer, but rarely in the outer granule layer, suggesting a feed-forward architecture for progressively complex feature extraction.

We then performed *in vivo* electrophysiological recordings using Neuropixels probes, targeting downstream regions of the OL cortex including the medulla and peduncle lobe. We found that receptive field sizes increased with OL depth, a hallmark of hierarchical visual processing. Medulla neurons often displayed additive integration of intensity and polarization contrasts, while others showed strongly nonlinear selectivity. Anatomical experiments, including single-neuron dye filling and brain-wide retrograde tracing, further supported a model of hierarchical visual information processing through the medulla's tree-like organization. Collectively, our study provides the first *in vivo* physiological characterization of the cephalopod visual system, offering new insights into the neural mechanisms underlying their specialized underwater vision as well as broader features of convergent evolution in visual systems.

Neuronal and circuit architecture of the mouse insular cortex underlying its diverse functions

Bart C. Jongbloets[1,2*], Yang Chen[1*], Ian K. Gingerich[1,3], Michael A. Muniak[1], Kayla A. Maanum[1], and Tianyi Mao[1]

[1]Vollum Institute, Oregon Health & Science University, Portland, Oregon, 97239;
[2]Current address: Department of Cellular and Computational Neuroscience, Swammerdam Institute for Life Sciences, Amsterdam Neuroscience, University of Amsterdam, Amsterdam, The Netherlands;
[3]Current address: Geisel School of Medicine, Dartmouth College, Hanover, New Hampshire, 03755

My laboratory is interested in elucidating the structure-function relationship of brain circuitry underlying sensori-motor integration and understanding how these circuits are changed and modulated by disease, brain state and behavioral context. We use cutting-edge technology including modern anatomy, imaging, computation, genetics, functional circuit mapping in the mouse model to examine the principles governing neuronal connectivity and their regulation. In parallel, my laboratory also develops and implement novel imaging tools and computational algorithms for monitoring and manipulation of these circuits.

In this summit, I will present our unpublished work utilizing the whole brain imaging-based mesoscopic connectome to understand how long-range inputs and diverse cell types are integrated in the insular cortex to process interoception information. The insular cortex integrates both interoceptive and exteroceptive information to mediate bodily homeostasis, emotion, learning, and potentially consciousness. However, the cellular and circuit substrates governing the insula are poorly understood compared to primary cortices. Recently, we have carried out large scale cell typing efforts to quantify the dendritic morphology together with projections, electrical properties, and/or local inputs over 1000 mouse insular pyramidal neurons. These neurons are mapped onto a quantitative anatomical model of the insula based on a Nissl-staining framework. Using improved algorithms, we define morphological, electrical, and input-based neuronal types, and identify several morphological and input types that are unique to the insula. In addition, we found that specific morphological types are differentially distributed between the functionally distinct anterior and posterior insula, facilitating a quantitative demarcation between the anterior and posterior insular subregions. Surprisingly, certain pyramidal types receive intra-insular excitatory inputs originating far beyond canonical cortical columns. Functionally, these connections bridge a long-range circuit that links sensory information to valence behaviorally. Our work establishes a structure-and-function foundation for investigating critical roles insula plays in integrating interoceptive and exteroceptive information to achieve optimal behavioral outcomes.

Mature Neutrophils Promote Resolution Of Inflammation And Long-term Recovery After Spinal Cord Injury

Mia R. Pacheco1, Ashley V. Tran2, Matthew L. Bradley2, Miranda E. Leal-Garcia2, Dylan A. McCreedy1,2

1Institute for Neuroscience, Texas A&M University College Station, TX USA

2Department of Biology, Texas A&M University, College Station, TX USA

dmccreedy@bio.tamu.edu

Inflammation after spinal cord injury can substantially influence long-term outcomes. Neutrophils are the most common circulating immune cell type in humans and the first to enter the injured spinal cord in large numbers. While neutrophils have been commonly associated with secondary tissue damage, antibody-mediated depletion of neutrophils has yielded conflicting results to date, potentially due to removal of heterogeneous neutrophil subsets and functions. Using flow cytometry and analysis of publicly available scRNAseq data, we have found that neutrophil phenotype markedly shifts in a sex-dependent manner after spinal cord injury. Specifically, we found that mature neutrophils adopt a pre-resolving phenotype in the late acute phase of injury. To determine the temporal and sex-specific roles for mature neutrophils in long-term functional outcomes, we performed antibody-mediated depletion of neutrophils by injecting anti-Ly6G (1A8) or IgG (2A3) control antibody, which we found specifically abrogates the accumulation of mature neutrophils in the acutely injured spinal cord. While antibody-mediated neutrophil depletion at 1-day prior to SCI had no impact on long-term functional recovery, neutrophil depletion immediately post-injury markedly impaired long-term hindlimb locomotor recovery in male mice only. Post-injury neutrophil depletion did not alter long-term white matter tissue sparing, however, macrophage accumulation was exacerbated in male mice alone suggesting that mature neutrophils in the acutely injured spinal cord may play a sex-dependent role in mitigating chronic inflammation. Collectively, our findings indicate temporally restricted and sex-specific roles for mature neutrophils in mediating resolution of inflammation and long-term recovery following SCI.

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Developing systematic antibody panels for neuronal receptor hubs

Shaotong Zhu[1], Nirakar Basnet[1], Celine Santiago[1], Rob Meijers[1,2]

[1]Institute for Protein Innovation, Boston, MA 02115, United States
[2]Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School

The Institute for Protein Innovation is a non-profit organization developing recombinant antibody panels targeting the human and mouse neuronal surfaceome. We focus on neurobiological pathways where there is a need for validated, reproducible reagents.

Using display technologies and machine learning, we systematically generate FAB and VHH based panels that cover entire receptor families. This approach reduces antibody cross-reactivity and produces large, consistent sequence datasets that can be used for machine learning applications to further develop and optimize these antibodies.

Our synaptic cleft panel includes antibodies for receptor families like Neurexins, Neuroligins, Teneurins, Latrophilins and Eph receptors. We are also developing panels for axon guidance receptor/ligand families and for glial cell markers. We are mapping cross-family interactions and identifying how they can be modulated using our antibodies. Each reagent is evaluated for binding kinetics, potency, specificity, and aggregation, and formulated as chimeric human/rabbit antibodies.

These antibodies are distributed through Addgene following community validation. We are establishing a crowdsourced validation system with Addgene to build a reliable set of reagents supporting studies in neuronal migration and synaptogenesis. We also welcome input on additional targets that would benefit the field.

Reference:

Kothiwal, D. et al. (2025) “High-Throughput Machine Learning-Aided Antibody Discovery for Cell Surface Antigens.” bioRxiv, p. 2025.05.15.650607. Available at: https://doi.org/10.1101/2025.05.15.650607.

Phospholipase A1 Isoform Ddhd2 Controls Memory Formation And Long-term Potentiation

Frederic A Meunier

Affiliation: Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, St Lucia, Queensland, Australia.

One of the last frontiers in neurobiology is to understand how our brain can learn and store memories - some of them enduring for a lifetime. Saturated FFAs, particularly myristic and palmitic acids, strongly increase during neuronal stimulation (Narayana et al, 2015) and memory acquisition (Wallis et al, 2021), suggesting the involvement of phospholipase A1 (PLA1) activity in synaptic plasticity. I will present our new studies (Akefe et al, 2024; Matthews et al, 2025), demonstrating that the DDHD2 isoform of PLA1 generates these saturated FFAs across the brain thereby controlling memory acquisition in reward-based learning and spatial memory models. We found that DDHD2 interacts with key synaptic protein STXBP1/Munc18-1. Both DDHD2 knockout and haploinsufficient STXBP1+/- mice display intellectual disability and motor dysfunction. We also demonstrate that STXBP1 controls the targeting of DDHD2 to the plasma membrane and the generation of saturated FFAs in the brain. Our latest study shows that myristic acid generated during synaptic plasticity is used for lysine myristoylation which controls the establishment of long-term potentiation in cultured hippocampal neurons and in hippocampal slices. Our findings suggest key roles for DDHD2 and myristoylation in the lipid metabolism underlying synaptic plasticity, learning and memory.

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Single-cell Synaptome Mapping Of Different Protein Subpopulations In The Brain

Takayasu Mikuni

Department of Cellular Neuropathology, Brain Research Institute,

Niigata University, JAPAN

Thousands of synapses within individual neurons are diverse in their function. This synaptic diversity is a significant topic in neuroscience due to its critical role in shaping the complexity and functionality of neural circuits. Proteins, concentrated at synapses, regulate synaptic function through their spatial and temporal dynamics. Notably, different spatial or temporal protein populations, such as cell-surface/intracellular or pre-existing/nascent subpopulations, determine the basal and activity-induced functions of each synapse. Thus, selective mapping of different spatial and temporal subpopulations of endogenous proteins at thousands of synapses within single neurons in vivo would advance our understanding of synaptic diversity.

In this study, we developed a simple and generalizable platform to image different spatial and temporal subpopulations of endogenous proteins at thousands of synapses in single neurons in the mouse brain. The platform is based on the development/improvement and integration of CRISPR-Cas9-mediated protein labeling methods, chemical tag labeling techniques and a semi-automatic analytical pipeline. This integrated platform enables whole-cell mapping of total, cell-surface, intracellular, pre-existing, nascent or nascent-and-surface populations of endogenous proteins, such as receptor, scaffold and signaling proteins, at thousands of synapses in single neurons in living or fixed brain. Using this platform, we quantified endogenous glutamate receptor subpopulations at over 4,000 synapses in single neurons in the neocortex, providing a whole-cell map of the strength and plasticity of each excitatory synapse.

Our single-cell synaptome mapping of endogenous protein subpopulations visualizes the spatial organization of synaptic diversity in protein expression, trafficking and turnover, providing a more accurate and informative representation of the synaptic landscape within individual neurons in vivo. Furthermore, single-cell synaptome mapping allows for the detection and characterization of minority but influential synapses, such as silent and potentiated synapses, which might be overlooked in conventional bulk analysis.

Synaptic-level organization of reciprocal cortico-cortical circuits in the marmoset prefrontal cortex revealed by large-volume EM

Takaaki Miyazaki[1, 2], Estilla Z. Tóth[1], Shobha Upreti[1], Nilton L. Kamiji[1, 2, 3], Mitsuo Suga[2, 4], Akiya Watakabe[2], Yasuo Kawaguchi[1], Ryo Sasaki[1, 5], Yoshiyuki Kubota[1, 2, 3]

1 Natl. Inst. for Physiological Sci., Okazaki, Japan
2 Riken Ctr. for Brain Sci., Wako, Japan
3 Hamamatsu Univ. Sch. of Med., Hamamatsu, Japan
4 JEOL Ltd., Akishima, Japan
5 Grad. Inst. for Advanced Studies, SOKENDAI, Okazaki, Japan

The prefrontal cortex (PFC), which has expanded dramatically in primates, is fundamental to higher cognitive functions. A recent mesoscale study in marmosets (Watakabe et al., 2023) suggested the existence of columnar structures and their reciprocal interconnections. However, the synaptic-level connection patterns underlying these circuits remain unexplored. To address this, we utilized ATUM-Blade-TEM, a large-volume electron microscopy (vEM) system, to acquire high-resolution (2.4 nm/pixel) images over a large area (1.1 × 1.7 mm²) encompassing cortical columns.

We aimed to visualize the synaptic connectivity between area 10 (A10) and area 9 (A9) of the PFC by co-injecting anterograde and retrograde viral tracers into A10. Using Correlated Light and Electron Microscopy (CLEM), we found that A10-originated axons directly formed synapses onto the dendrites of A9 neurons that project back to A10, providing direct synaptic-level evidence for reciprocal connectivity between these prefrontal areas.

Quantitative analysis of A10-to-A9 projection targets revealed that approximately 90% were the spiny dendrites of pyramidal cells, while 10% were the aspiny dendrites of putative fast spiking basket cells (FSBCs; a specific type of inhibitory local interneuron). These innervated FSBCs exhibited highly specific targeting, with 96% of their output synapses directed onto pyramidal cells and the remaining 4% onto FSBCs (including self-connections). Furthermore, we analyzed the local axonal collaterals of the labeled A9-to-A10 projection neurons within A9. Their synaptic targets consisted of pyramidal dendrites (63%), FSBCs (35%), and putative double bouquet cells (2%), another type of inhibitory interneuron.

These findings demonstrate a sophisticated synaptic architecture where interareal inputs, local axonal collaterals, and inhibitory microcircuits are coordinately organized. This study provides novel insights into the structural logic of cortico-cortical communication in the primate brain.

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Large-scale Ca^{2+} imaging reveals segregated cortical functional networks during unconsciousness

Masa Murayama[1]

[1] RIKEN Center for Brain Science, Wako-city, Japan

Even during non-REM sleep or general anesthesia, individual neurons remain spontaneously active and respond to stimuli, yet the information is not perceived. How can ongoing neuronal activity fail to generate conscious experience? To tackle this puzzle, we focus on how functional network structure changes with conscious state. Prior fMRI studies report that large-scale functional networks become segregated into subnetworks in unconscious states, but fMRI lacks cellular resolution and cannot reveal how single neurons across regions form and reconfigure functional networks. To bridge this gap, we developed a wide–field-of-view two-photon microscope that simultaneously records activity from >10,000 neurons across >10 cortical areas in mice, enabling large-scale functional network analysis at single-cell resolution. Using this approach, we compared wakefulness with unconscious states (sleep and anesthesia) and quantified functional network organization in terms of small-worldness and modularity. We find that brain-state transitions are accompanied by a switch between integrated and segregated network configurations at the cellular level, with distinctive spatial distributions of module membership across the cortex. Moreover, neurons in different degree classes contribute unequally to these state-dependent network reorganizations. I will discuss how these cellular-scale network dynamics map onto consciousness, and outline future directions enabled by next-generation wide-field microscopes.

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Ectodomain Shedding (es) Is A Post-translational Protein Modification Process That Plays Key Roles In Health And Disease.

Many neuronal and synaptic membrane proteins are known to undergo ES, but the complexity of functions regulated by the shed peptides is only beginning to be unraveled.

Here, we provide an overview of emerging evidence demonstrating that synaptic ES can mediate autocrine and paracrine signaling.

We also discuss how advances in large-scale proteomic analyses are leading to the identification of novel synaptic proteins undergoing ES, as well as the targets and functions of their soluble ectodomains.

Finally, we provide an overview of how cerebrospinal fluid (CSF) analyses of shed proteins could be used as a potential source of new biomarkers for neuropsychiatric disorders.

Nanoscale Imaging Of The Extracellular Space In Amyloid Brain Tissue *In Vivo*

U. Valentin Nägerl

Department of Anatomy and Cell Biology, University Medical Center & Georg-August Universität of Göttingen, Germany

A defining pathological feature of Alzheimer's disease (AD) is the accumulation of amyloid plaques composed primarily of misfolded amyloid-β (Aβ) peptides. While plaques are traditionally described as dense and diffusion-limiting structures, their true penetrability and their impact on extracellular space (ECS) rheology in vivo remain insufficiently resolved. In this work, we combine complementary high-resolution imaging modalities to quantitatively characterize nanoscale transport properties within and around cortical amyloid plaques in a mouse model of AD.

Central to our approach is the development and application of an advanced in vivo two-photon shadow imaging strategy tailored to resolve plaque–ECS interfaces with minimal perturbation. By fluorescently labeling the interstitial fluid rather than cellular structures, shadow imaging renders cells and plaques as negative contrasts against a bright extracellular background. This configuration enables direct visualization of ECS topology surrounding plaques and precise delineation of the plaque boundary in the intact brain. Using this method, we demonstrate that cortical plaques are encapsulated by a dense cellular ring, yet the amyloid core itself remains diffusively accessible, challenging the notion of plaques as impermeable barriers.

To quantify local transport dynamics, we performed single-particle tracking using quantum dots and carbon nanotubes as nanoscale probes of ECS rheology. Quantum dot tracking reveals marked heterogeneity in diffusional parameters in and around plaques, with elevated effective diffusivity compared to wild-type tissue. Notably, the amyloid core exhibits low nanoparticle occupancy, with variations depending on plaque phenotype. Carbon nanotube tracking further confirms altered viscoelastic properties at the scale of the whole cortex in AD mice, indicating that plaque-associated ECS remodeling extends beyond the immediate plaque microenvironment.

Finally, we identify dysregulation of extracellular matrix components within plaques, providing a potential mechanistic basis for the observed increases in diffusivity. Together, these findings redefine amyloid plaques not as static diffusion barriers, but as dynamic microdomains with distinct structural and rheological properties. Our multimodal imaging framework—anchored by in vivo shadow imaging—offers a powerful platform to interrogate plaque penetrability, with important implications for therapeutic delivery strategies targeting Aβ pathology.

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Ampa Receptor Structure And Function

Terunaga Nakagawa, MD, PhD

Department of Molecular Physiology and Biophysics, Center for Structural Biology, and Vanderbilt Brain Institute,

Vanderbilt University, School of Medicine,

707 Light Hall, Nashville, TN 37232

Abstract

Fast excitatory synaptic transmission underlying various behaviors and thought processes requires signaling at high temporal resolution provided by the AMPA-type ionotropic glutamate receptors (AMPARs), the ligand-gated ion channels in synapses that are activated by neurotransmitter L-glutamate. In fact, AMPARs mediate most fast excitatory synaptic transmission in brain and distinguishes itself among the ionotropic glutamate receptors for having the fastest gating kinetics, whose channel opening and closure occurs within a few milliseconds. Furthermore, their function is fine-tuned by various AMPAR auxiliary subunits, small membrane proteins which binds to the exterior of the channel core. Given the pivotal roles of AMPARs in basal synaptic transmission and in learning and memory, accurate mechanistic understanding of their function is essential for advancing our knowledge on brain function. Molecular structures of AMPAR complexes in various functional states are expected to facilitate therapeutic development because AMPAR dysfunction is related to various neurological and psychiatric disorders, such as Alzheimer's disease, stroke, intellectual disability, schizophrenia, autism, seizure, limbic encephalitis, ALS, and certain types of brain cancer. In this talk, I will introduce our recent results on the mechanism of AMPAR gating modulation produced by utilizing approaches in both conventional and time-resolved cryo-EM, and electrophysiology.

Decoding spontaneous activity patterns for olfactory receptor-specific glomerular segregation

Ai Nakashima[1,2], Yuji Ikegaya[1,2] and Haruki Takeuchi[3]

[1] Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokyo;
[2] Institute for AI and Beyond, The University of Tokyo;
[3] Department of Biological Sciences, Graduate School of Science, The University of Tokyo

The formation of precise sensory maps depends on the ordered projection of neurons, a process initially dictated by genetic programming and later fine-tuned through activity-dependent mechanisms. In the field of developmental neuroscience, numerous studies have suggested that correlated neural activity drives sensory map refinement through the Hebbian synaptic plasticity mechanism.

In contrast, spontaneous activity in the primary olfactory system has been reported to lack spatiotemporal correlation, challenging the predictions of Hebb's theory. In mice, individual olfactory sensory neurons express only one functional olfactory receptor (OR) gene, and axons from olfactory sensory neurons expressing a given type of OR converge onto a specific pair of glomeruli at stereotyped locations in the olfactory bulb. It has been shown that ORs regulate various cell adhesion molecules to generate the combinatorial molecular code for olfactory circuit formation.

We have previously found that olfactory sensory neurons exhibit subtype-specific temporal patterns of spontaneous activity that induce specific expression patterns of axon-sorting molecules required for axon convergence. Our recent finding implies a novel form of activity-dependent mechanism, in which cell-intrinsic patterned activity regulates gene expression programs for circuit refinement. I will discuss how neural activity is involved in OR-dependent circuit formation.

Cell Type Evolution And Species-specific Brain Functions Revealed From The Gene Expression Map Of The Marmoset Developing Brain

Tomomi Shimagori

RIKEN CENTER FOR BRAIN SCIENCE, Wako, Japan;

Recent advances in spatial transcriptomics and single-cell analysis have enabled high-resolution characterization of the timing of emergence, differentiation pathways, and functional maturation of diverse cell types in the developing brain. We are comprehensively analyzing gene expression patterns in the postnatal developing marmoset cortex to elucidate the temporal and spatial architecture of maturation of diverse neurons and glial cells. Furthermore, by comparing similar data from mice and humans, we will examine how cell type development and gene regulatory networks have evolved and form the basis of species-specific brain functions and information processing characteristics.””Marmosets are important models for understanding the uniqueness of the primate brain, as their developmental time scale and circuit construction characteristics are similar to those of humans. This research has the potential to reveal cell type-specific expression programs acquired during evolution and the molecular mechanisms that support primate-specific circuit formation. These findings will provide new perspectives not only for the evolutionary understanding of brain function through interspecies comparisons, but also for elucidating the pathological basis of human neurodevelopmental disorders.

Population-level sleep homeostasis in social insects

Shinnosuke Nomura[1,2], Juliet Ngo[1], Saori Yada[1], Haruna Fujioka[3], Makoto Hiroi[4], Masato Sorida[1], Sam Reiter[4], and Shoi Shi[1, 5, 6]

[1] International Institute for Integrative Sleep Medicine (IIIS), University of Tsukuba, Tsukuba, Japan;
[2] The University of Tokyo, Tokyo, Japan;
[3] Okayama University, Okayama, Japan;
[4] Okinawa Institute of Science and Technology (OIST), Onna-son, Japan;
[5] Tsukuba Institute for Advanced Research (TIAR), University of Tsukuba, Tsukuba, Japan;
[6] Institute of Medicine, University of Tsukuba, Tsukuba, Japan

Sleep is regulated homeostatically in many species, but how such regulation scales in social animals remains unclear. Ants offer a unique model: genetically homogeneous individuals display strikingly different behaviors, which allows for the study of population-level sleep regulation under naturalistic yet controlled condition.

Previous observations by ecologists revealed that ants performing different behavioral roles display distinct circadian rhythms[1]. In addition, their antennae—known to be critical for environmental sensing and social communication—appear to reflect internal states such as stationary wakefulness or a putative "sleep" state[2]. However, how individual sleep homeostasis is regulated in response to social demands, and even whether this putative "sleep" state satisfies behavioral criteria for sleep, had not been elucidated.

Using a high-resolution camera system, we acquired nearly a hundred ants with fine antennae movements simultaneously. Modern data science approaches, including deep neural network–based posture estimation[3] and individual tag–tracking systems[4], confirmed that the putative sleep state in ants is characterized by immobility, reduced responsiveness to external stimuli, and population-level homeostatic rebound following sleep deprivation. These features satisfy established behavioral criteria for sleep. Furthermore, we identified several subtypes of sleep phenotypes that appear to sacrifice sleep homeostasis for the benefit of the colony. Notably, some subgroups showed minimal recovery sleep after sleep deprivation or lacked clear circadian rhythms, which includes ants engaged in egg and larval nursing.

How is such behavioral flexibility achieved despite a genetically homogeneous background? To address this question, we employed three complementary approaches. First, we used mass spectrometry and real-time gas detection technologies to investigate substance-based communication involved in sleep homeostasis regulation. This analysis identified several candidate substances that were specifically detected during interactions between nursing ants and eggs. Second, to identify neural substrates, we performed whole-brain fluorescence in situ hybridization targeting immediate early genes and calcium imaging of the ant brain. Finally, we are developing gene-editing tools based on the CRISPR–Cas9 system to directly link gene function to sleep-related behaviors.

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Cortical Circuit Dynamics During Learning And Memory

Lucy Palmer

Florey Institute of Neuroscience and Mental Health, University of Melbourne

Central to learning and memory is the ability of the cortex to dynamically encode and store learned information through changes in neural activity and connectivity. While dendrites serve as the primary site of synaptic input, their role in learning and memory processes within the cortex is unclear. To assess this, we performed two-photon calcium imaging from the dendrites of cortical layer 2/3 (L2/3) pyramidal neurons, as well as the perirhinal axonal projections, during a closed-loop visuomotor choice wheel task. Following learning, both cortical dendritic and perirhinal axonal calcium signalling were selectively enhanced during correct task performance. Disrupting the closed-loop behaviour further altered cortical signalling, significantly changing the frequency of evoked calcium events. These findings suggest that the perirhinal-to-frontal cortex microcircuit not only contributes to the transfer of learned information, but is also strongly influenced by memory disruption. Together, these findings advance our understanding of how long-term memories are stored in the brain and highlight the critical role of the frontal cortex and perirhinal cortex in this process.

Excitatory Glycine Receptors: Atypical NMDA Receptors in Brain Signaling

Dr. Pierre Paoletti

Institut de Biologie de l'ENS (IBENS), Ecole Normale Supérieure, Université PSL, CNRS, INSERM

Understanding how the activity of individual neurons ultimately relates to behavior in both normal and disease states is a central quest in neuroscience. To this end, it is essential to identify and dissect the various signaling mechanisms that drive and orchestrate cellular excitability and communication in the brain. Ionotropic glutamate receptors (iGluRs) are key players of the CNS as effectors of excitatory neurotransmission at glutamatergic synapses. However, of the 18 mammalian iGluR genes, five do not respond to glutamate but rather to glycine or D-serine. Of these, GluN3, which belong to the NMDA receptor (NMDAR) family, have long been considered as oddities with a limited role in brain function. Recent studies from our laboratory and others, have shown that NMDARs composed of the GluN1 and GluN3A subunits form glutamate-insensitive excitatory glycine receptors (eGlyRs) responsible for a novel signaling modality by which ambient glycine controls neuronal excitability and behavior. In contrast to conventional GluN1/GluN2 NMDARs, which are ubiquitously expressed in the CNS, eGlyRs show a patchy distribution in the adult brain with strong enrichment in circuits that control internal states, emotionality and stress responses (including the basolateral amygdala, medial habenula and ventral hippocampus). Molecular, cellular, behavioral and clinical studies identify eGlyRs as uniquely tailored, challenging the traditional views of NMDAR diversity and glycinergic signaling as inhibitory. The discovery of native excitatory glycine receptors expands the scope of iGluR signaling in brain operation, with important implications for neurophysiology and neuropharmacology.

Soluble α2δ-1, Altered in Disease CSF, Modulates Network Homeostasis and Rescues Neuropsychiatric Deficits

Marc Dos Santos[1,2], Marc P. Forrest[1,2], Ewa Bomba-Warczak[3], …, Marco Martina[1,13], Akira Sawa[5,8–12], Jeffrey N. Savas[3], Peter Penzes*[1,2,13,14]

[1] Department of Neuroscience, Northwestern University Feinberg School of Medicine, Chicago, USA; [2] Center for Autism and Neurodevelopment, Northwestern University Feinberg School of Medicine, Chicago, USA; [3] Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, USA; [5,8–12] Departments of Neuroscience, Psychiatry, Genetic Medicine, Biomedical Engineering, Pharmacology, and Public Health, Johns Hopkins University School of Medicine, Baltimore, USA; [13] Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, USA; [14] Department of Pharmacology, Northwestern University Feinberg School of Medicine, Chicago, USA

Excitation-inhibition (E/I) balance depends on dynamic communication between neuronal subtypes beyond classical neurotransmission. While membrane-bound ion channels are essential for neuronal function, their potential roles as extracellular regulators of network dynamics remain largely unexplored. Here, we identify a soluble form of the voltage-gated Ca^{2+} channel subunit α2δ-1 in human cerebrospinal fluid (CSF) and show that it acts as an activity-regulated intercellular modulator of network homeostasis. Soluble α2δ-1 is reduced in the CSF of individuals with schizophrenia (SZ). Its synthetic analog, SEAD1, modulates cortical activity by enhancing the function of parvalbumin-positive (PV^+) interneurons and restoring E/I balance. A single SEAD1 injection into the prefrontal cortex of a genetic mouse model of SZ reversed synaptic and behavioral deficits, including memory and social impairments. These findings reveal soluble synaptic ectodomains as a previously underappreciated class of extracellular signaling molecules with therapeutic potential in neuropsychiatric disorders.

Assessment Of The Mental Health Status In Neurosurgical Patients: Pilot Protocol

Manola Schlemper1, Vicentiu Saceleanu2

1 Psychiatric Services Aargau AG, Windisch, Switzerland;

2 “Lucian Blaga” University of Sibiu, Sibiu, Romania;

Understanding the impact of psychiatric symptoms on neurosurgical interventions offers potential for prevention, early diagnosis, and personalized intervention. This supports a multidisciplinary approach tailored to patients' complex needs and hospital systems, aiming to advance mental health and neurological health policies.

Depressive symptoms are highly prevalent, with preoperative and postoperative rates of in lumbar fusion patients, exceeding general population levels (Siempis et al., 2022). Depressive symptoms in general may be detected using the validated Beck Depression Inventory-II (BDI-II). Also, the BDI-II demonstrates strong psychometric properties in neurological contexts (Cuoco et al., 2021).

In this doctoral feasibility study, we will test psychological screening (BDI-II) in voluntary neurosurgical inpatients and refine procedures for the main study following ethics approval. Preliminary data will guide future research toward improved treatment outcomes.

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Translatome Profiling Of Inhibitory And Excitatory Neurons Of Fragile X Mice Identifies A Novel Therapeutic Target

Anand Suresh1, Nazim Kourdougli1, Toshihiro Nomura2, Jessie E. Buth3, Carlos A. Sánchez-León 1, Lauren T. Wall1, Anne T. Tran1, Sofia Nelson1, Soledad Miranda-Rottmann4,5, Roberto Araya4,5, Anis Contractor2, Michael J. Gandal6,7, and Carlos Portera-Cailliau1,8

1 Department of Neurology, David Geffen School of Medicine at the University of California Los Angeles LA, CA 90095, USA. 2 Department of Neuroscience, Feinberg School of Medicine, Northwestern University, Chicago Illinois, USA. 3 Neuroscience Interdepartmental Program, University of California Los Angeles LA, CA 90095, USA. 4 Department of Neurosciences, Faculty of Medicine, University of Montréal, Montréal QC H3T 1C5, Canada. 5 CHU Sainte-Justine Research Center, Montréal, QC H3T 1C5, Canada. 6 Departments of Psychiatry and Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA. 7 The Lifespan Brain Institute, Penn Med and the Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA. 8 Department of Neurobiology, David Geffen School of Medicine at the University of California Los Angeles LA, CA 90095, USA.

Symptoms of Fragile X Syndrome (FXS), the leading monogenic cause of intellectual disability and autism, are thought to arise from an excitation/inhibition (E/I) imbalance. We leveraged cell type specific mRNA sequencing to profile molecular alterations of cortical excitatory and inhibitory neurons in Fmr1 knockout (KO) mice, integrating transcriptomic results with circuit and behavioral readouts to prioritize novel therapeutic targets. Differentially expressed genes (DEG) were largely downregulated in Pvalb-expressing inhibitory neurons, whereas in Camk2a expressing excitatory neurons Up and Down DEGs were more balanced, and the underlying signaling pathways were often altered in opposite directions in each cell type. Among the 194 DEGs that were concordantly dysregulated across both cell types, only Rapgef4 (Epac2) was also an FMRP target, an ASD risk gene and brain enriched. EPAC2 has been implicated in synaptic maturation and plasticity. Genetic knockdown of Rapgef4 restored E/I balance and pharmacological inhibition with an EPAC2-specific antagonist rescued cortical circuit function in Fmr1 KO mice and ameliorated sensory behavioral phenotypes. Thus, EPAC2 is a potential target for therapy in FXS.

Movie-trained Transformer Reveals Novel Response Properties To Dynamic Stimuli

in mouse visual cortex

Prof. Nathalie Rochefort, University of Edinburgh

Abstract

Understanding how the brain processes complex visual stimuli remains a key challenge, but advances in machine learning and neuronal recordings now overcome previous limitations. This study introduces ViV1T, a transformer-based model trained on natural movies to predict neuronal responses in mouse primary visual cortex (V1). ViV1T outperformed state-of-the-art convolutional models on both natural and artificial dynamic stimuli, while being faster and more efficient. Movie-trained ViV1T accurately captured core V1 properties including orientation and direction selectivity and contextual modulation, despite lacking explicit feedback mechanisms. It also uncovered new insights, revealing a subpopulation of neurons that reverse their response to surround stimuli when contrast is lowered, and identifying properties of most-exciting natural and model-generated stimuli for both individual neurons and V1 population responses. These findings were validated by in vivo recordings. Overall, ViV1T provides a powerful, data-driven framework for exploring how the visual cortex processes dynamic stimuli over space and time.

Code and model weights available at github.com/bryanlimy/ViV1T.

Glutamate Spillover is Common in the Living Brain and May Help Memory Recall

Dmitri A. Rusakov

UCL Queen Square Institute of Neurology, University College London, United Kingdom

The numbers of glutamate molecules released into the synaptic cleft dwarf the numbers of its target intrasynaptic receptors, so that the bulk of released glutamate always escape outside the cleft. Here, the high-affinity transporters expressed by perisynaptic processes of brain astrocytes play a critical role in restricting extrasynaptic actions of glutamate, also taking up its excess in the extracellular space. How far glutamate can escape from its synaptic release sites has, however, remained debatable. Recent studies using genetically encoded optical glutamate sensors detect glutamate spillover over 0.5-1 μm from individually activated synapses in brain slices. We have advanced a similar approach in a whisker-stimulation paradigm *in vivo* and used high-speed high-resolution imaging to detect glutamate transients extending beyond 1 μm from individual thalamocortical synapses activated by brief sensory stimuli. Detailed Monte-Carlo modelling of probabilistic synaptic environment in the barrel cortex suggests that such conditions generate extrasynaptic glutamate transients reaching the bulk of local synapses. Simulations of Hopfield-type spiking neural networks reveal that volume-transmitted excitatory crosstalk can improve associative memory retrieval in a sparsely connected network under noisy input cues, reminiscent of brain activity. Our findings challenge the traditional view on excitatory circuits as a purely 'wired' network of one-to-one connections.

Acute Restraint Stress Hyperactivates Lateral Habenular Neurons

Hana Samejima[1] and Yuji Ikegaya[1,2]

[1] Laboratory of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan;
[2] Institute for AI and Beyond, University of Tokyo, Tokyo, Japan;

Major depressive disorder (MDD) is a leading cause of disability worldwide, characterized by persistent low mood, anhedonia, and cognitive impairment. Though hyperactivity of the lateral habenula (LHb) has been repeatedly implicated in the pathophysiology of MDD, and its experimental suppression can alleviate depressive-like behaviors [1], the precise subthreshold dynamics and temporal evolution of LHb activity during affective state transitions remain poorly understood, largely due to its deep anatomical location and technical limitations.

To address this gap, we investigated how LHb neuronal activity evolves during acute stress and sought to identify early electrophysiological markers that may predict vulnerability to depressive states. We combined in vivo whole-cell patch-clamp recordings from LHb neurons in head-fixed mice with high-density Neuropixels recordings to monitor ensemble activity longitudinally before, during, and after acute restraint stress.

Patch-clamp recordings revealed three major electrophysiological phenotypes in LHb neurons: silent, burst-firing, and tonic-firing cells, consistent with previous classifications [2]. We further found that under baseline conditions, burst-firing neurons exhibited higher frequencies of excitatory postsynaptic potentials (EPSPs), whereas tonic-firing neurons showed larger EPSP amplitudes, suggesting distinct modes of synaptic integration and excitability for each subtype.

Using Neuropixels, we demonstrated a progressive, stress-dependent hyperactivation of LHb populations. Compared with controls, acutely stressed mice showed time-dependent increases in overall firing rates, burst firing rates, and population synchrony (quantified as the variance of population firing rates). Crucially, among these metrics, burst firing displayed the most rapid and pronounced escalation during the early phase of restraint, preceding the full increase in mean firing and synchrony.

Our findings indicate that LHb burst firing is a sensitive and early readout of acute stress exposure and may act as a key driver of subsequent network hyperactivity leading to depressive pathology. By mapping the temporal progression of single-cell and population-level changes, this study refines mechanistic models of MDD onset and suggests that early attenuation of LHb bursting could represent a novel preventive therapeutic strategy. Future work will test whether pharmacological interventions, including psychedelic compounds such as psilocybin, can selectively modulate these stress-induced LHb dynamics and thereby reduce depression risk.

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Convergent Alterations in Motor Learning and Cortical Cellular Organization Following Early-Life Adversity

Xiaoyi Zhan[1], Zhiyuan Li[1], Jinyun Miao[1], Pengcheng Tan[1], Runze Liu[1], Chenrui Xu[1], Chia-Chien Chen[1].

[1] Behavior Science Program Neuroscience Track, Duke Kunshan University, Kunshan, China.

Cortical development is strongly shaped by experience, particularly by adverse experiences in early life. However, how such experiences relate to the cellular and structural integrity of the cortex across regions and layers remains incompletely understood. Using maternal separation (MS) as a model of early-life adversity, we characterized behavioral performance and cortical microcircuit-related features across sensory and motor cortices. MS was associated with altered motor learning, assessed using a skilled reaching task, reflected by reduced endpoint performance and greater variability in learning trajectories. At the cellular level, MS was accompanied by changes in microglial morphology, including increased territory covered by microglial processes and reduced process complexity within sensory cortical regions. In addition, immunohistochemical analyses revealed region- and layer-specific alterations in inhibitory circuit markers, including reduced parvalbumin (PV) interneuron density and decreased PV–perineuronal net (PNN) colocalization in primary somatosensory cortex. Ongoing Golgi-based analyses are evaluating dendritic spine distribution and neuronal morphology. Together, these observations suggest that early-life adversity may alter the developmental trajectory of cortical circuit maturation, potentially through disrupted microglial–neuronal interactions, and that such changes may contribute to long-lasting vulnerability in motor learning behavior, even though directionality among these processes remains to be determined.

Reorganization of Insular Social Representations During Conspecific Familiarization and Discrimination

Masaaki Sato[1], Eric T. N. Overton[2], Shuhei Fujima[1,3] and Toru Takumi[3]

[1] Faculty of Applied Biology, Kyoto Institute of Technology, Kyoto, Japan;
[2] RIKEN Center for Brain Science, Wako, Japan;
[3] Department of Physiology and Cell Biology, Kobe University School of Medicine, Kobe, Japan

Familiarity with social partners profoundly shapes behavior, yet how the social brain distinguishes known individuals from novel conspecifics remains unclear. Building on our previous work showing that neurons in the agranular insular cortex encode ongoing social interactions, we used microendoscopic calcium imaging to track neuronal activity in this region of mice during a social recognition memory task and a linear-chamber social discrimination task. In the social recognition memory paradigm, repeated encounters with the same target activated largely distinct neuronal populations across sessions. The proportion of neurons associated with social investigation (hereafter referred to as social cells) progressively declined across repeated interactions with the same individual. In contrast, replacing the target with a novel conspecific—and subsequently switching back to the familiar one—recruited many new social cells. In the linear-chamber discrimination task, introducing a novel conspecific transiently increased the number of neurons responding to both targets, followed by a selective rise in neurons responding to the novel individual. Together, these findings show that social cell ensembles in the agranular insular cortex shrink while shifting their constituent neurons during familiarization, and rapidly reorganize at the single-cell level to preferentially encode interactions with novel rather than familiar conspecifics during discrimination.

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Better Together: Neuron-Glia Interactions Shape Synaptic Maturation and Plasticity in Human iPSC-Derived Networks

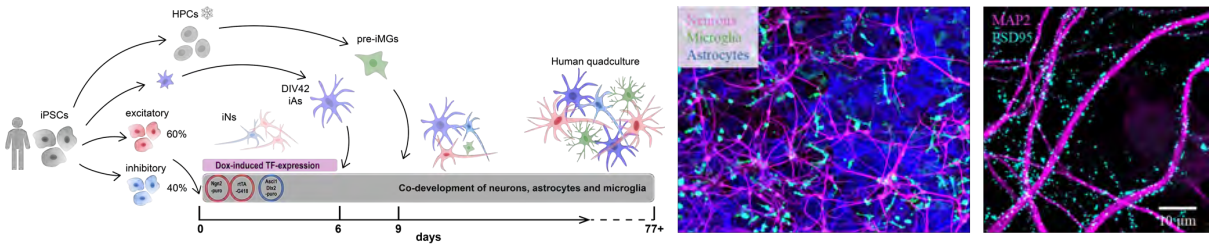
Nicky Scheefhals[1], Annika Mordelt[1,2], Noëlle van Egmond[1], Marina Hommersom[1], Carlos Gonzales[1,2], Imke Schuurmans[1], Chantal Schoenmaker[1], Sofia Puvogel[1], Marie Le Bihan[1,2], Ka Man Wu[1], Dirk Schubert[2], Lot de Witte[1,2,3], Nael Nadif Kasri[1,2]

[1]Department of Human Genetics, Radboud university medical center, Nijmegen, The Netherlands; [2]Department of Medical Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands; [3]Department of Psychiatry, Radboud university medical center, Nijmegen, The Netherlands

Synaptic molecular diversity shapes neuronal connectivity and information processing in the brain. A unique feature of human neurodevelopment is the prolonged maturation of synapses, during which this diversity refines neural circuits, supporting advanced cognitive abilities while increasing susceptibility to genetic disruptions. The scarcity of human brain tissue and translational limitations of animal models create significant barriers to understanding human-specific synapse development and function. Human induced pluripotent stem cell (iPSC)-derived neurons offer a promising alternative, yet their utility for synaptic research remains questioned due to limited synaptic maturation and often excitatory neuron-only cultures. This raises a critical question: what defines a suitable *in vitro* model for studying human synapses?

We reasoned that a good model should be as complex as necessary, yet as simple as possible, to capture the essential processes underlying synaptic maturation. A key element missing from many current iPSC-based models is the presence of human glial cells, which are known to play crucial roles in synapse development and maturation. To address this, we developed and systematically characterized an all-human iPSC-derived co-culture model containing excitatory and inhibitory neurons, astrocytes, and microglia. These all-human quadcultures faithfully recapitulate prolonged synaptic maturation while reaching postnatal-like stages within feasible culturing periods, marked by GABAergic maturation, functional excitatory and inhibitory synapses and dendritic spines. Using microelectrode array (MEA) recordings, we non-invasively track network activity over extended periods, revealing a transition from intrinsic to synaptically driven firing that is enhanced by the presence of human glia. By integrating MEA recordings, single-cell electrophysiology, and microscopy, we identify hallmarks of synaptic maturation and plasticity, including a developmental NMDA receptor subunit switch and long-lasting synaptic potentiation.

Together, our findings demonstrate that human glial cells promote synaptic maturation and plasticity in iPSC-derived neuronal networks, establishing this all-human quadculture model as a powerful and translational platform to study human synaptic development, function, and neuron–glia interactions in neurodevelopmental disorders.



Molecular Mechanisms Of Cortical Wiring And Plasticity

Peter Scheiffele

Our laboratory is exploring cell biological mechanisms underlying formation and plasticity of neuronal networks in development, physiological states, and disorders. We will discuss our recent studies on gene regulatory programs in the developing mouse neocortex and their control by spontaneous neuronal activity.

The formation of sensory cortical circuits in the mammalian brain is largely completed at the onset of sensation, with individual cortical neurons exhibiting specific and selective response properties that undergo only minor refinement thereafter. Before sensation, all sensory systems exhibit spontaneous patterned activity that propagates through ascending sensory pathways to primary cortical areas. Simultaneously, transcriptional programs unfold that specify cortical cell types, steer their anatomical projections, and may instruct wiring specificity. The structure and spatio-temporal dynamics of spontaneous patterned activity are thought to have a major impact on cortical wiring. However, the molecular mechanisms engaged by spontaneous activity are unknown. We will discuss our recent findings on the development of primary visual cortex circuitry in mice. We applied a combination of deep transcript isoform profiling using long-read sequencing, CAGE-Seq, in vivo two-photon calcium imaging in newborn mice, and spatial transcriptomics. Our work demonstrates how spontaneous activity in developing sensory systems instructs transcript isoform programs and will advance our understanding of how developmental processes mediate the acquisition of functional specificity in mature cortical networks.

Four Phases And A Temporal Threshold Of Population Calcium Response In Cortical Astrocytes During Locomotion.

Anna Fedotova, Alexey Brazhe, and Alexey Semyanov

Calcium activity is a crucial form of excitability in astrocytes. Calcium events represent unitary responses in individual astrocytes and astrocytic networks. However, the contribution of calcium events to the overall population response in astrocytic networks during behavioral tasks remains unclear. In this study, we performed two-photon imaging of astrocytic calcium activity in the somatosensory cortex of mice during locomotion.

During locomotion episodes, the population response went through four distinct phases:

Phase One: New calcium events appeared at the onset of locomotion.

Phase Two (Superevent): The events merged into a ‘superevent.’

Phase Three: The superevent splits into individual calcium events.

Phase Four (Afterburst): The events terminated, accompanied by a surge in new calcium events.

The population response exhibited a temporal threshold dependent on the duration of locomotion. Following short (subthreshold) episodes of locomotion, the first phase transitioned directly into the third phase without forming a superevent. In contrast, longer (suprathreshold) episodes of locomotion that extended beyond the first phase resulted in the formation of a superevent. The afterburst was also more pronounced in suprathreshold responses.

Our study elucidates the fundamental mechanisms behind the formation of population calcium activity in astrocytic networks during animal locomotion.

Characterization of an Optogenetically Induced Epilepsy Mouse Model: From Behavior to Microstructure

Na-Young Seo[1], Hyunyoung Kim[2,3], Hyungju Park[2] and Kea Joo Lee[1]

[1]Neural Circuits Research Group, Korea Brain Research Institute
[2]Neurovascular unit Research Group, Korea Brain Research Institute
[3]Department of Brain Sciences, Daegu Gyeongbuk Institute of Science and Technology

Temporal lobe epilepsy (TLE) typically arises from a unilateral focal region, yet how localized hyperactivity evolves into generalized seizures remains unclear. Here, we employed an established optogenetic kindling (OpK) paradigm to repeatedly activate unilateral ventral CA1 pyramidal neurons, which led to progressively intensified seizures that persisted for up to one month. Behavioral analyses showed that OpK mice did not develop anxiety- or depression-like behaviors but exhibited marked impairments in hippocampal-dependent contextual memory. Histological assessments revealed that preserved neuronal integrity accompanied by pronounced changes in glial cells, including ipsilateral microglial alterations and bilateral astrocyte reactivity. Ultrastructural analyses using transmission electron microscopy further demonstrated synaptic remodeling, characterized by increased excitatory shaft synapses and multisynaptic boutons. These multi-scale alterations suggest that unilateral vCA1 hyperactivation can recruit bilateral hippocampal networks to generate generalized seizures and drive TLE-relevant dysfunctions through cell- and circuit-level remodeling. Collectively, our findings establish the OpK model as a robust and reproducible platform for investigating comprehensive mechanisms underlying TLE pathophysiology.

KEYWORDS:
temporal lobe epilepsy, optogenetic kindling, hippocampus, synapse, glia

Synergistic Neuroprotective Effects of a Plant-Derived Alkaloid and Insulin-like Growth Factor-1 in a Rat Model of Alzheimer's Disease: Targeting the Wnt/β-Catenin Pathway

Prajjwal Sharma[1], and D. Harikrishna Reddy[1]

[1]Department of Pharmacology, Central University of Punjab, Ghudda, Bathinda, Punjab, 151401, India

Alzheimer's disease (AD) is characterized by progressive synaptic loss and cognitive decline, highlighting the urgent need for effective therapeutics that restore neuronal communication. The present study investigates the neuroprotective synergy between a plant-derived alkaloid and Insulin-like Growth Factor-1 (IGF-1) against amyloid-β (Aβ)-induced neurotoxicity, with a particular focus on the Wnt/β-catenin signaling pathway. Adult Wistar rats received bilateral intrahippocampal injections of $A\beta_{1-42}$ (4 µg/4 µL) to induce AD-like pathology, followed by 14 days of treatment with the alkaloid (20–80 mg/kg) and IGF-1 (25–50 µg), alone and in combination. Donepezil (1 mg/kg) served as a reference standard. Behavioral performance was assessed using the Morris water maze, open field, and novel object recognition tests to evaluate spatial learning, exploration, and recognition memory. Biochemical analyses measured antioxidant status, apoptotic markers, and lipid peroxidation levels. Immunoblotting studies revealed significant activation of β-catenin and inhibition of GSK-3β phosphorylation, indicating restoration of Wnt/β-catenin signaling. The combination treatment markedly improved behavioral outcomes and preserved synaptic integrity by mitigating oxidative stress and apoptosis. These findings demonstrate that co-administration of the alkaloid and IGF-1 exerts synergistic neuroprotection, linking molecular and behavioral recovery in Aβ-induced neurotoxicity. This combinatorial approach holds promise for developing targeted therapeutic strategies against AD by reinforcing synaptic resilience through Wnt/β-catenin pathway modulation.

Virus-like Intercellular Synaptic Plasticity

Kaelan Sullivan[1], Alicia Ravens[1], Eric de hoog[1], and Jason Shepherd[1]

[1] Department of Neurobiology, Spencer Fox Eccles School of Medicine, University of Utah, USA.

Current models of learning and memory have focused on cell-autonomous regulation of synaptic strength; however, intercellular signaling between cells in the brain is critical for normal cognition. The immediate early gene *Arc* is a repurposed retrotransposon critical for long-term forms of synaptic plasticity and memory[1-4]. Arc protein forms virus-like capsids released in extracellular vesicles (EVs) that signal cell-to-cell[2], but the function of Arc EVs is unknown. Here, we find that long-term potentiation stimuli induce the biogenesis of Arc EVs by recruiting the I-BAR protein IRSp53, which facilitates Arc capsid assembly, trafficking, and release from actin-rich filopodial structures in dendrites. Arc EVs transfer Arc protein and mRNA to neighboring dendrites, where translation of transferred *Arc* mRNA induces a loss of surface AMPA-type glutamate receptors. These results show that Arc EVs mediate an intercellular form of synaptic plasticity that may be critical for memory consolidation and reveals a new neuronal EV biogenesis pathway.

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Synaptic Regulation of Homeostatic Sleep Pressure

Shoi Shi[1,2,3]

[1] International Institute for Integrative Sleep Medicine (IIIS), University of Tsukuba, Tsukuba, Japan;
[2] Tsukuba Institute for Advanced Research (TIAR), University of Tsukuba, Tsukuba, Japan;
[3] Institute of Medicine, University of Tsukuba, Tsukuba, Japan.

Sleep is an inevitable and fundamental brain process required for maintaining brain function and adaptive behavior. Sleep homeostasis reflects the accumulation and dissipation of sleep pressure across wakefulness and sleep, yet its underlying biological basis remains incompletely understood.Our research investigates how synaptic regulation contributes to the generation and control of homeostatic sleep pressure. Using a combination of in vivo and in vitro experimental systems, molecular and genetic perturbations, and mathematical modeling, we examine how changes in synaptic strength causally induce sleep and how sleep, in turn, regulates synaptic strength across sleep–wake cycles. Focusing on excitatory neurons in the medial prefrontal cortex (mPFC), we demonstrate that synaptic potentiation modulates sleep pressure and promotes longer and deeper NREM sleep. Conversely, sleep induces synaptic downscaling in the mPFC, whereas sleep deprivation prevents this homeostatic process. Together, these findings suggest that synaptic processes in mPFC excitatory neurons are not merely downstream consequences of sleep but function as active regulators of sleep need itself [1)]. Consistent with this view, our recent results further indicate that gradual synaptic potentiation during wakefulness is driven by specific molecular mechanisms, supporting the idea that synaptic dynamics serve as an integrative substrate of sleep pressure in the mammalian brain.

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Release Your Inhibitions: Understanding The Nanoarchitecture Of GABAergic Inhibitory Synapses.

Katharine R. Smith

Department of Pharmacology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA

GABAergic inhibitory synaptic transmission is crucial for regulating circuit function and plasticity, essential processes for learning and cognition. In the central nervous system, synaptic inhibition is mediated by $GABA_A$ receptors ($GABA_ARs$), hetero-pentameric ligand-gated ion channels that are activated by GABA and clustered at the inhibitory post-synaptic domain iPSD. The number of $GABA_ARs$ clustered at the iPSD is a major driver of synaptic strength and this clustering changes during plasticity and pathology to increase or reduce synaptic efficacy. Here we combine multiple super-resolution microscopy approaches to investigate novel nanoscale subsynaptic mechanisms that contribute to the diversity and plasticity of inhibitory synaptic structure and function.

From Scar To Repair: Defining The Cellular And Molecular Roadmap For Mammalian Spinal Cord Regeneration

Monica M Sousa

i3S, University of Porto, Portugal

It is widely documented that the adult mammalian central nervous system (CNS) lacks regenerative capacity. This is attributed to both the inhibitory environment of the scar and the downregulation of developmental growth programs. Challenging this paradigm, our group identified the spiny mouse (Acomys cahirinus) as a unique mammal capable of spontaneous spinal cord repair following complete transection, achieving remarkable functional recovery. Our initial analyses at a chronic post-injury timepoint (8 weeks post-injury) revealed that Acomys forms a pro-regenerative extracellular matrix (ECM) at the lesion site, enriched in keratan sulfate proteoglycans (KSPGs). While this ECM signature is essential for repair, longitudinal bulk transcriptomic profiling of the injury site (from 1 day to 8 weeks post-injury) in Acomys and the non-regenerative laboratory mouse (Mus musculus) revealed that a critical switch in transcriptional trajectories occurs earlier. In Acomys, inflammation, ECM remodeling, and fibrotic pathways are initially activated similarly to Mus, peaking between 1 day and 1 week post-injury. However, these programs are subsequently downregulated from 1 to 3 weeks post-injury, coinciding with the upregulation of gene networks involved in axonal growth and synaptogenesis. By contrast, Mus maintains sustained activation of inflammatory and fibrotic pathways alongside persistent repression of neuroregenerative programs. These findings suggest that in Acomys, an initial scar-forming response facilitates wound closure but is subsequently resolved to allow regeneration. To elucidate the cellular populations and molecular programs enabling this switch thereby promoting scar resolution and regenerative permissiveness, we generated a single-nucleus RNAseq/ATACseq atlas of the spinal cord injury site in Acomys and Mus at 3 days, 1 week, and 3 weeks post-injury. Our data identify specific microglial subpopulations as key mediators of spinal cord regeneration in Acomys. These findings will be discussed as well as our ongoing efforts to engineer Mus models with Acomys-like spinal cord regenerative competence.

Interhemispheric Communication In Binocular Visual Cortex

Greg Stuart

How the brain combines information received independently by the two hemispheres is not fully understood. Here we describe a non-reciprocal circuit architecture in mouse binocular visual cortex that enables interhemispheric integration via anatomically and functionally segregated neuronal populations. Callosal projecting neurons (CPNs) receive weak or no callosal input. In contrast, callosal receiving neurons (CRNs) make weak or no callosal projections. Both populations receive direct input from the thalamus. These two populations had different cellular properties. CRNs had reduced excitability due to elevated Kv1 potassium channel expression, encoded by the Kcna2 gene, with excitability in CRNs correlated with the magnitude of callosal input. Functionally, CPNs were predominately monocular, whereas CRNs are predominately binocular, with binocularity in CRNs also correlated with callosal input. In summary, we find that non-reciprocal callosal projections between CPNs and CRNs together with differences in excitability shaped by callosal input underlies interhemispheric communication in binocular visual cortex.

Early Song Learning Experiences Regulate Developmental Dynamics of The Auditory to Motor Circuit in Zebra Finches

Joanna A. Komorowska-Muller, Yuichi Morohashi, Yoko Yazaki-Sugiyama

Okinawa Institute of Science and Technology (OIST) Graduate University, Okinawa, Japan

Brain functions develop in a sequential manner after birth - first sensory, then motor, and finally higher cognitive functions as later functional development requires proper skills acquired earlier. Like human infants learning to speak, juvenile songbirds learn to sing by memorizing and then vocally matching their tutor's song (TS) to establish their stereotyped own song during the auditory and then sensorimotor song learning critical periods. However, neural mechanisms supporting auditory memory-guided sensorimotor learning have remained elusive.

We recently found that the projections into the premotor song nucleus, HVC from the neurons responsive to TS in the caudomedial nidopallium (NCM), a brain area analogous to mammalian higher auditory cortex, are dense during early sensorimotor period but become sparse in later sensorimotor period (Louder et al., 2024). We further examined whether song experiences and their timing affect the time course of NCM-HVC projection dynamics. Juvenile zebra finches were raised by the first tutor (T1), and then by the second tutor (T2) after an isolation period. These sequentially tutored zebra finches learned songs from T2 beyond the normal learning period and produced less stable songs at the end of the typical sensorimotor period. We found that the projections into HVC from the NCM tutor song responsive neurons retained in adulthood when NCM-HVC projections were are normally sparse in these sequentially tutored birds, suggesting development of auditory-motor neuronal circuits and its time course are shaped based on early song learning experiences. Taken together, our results suggest the transient auditory to motor projections are engaged in developmental auditory TS memory guided song learning. Dynamic inter-areal neuronal circuit wiring might underly the coordinated functional development and its developmental time window in the brain.

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Wolbachia-mediated Reduction In The Glutamate Receptor Mglur Promotes Female Promiscuity And Bacterial Spread

Brandt Warecki1, Giovanni Vega1, Sommer Fowler1, Grant Hartzog1, Timothy L. Karr2, William Sullivan1

1Department of Molecular, Cell, and Developmental Biology, University of California, Santa Cruz, Santa Cruz, California, 95064, USA

2ASU-Banner Neurodegenerative Disease Research Center, Biodesign Institute, Arizona State University, Tempe, Arizona, 85287, USA

The molecular mechanisms by which parasites mediate host behavioral changes remain largely unexplored. Here, we examine Drosophila melanogaster infected with Wolbachia, a symbiont transmitted through the maternal germline, and find Wolbachia infection increases female receptivity to male courtship and hybrid mating. Wolbachia colonize regions of the brain that control sense perception and behavior. Quantitative global proteomics identify 177 differentially abundant proteins in infected female larval brains. Genetic alteration of the levels of three of these proteins in adults, the metabotropic glutamate receptor mGluR, the transcription factor TfAP-2, and the odorant binding protein Obp99b, each mimic the effect of Wolbachia on female receptivity. Furthermore, >700 Wolbachia proteins are detected in infected brains. Through abundance and molecular modeling analyses, we distinguish several Wolbachia-produced proteins as potential effectors. These results identify potential networks of host and Wolbachia proteins that modify behavior to promote mating success and aid the spread of Wolbachia.

Rethinking MAP2 as a Target for Recovery in Neuropsychiatric Illness

Robert A. Sweet, MD*, Melanie J Grubisha, MD, PhD

Objective: To characterize the MAP2 protein interactome and the impact of disease-associated phosphorylations on MAP2 interactions and functions.

Methods: The MAP2 interactome was characterized in two ways. First by immunoprecipitation of MAP2 from cerebral cortex of WT mice and mice in which a phosphomimetic mutation at a residue known to be hyperphosphorylated in schizophrenia was knocked in (S1782E MAP2 mice) followed by LC/MS. Second, the human MAP2 interactome was identified via proximity labeling followed by LC/MS. Confirmation of selected interactors was confirmed by tandem immunoprecipitation after co-expression of MAP2 and the interactor in HEK293 cells. Functionality of the S1782E and other schizophrenia associated phosphorylations were evaluated in cell-free assays of tubulin polymerization, microtubule binding, actin-binding, and actin polymerization and assays of process formation in HEK293 cells.

Results: We identified 100 candidate proteins interacting with both WT and S1782E MAP2 (common interactors), 807 interacting with WT only, and 13 proteins interacting with S1782E only. Of interest, 53 of the detected MAP2 interactors were annotated as risk genes for schizophrenia. The greater number of WT only interactors suggested that S1782E acts primarily as a loss of function modification, thus we conducted over-representation analysis of the WT only interactors to better understand the functions impaired by the loss of MAP2 interactions present in S1782E. In addition to microtubule binding proteins, WT only interactors were highly enriched for Neurodegenerative Pathway proteins, Zinc-finger proteins, Ribosome proteins, GEF proteins, Calmodulin binding proteins, and PDZ domain containing proteins. Speaking to the validity of our approach, a number of the common and WT interactors have previously been demonstrated to directly interact with MAP2. Thus, we focused our confirmatory studies on two novel interactors with increased selectivity for S1782E MAP2 relative to WT. These were Ppm1l (Protein Phosphatase, Mg2+/Mn2+ Dependent 1 L), a phosphatase that may potentially target pS1782 MAP2 for dephosphorylation and Klhl8 (Kelch Like Family Member 8), an E3 ubiquitin ligase adaptor that may target S1782E MAP2 for degradation. As predicted, significantly more S1782E MAP2 than WT was pulled down by immunoprecipitation of KLHL8 and PPM1L.

Phosphomimetic mutations in the proline-rich domain of MAP2 impaired microtubule assembly and actin-binding affinity but did not affect microtubule binding, whereas C-terminal domain phosphomimetic mutants (including S1782E) impaired all three functions. S1782E also reduced process formation relative to WT in HEK cells.

Conclusions: MAP2 subserves multiple functions critical to dendritic structure and function. Hyperphosphorylation of MAP2 at S1782, as found in schizophrenia, is sufficient to impair multiple MAP2 protein interactions and MAP2 functions. Ppm1l and Klhl8 may represent druggable targets to eliminate MAP2 that is hyperphosphorylated at S1782.

Apoe4-driven Splicing Defects Disrupt Neurite Projection In Excitatory Neurons

Julia TCW

Objectives: The apolipoprotein E e4 allele (APOE4), present in around 20% of the population, is the leading genetic risk factor of late-onset Alzheimer's disease (AD), with APOE4 homozygote (APOE 44) having more than 90% chance undergoing AD at 65 years old. Despite this near full penetrance, major gaps remain in our understanding of APOE4-mediated neuropathology.

Methods: We compared population-based human iPSC-derived mixed cortical culture (iPSC-MCC) from APOE 44 and APOE 33 carriers by using proteomics and deeply sequenced transcriptomics data integration. We validated our findings in vitro and in silico using CRISPR/Cas9-edited isogenic APOE 44 vs. APOE 33 hiPSC-MCCs and postmortem brains multi-omics data from large and highly phenotyped brain bank cohorts.

Results: Transcriptomics and proteomics integration confirm the APOE4 effects in matrisome and lipid metabolism pathways, consistent with our previous findings with transcriptomics. Here, we further identified that APOE4 induces a robust reduction of the mRNA spliceosome protein machinery. We found that APOE4 indeed systematically induces mRNA splicing defects, and more specifically intron retention in genes regulating neuronal projection and associated with concordant protein reduction. Single cell RNA-seq data of hiPSC-MCC reveal that APOE4 induces the splicing defect specifically in a subpopulation of excitatory neurons with intense mRNA splicing activity for cytoskeletal reorganization. In vitro validation confirmed that APOE4 iPSC-MCC displays decreased neurite outgrowth. Finally, these splicing defects impacting neuronal projection genes are present in APOE4 carrier postmortem brains at early stage of disease progression and found it strongly associated with amyloid plaque and neurofibrillary tangles burden.

Conclusions: The integrative genomics analyses highlight the disruption of mRNA splicing in excitatory neurons, leading to neuronal projection defects as a key element of the APOE4-mediated neuropathology and suggests new therapeutic pathways.

Keywords: APOE, neurons, splicing, iPSC

In Vivo Programming Of Adult Pericytes Aids Axon Regeneration By Providing cellular bridges for SCI repair

Andrea Tedeschi

Pericytes are contractile cells of the microcirculation that play a role in wound healing following spinal cord injury (SCI). Thus far, the extent to which pericytes cause or contribute to axon growth and regeneration failure after SCI remains controversial. Here, we found that SCI induces significant alterations in vasculature architecture and pericyte coverage. Notably, pericytes physically constrain sensory axons on their surface, leading to detrimental structural and functional changes in adult dorsal root ganglion neurons that impair axon regeneration. Importantly, we demonstrate that in vivo programming of adult pericytes via localized delivery of platelet-derived growth factor BB (PDGF-BB) promotes axon regeneration and recovery of hindlimb function by contributing to the formation of cellular bridges that span the lesion. Ultrastructural analysis reveals that PDGF-BB induces alignment and extension of fibronectin fibrils, converting adult pericytes into a permissive substrate for axon growth. In addition, PDGF-BB positively affects the physical and chemical nature of the lesion environment, thereby creating more favorable conditions for SCI repair. Thus, therapeutic manipulation rather than wholesale ablation of pericytes can be exploited to prime axon regeneration and SCI repair.

Establishment of a Neuronal-like Cell Model for the Control of Intracellular Tau Using Optogenetics

Tomoya Uchida[1], Naoki Kato[1], Shigeo Sakuragi[1], Toshiki Takahashi[1], Yoshiyuki Soeda[2], Hideaki Yoshimura[3], Akihiko Takashima[4], Hiroko Bannai[1]

[1]School of Advanced Science and Engineering, Waseda University, Tokyo, Japan;
[2]School of Pharmacy, Nihon University, Chiba, Japan;
[3]School of Science, The University of Tokyo, Tokyo, Japan;
[4]Faculty of Science, Gakushuin University, Tokyo, Japan

Tauopathies, including Alzheimer's disease, Pick's disease, corticobasal degeneration, and progressive supranuclear palsy, are a group of neurodegenerative disorders characterized by the pathological accumulation of tau, which is a microtubule-associated protein. While tau is primarily monomeric under physiological conditions, pathological hyperphosphorylation promotes its transition into oligomers and fibrils that form neurofibrillary tangles. Recent studies suggest that tau oligomers are the primary toxic species. However, direct comparisons of toxicity across different tau species remain limited.

To address this gap, we established a cellular model to manipulate intracellular tau dynamics. We previously developed an optogenetic tool, OptoTau, which enables blue-light-dependent clustering of intracellular tau [1]. OptoTau consists of human 2N4R tau carrying P301L mutation, which accelerates aggregation, fused to the photosensitive protein CRY2olig. Using an OptoTau knock-in Neuro2a cell line, we successfully induced stable tau aggregates driven by tau-tau interactions rather than CRY2olig-mediated cross-linking under intermittent blue-light illumination [2]. However, in this system, rapid cell proliferation attenuated intracellular tau accumulation, thereby limiting long-term tau aggregation.

To overcome this limitation, we developed a new neuronal-like cell model with suppressed proliferation based on the human neuroblastoma cell line SH-SY5Y, which is amenable to differentiation. An N-terminally cleaved OptoTau construct carrying the P301L mutation was introduced into the AAVS1 safe-harbor locus, performed puromycin selection to generate a stable cell line via puromycin. Following a 3-day differentiation period, cells were continuously exposed to blue light for 5 days, resulting in the accumulation of tau aggregates that co-localized with the anti-oligomeric tau antibody T22, as confirmed by immunostaining. The combination of OptoTau and differentiated stable cell lines enabled the generation of a cell population exhibiting widespread T22-positive aggregation, representing a specific assembly state of tau. Taken together, this model provides a versatile foundation for manipulating tau aggregation states and facilitating comparative analyses of tau species-specific toxicity.

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Characterizing the Role of MEC Projections to the PFC in Sequence Abstraction

Shimpei Uchiyama[1,2] and Thomas McHugh[1,2]

[1] Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan;
[2] Laboratory for Circuit and Behavioral Physiology, RIKEN Center for Brain Science, Saitama, Japan

Our daily lives are composed of countless behavioral sequences, such as following a recipe for dinner or playing a piece of music. However, it would be incredibly inefficient to learn every single sequence from scratch, which suggests the brain leverages a common, generalizable mechanism to understand this sequential structure.

Prior work suggests that the entorhinal and prefrontal cortices are critical for abstracting and generalizing the structure of problems (Baram et al., 2021). Furthermore, recent studies have shown that the prefrontal cortex (PFC) maps the structure of behavioral sequences (El-Gaby et al., 2024). Together, these findings raise the possibility that the circuit connecting the medial entorhinal cortex (MEC) to the PFC is fundamental for the abstraction of sequential knowledge.

Prior work implicates MEC layer Va projections in shaping PFC engrams and the later expression of remote memory (Kitamura et al., 2017), while whole-brain monosynaptic input atlases indicate that input from the MEC to the PFC may be comparatively limited (Ährlund-Richter et al., 2019), creating an ambiguity about its anatomical basis. To build a precise anatomical foundation for investigating this circuit, we began by confirming the layer Va specificity of this projection. We injected a retrograde AAV-Cre into the PFC and a Cre-dependent reporter into the MEC, and confirmed this layer Va origin by immunohistochemistry. Building on this, we then performed dual-color, Cre-dependent labeling—DIO-mCherry in the dorsal MEC (dMEC) and DIO-EYFP in the ventral MEC (vMEC)—to resolve the fine-scale anatomical organization of this projection.

Building on this anatomical foundation, we are investigating this circuit's role in sequence learning using "OperantHouse," a versatile home-cage operant conditioning platform (Otsuka et al., 2025). In this task, mice must learn a sequence of actions on a touchscreen to receive a reward.

This poster presents our anatomical characterization of the MEC-PFC projection, including its layer Va specificity and the differential contributions of dMEC and vMEC, alongside the design of our sequential task and preliminary behavioral data. These results provide a foundation for future investigations into how this circuit supports the abstraction and learning of complex, structured behaviors.

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Modelling the impact of vesicular release site heterogeneity within active zones on presynaptic information processing

Paraskevi Mylona[1], Yulia Timofeeva[1] and Kirill Volynski[1,2]

[1] Department of Computer Science, University of Warwick, Coventry, UK;
[2] Department of Epilepsy, UCL Queen Square Institute of Neurology, London, UK

Small central glutamatergic synapses display substantial diversity in release kinetics and short-term plasticity, enabling individual presynaptic boutons to act as frequency-selective filters and support target-specific communication within neuronal circuits. This variability arises from differences in vesicle-Ca^{2+} channel coupling distance and in Ca^{2+}-dependent regulation of vesicle replenishment and priming across synapses. Importantly, release sites within a single active zone are themselves heterogeneous. However, it remains unclear whether such intra-active zone heterogeneity merely modulates synaptic strength or fundamentally alters the type of frequency filtering that a terminal can implement.

To address this, we developed a computational framework to determine how intra-active zone heterogeneity shapes presynaptic information processing. This framework incorporates a mechanistic model that unifies spatially resolved and global Ca^{2+} dynamics within a single active zone. Fast synchronous release is governed by nano- and microdomain Ca^{2+} signals at individual release sites during each action potential, whereas asynchronous release, short-term plasticity, and vesicle replenishment depend on residual Ca^{2+} dynamics between stimuli. The framework also generates electrophysiological and optical readouts from simulated release events that mirror experimental recordings, enabling systematic evaluation of how modulation of processes such as vesicle replenishment or short-term facilitation is reflected in measured synaptic responses from heterogeneous synaptic populations.

Our results demonstrate that individual release sites act as discrete units of information transfer, recruited according to their coupling geometry and activity-dependent Ca^{2+} dynamics. Systematic comparison of homogeneous and heterogeneous synapses with identical mean release probability reveals distinct frequency-dependent transmission profiles, indicating that intra-active zone heterogeneity can qualitatively reshape synaptic filtering. Heterogeneous coupling thus expands the computational repertoire of a single presynaptic terminal.

Unique Adolescent Plasticity of Frontal Dopaminergic Circuits: From Cellular Mechanisms to Therapeutic Potential

Kuan Hong Wang[1]

[1] University of Rochester Medical Center, Rochester, New York, USA

Midbrain dopaminergic neurons provide critical modulatory input to the frontal cortex to support higher-order cognitive functions, yet the developmental maturation and long-term plasticity of these projections remain poorly understood. Our work identifies adolescence as a uniquely sensitive period during which frontal dopaminergic circuits exhibit heightened and experience-dependent plasticity. We show that motor exercise or phasic activation of dopamine neurons during adolescence, but not adulthood, robustly enhances dopaminergic innervation of the frontal cortex, revealing a temporally restricted window for enduring circuit remodeling. Importantly, targeted stimulation of adolescent dopamine circuits produces a long-lasting rescue of circuit dysfunction and cognitive impairments in genetic models of frontal cortical pathology, highlighting the enduring impact of developmentally timed intervention. At the cellular level, we find that frontal cortical microglia exhibit heightened responsiveness to dopamine during adolescence, increasing their surveillance and promoting dopaminergic axonal bouton formation. These findings identify a previously unrecognized neuroimmune mechanism that actively gates dopamine circuit maturation and may underlie the persistence of therapeutic effects. Together, this body of work establishes adolescence as a critical period for frontal dopaminergic plasticity, integrates neuronal and microglial mechanisms, and suggests novel, developmentally timed strategies for durable circuit-based interventions in neuropsychiatric and neurodevelopmental disorders.

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Membrane Mechanics Dictate Axonal Morphology And Function

Shigeki Watanabe

Neurons are known for their intricate cellular morphology. Axons in particular are exceptionally long (100-1000 mm) and ultrathin (100 nm). Their cable-like morphology is essential for conduction of electrical signals, or action potentials, throughout the brain and body. Thus, it has been long assumed that axons are tubular structures with occasional synaptic varicosities. However, our work has challenged this assumption. Using high-pressure freezing to preserve membrane morphology for electron microscopy or super-resolution imaging of live neurons, we performed ultrastructural analysis of axons in Caenorhabditis elegans motor neurons, mouse hippocampal neurons, and human cortical neurons. We discovered that axons are not simple tubes but rather exhibit a pearls-on-a-string morphology through their entire length, with the pearls being ~250 nm and the strings ~70 nm in diameter. This morphology is reminiscent of membrane tubes undergoing tension-driven instability. Consistent with this notion, the pearled area becomes smaller when hyperosmotic solution is applied and larger when hypoosmotic solution is applied. Interestingly, pharmacological perturbation of the cytoskeleton did not greatly alter axon morphology, suggesting that membrane mechanics drives axon morphology. In further support of this, increasing the membrane fluidity by cholesterol depletion from the plasma membrane led to a shrinking of the pearled membrane regions. Functionally, when axon morphology is altered with pharmacological cholesterol depletion, action potential velocity decreases. Similarly, neuronal stimulation that induces plasticity alters the pearled axon morphology. Our in silico modeling further supports our experimental data that membrane mechanics can cause pearled axon morphology and that pearled morphology greatly impacts action potential conductance. These data have revealed for the first time that axons are pearled not tubular, and that pearled axon morphology has an important functional role in neuronal activity and plasticity.

Mixed selectivity and low-dimensional dynamics in STN couple movement and licking

Bing-Shiuan Wu1,2, Chih-Ching Chung1,3**, Hao-Yun Teng1,3**, Ming-Yuan Min2, Yu-Wei Wu1,2,3,4,5,6,7*

1 Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan; 2 Department of Life Science, College of Life Science, National Taiwan University, Taipei, Taiwan; 3 Taiwan International Graduate Program in Interdisciplinary Neuroscience (TIGP-INS), National Taiwan University and Academia Sinica, Taipei, Taiwan; 4 Molecular and Cell Biology Program, Taiwan International Graduate Program (TIGP-MCB), Academia Sinica, Taipei, Taiwan; 5 Genome and Systems Biology (GSB) Degree Program, College of Life Science, National Taiwan University, Taipei, Taiwan; 6 Graduate Institute of Life Sciences, National Defense Medical University, Taipei, Taiwan; 7 Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei, Taiwan

The subthalamic nucleus (STN) is a key hub in basal ganglia circuits and a major target for deep brain stimulation in Parkinson's disease, yet what individual STN neurons encode during natural behavior remains unclear. We used in vivo two-photon calcium imaging in behaving mice to record single-neuron STN activity while animals engaged in locomotion, licking (orofacial action), and reward-guided behavior. STN neurons displayed strong mixed selectivity: many cells responded to multiple behaviors with distinct temporal dynamics and either excitatory or inhibitory profiles. Across neurons, this multiplexed representation robustly encoded movement vigor—locomotion speed and licking intensity—while also capturing shifts in behavioral state and reward context.

Parallel recordings in the neighboring zona incerta (ZI) revealed regional specialization. Both regions represented locomotion, but STN activity tracked moment-to-moment motor state more faithfully, whereas ZI responses were dominated by prolonged calcium events with weaker coupling to ongoing movement. At the population level, STN activity evolved within a compact low-dimensional manifold, with dominant components aligned with movement velocity and orofacial vigor. Importantly, the locomotion representation was context dependent: trajectories diverged when movement was self-initiated versus reward-modulated, indicating flexible remapping rather than a fixed "speed axis."

Together, these results suggest that STN integrates whole-body and orofacial motor control with motivational signals through low-dimensional population dynamics built from mixed-selective neurons. This cellular-resolution framework refines models of basal ganglia computation and provides a principled way to interpret how STN dysfunction or neuromodulation reshapes coordinated behavior in health and disease.

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Mesoscale Simulation of Phosphorylation-Dependent Reorganization of Postsynaptic Density Condensates

Risa Yamada[1] and Shoji Takada[1]

[1] Graduate School of Science, Kyoto University, Kyoto, Japan

Postsynaptic density (PSD), a protein complex observed beneath the postsynaptic membrane, plays crucial roles in synaptic plasticity by controling receptor localizations. Recent studies have revealed that PSD constituent proteins undergo liquid-liquid phase separation (LLPS), creating biomolecular condensates[1,3]. After long-term potentiation (LTP) induction, phosphorylation by signaling enzymes dramatically alters protein interactions or multimerization within these condensates, thought to reshape PSD condensate architecture.

Among PSD proteins, calcium/calmodulin-dependent protein kinase II (CaMKII) occupies a particularly important position, functioning both as a structural constituent of the condensate itself and as a trigger initiating interaction change with phosphorylation. However, fundamental questions remain regarding how phosphorylated proteins behave within PSD condensates before and after LTP. For example, CaMKII holoenzyme, a large dodecameric assembly, occupies substantial excluded volume[2] and yet binds directly and multivalently to NMDA receptors to form nanodomains[3], raising questions about whether other PSD condensate components interfere with this organization. Furthermore, how phosphorylation of various proteins influences receptor clustering remains largely unexplored.

To address these questions, we employ mesoscale molecular simulations to investigate collective behavior of protein mixtures within PSD condensates. Our model is parameterized using experimentally measured dissociation constants and critical concentrations from *in vitro* experiments with soluble protein variants in 3D systems. After parameter calibration, we systematically examine how CaMKII-mediated phosphorylation of itself and other PSD proteins influences condensate properties. Using membrane-mimicking 2D systems, we compare PSD organization before and after LTP induction. We specifically analyze how phosphorylation-induced changes in protein interaction networks affect spatial distribution, clustering behavior, and nanodomain formation of receptor populations, providing mechanistic insights into phosphorylation-dependent PSD reorganization during synaptic plasticity.

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Large-scale microscopic-level brain simulation on a supercomputer

Tadashi Yamazaki

Graduate School of Informatics and Engineering, The University of Electro-Communications, Tokyo, Japan

Understanding brain function requires bridging the gap between microscopic biophysics and macroscopic phenomena. Recent research in mice has identified complex higher-order structural motifs (Reimann et al., 2024), while comparative studies reveal that mice and humans exhibit divergent graph-theoretical properties in their neuronal networks (Kanari et al., 2025). Capturing the functional impact of such microscale connectivity requires large-scale simulations that explicitly model the detailed topology of neural circuits.

However, the computational complexity of such detailed models has limited their application to small-scale circuits. To overcome this, we developed Neulite, a light-weight neuron simulator optimized for High-Performance Computing (HPC). Neulite features a Brain Modeling ToolKit (BMTK)-compliant frontend for biological plausibility and a portable numerical kernel that maximizes throughput on massively parallel systems like the Supercomputer Fugaku.

We demonstrated Neulite's capability by simulating the Allen Institute's whole mouse cortex model (Kuriyama et al., 2025), consisting of 9 million biologically detailed neurons and 26 billion synapses (Liz, 2025). Under AMED Brain/MINDS 2.0, we will integrate this technology with actual micro-connectome data to investigate how species-specific graph structures influence global brain dynamics and learning capability. This framework provides an essential infrastructure to decode the causal links between microscopic network topology and overall neural circuit function.

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Decoding Synaptic Signaling Dynamics Underlying Plasticity

Ryohei Yasuda

Max Planck Florida Institute for Neuroscience

Learning and memory depend on activity-dependent changes in synaptic strength and structure, yet the molecular mechanisms orchestrating these changes remain incompletely understood. These processes are mediated by complex biochemical signaling networks involving hundreds of intracellular and extracellular molecules operating on fine spatial and temporal scales. To dissect these networks, we have developed innovative imaging and optogenetic tools that allow visualization and perturbation of protein activity at individual synapses in freely behaving animals. These approaches have revealed how specific signaling events drive synaptic plasticity, modulate circuit function, and contribute to behavior, providing a new framework for understanding information storage in the brain.

CPTX modulates GluA1 surface mobility in hippocampal neurons revealed by quantum dot single-particle tracking

Boxiao Zhao[1], Shigeo Sakuragi[1], Michisuke Yuzaki[2], Hiroko Bannai[1]

[1]School of Advanced Science and Engineering, Waseda University, Tokyo, Japan;
[2]Human Biology-Microbiome-Quantum Research Center (Bio2Q), Keio University, Tokyo, Japan

CPTX, a synthetic synaptic organizer developed by Suzuki and colleagues which bridges presynaptic neurexins and postsynaptic AMPA-type glutamate receptors (AMPARs), demonstrating therapeutic effects in multiple neurodisease models characterized by synaptic loss[1]. Excitatory synaptic strength depends in part on the enrichment of AMPARs at postsynaptic sites. Such enrichment reflects not only trafficking to and from the surface but also rapid exchange between synaptic and extrasynaptic pools through lateral diffusion and reversible trapping at postsynaptic sites[2]. However, given that CPTX directly binds to AMPARs, it remains unclear whether CPTX alters their membrane mobility.

In this study, we quantified the surface dynamics of GluA1-containing AMPARs in cultured hippocampal neurons using quantum dot single-particle tracking (QD-SPT). Postsynaptic sites were defined with FingR.PSD95 to classify trajectories as synaptic or extrasynaptic. CPTX produced a time and compartment-dependent shift in GluA1 mobility: extrasynaptic diffusion coefficients were reduced within 2 hours of CPTX application, whereas synaptic diffusion coefficients decreased only after 24 hours. This delayed synaptic decrease was accompanied by reduced synaptic confinement, whereas extrasynaptic confinement was unchanged at both time points.

In summary, these results suggest that CPTX produces an early-stage change in GluA1 surface mobility at 2 h and a later change at postsynaptic sites, with reduced synaptic mobility and smaller confinement domains at 24 h.

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In Vivo Imaging Of Second Messenger Signaling Underlying Circuit Control

Haining Zhong

Nearly all neuromodulators converge onto a small handful of second-messenger pathways. Particularly, Gs and Gi coupled receptors regulate intracellular cAMP concentrations and in turn the activity of cAMP-dependent kinase (also called PKA), whereas Gq coupled receptors regulate DAG/IP3 productions, which then activates protein kinase C (PKC). These signaling activities then impose powerful controls over synaptic transmission, neuronal excitability, plasticity and other functions. Neuromodulatory signaling events are thought to be heterogeneous across neurons during animal behavior to differentially regulate individual brain circuits. However, little is known about their precise spatiotemporal dynamics or their functional importance. In this talk, I will discuss our recent work to develop novel genetically encoded sensors, which, in combination with two-photon fluorescence lifetime imaging, have enabled the visualization of cAMP, PKA and PKC signaling activities in vivo with cellular and subcellular resolutions. I will also discuss recent applications of our technologies, which have led to novel insights into the neuromodulatory regulation of brain circuits in the striatum underlying animal locomotion. The finding suggests mitigation strategies for Parkinson's disease.

From snowflakes to synapses: how environmental cues shape Ephexin5-mediated synaptic plasticity

Samuel Petshow, Azariah Coblentz, Heather Spooner, Nathaniel Clarke, Andrew Hamilton, and Karen Zito

Center for Neuroscience,

University of California, Davis, CA 95618, USA.

ABSTRACT

Synaptic RhoGEFs play vital roles in regulating the activity-dependent neuronal plasticity critical for learning. Ephexin5, a RhoGEF implicated in the etiology of Alzheimer's disease and Angelman Syndrome, was originally reported in neurons as a RhoA-specific GEF that negatively regulates spine synapse density. We used biochemistry and live imaging of GTPase biosensors to demonstrate that, surprisingly, Ephexin5 activates Cdc42 at single synapses, where it positively regulates plasticity-induced long-term dendritic spine growth. Notably, despite that synaptic activity drives activation of both RhoA and Cdc42, we show that Ephexin5 selectively promotes activity-dependent Cdc42 signaling. This selectivity of Ephexin5 for Cdc42 activation is regulated by tyrosine phosphorylation, which is regulated by neuronal activity. Our results support a model in which neuronal activity regulates Ephexin5 tyrosine phosphorylation, driving Ephexin5-dependent Cdc42 signaling and the spine structural plasticity vital for learning.

Planar cell polarity proteins in glutamatergic synapse formation and function

Yimin Zou

University of California, San Diego.

The local signaling mechanisms that directly assemble glutamatergic synapses are not fully understood. Our lab demonstrated that the highly conserved planar cell polarity (PCP) pathway, which creates asymmetric cell-cell junctions, is crucial for the formation and maintenance of most glutamatergic synapses in the hippocampus and cortex. It does so by physically interacting with key presynaptic active zone proteins, postsynaptic density proteins, and glutamate receptors (Ban et al., 2021; Feng et al., 2021; Thakar et al., 2017). The PCP pathway is a direct target of amyloid-β–induced synapse degeneration and mediates synapse recovery triggered by the antidepressant ketamine (Feng et al., 2021; Freitas et al., 2024). Mutations in PCP genes are linked to neurological disorders (Ban et al., 2022). We now find that several components of the PCP pathway, Vangl2, Prickle1, and Dishevelled2, which are localized specifically in the postsynaptic density, are essential for synaptic plasticity. I will also present updates on how the PCP pathway interacts with synaptic adhesion molecules and a new organizational principle of signaling systems in glutamatergic synapses.

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Unraveling the Synaptic Basis of Motor Learning

Yi Zuo

UC SantaCruz

As the fundamental information-processing units of the brain, neurons communicate through specialized connections called synapses. Experience-dependent reorganization of synaptic circuits is a key mechanism by which the brain acquires and stores new information and adapts behavioral output. Learning new skills and adapting behaviors further reshape the synaptic network. Our earlier work demonstrates that acquisition of novel forelimb tasks induces rapid formation of dendritic spines—the postsynaptic sites of excitatory synapses—on pyramidal neurons in the primary motor cortex, and that subsequent training selectively stabilizes these spines. Such persistent synaptic changes provide a structural basis for long-term motor memory. Yet, the determinants of learning ability remain poorly understood. Abundant evidence indicates that environmental enrichment enhances synaptic formation and confers broad benefits to brain function. Using transcranial two-photon microscopy to repeatedly image fluorescently labeled neurons, we tracked dynamics of the same dendritic spines *in vivo* over weeks to months. This study explores how environmental enrichment reshapes synaptic circuits and impacts motor skill learning through modulating new spine formation.

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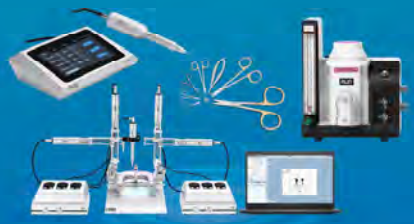

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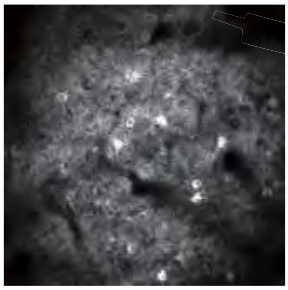

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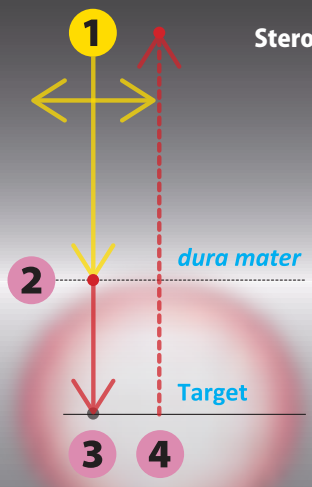

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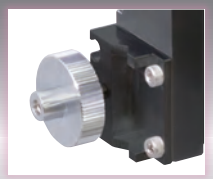

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*Set the distance and time in advance, and press START **
**FREE drive mode selectable; set the speed in advance and press START*

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Set the retreat speed in advance (independent from the SET/FREE drive), and press UPPER LIMIT.

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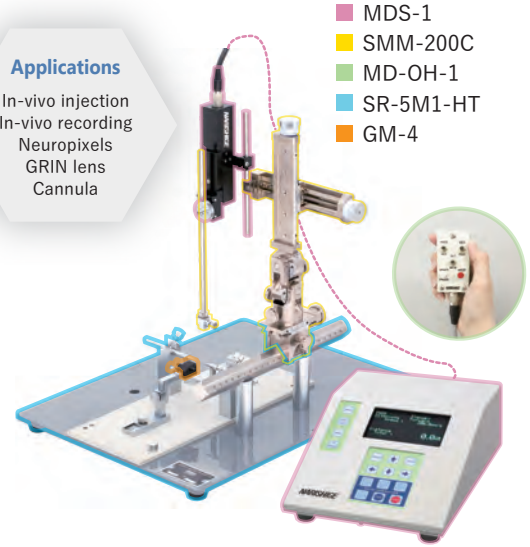
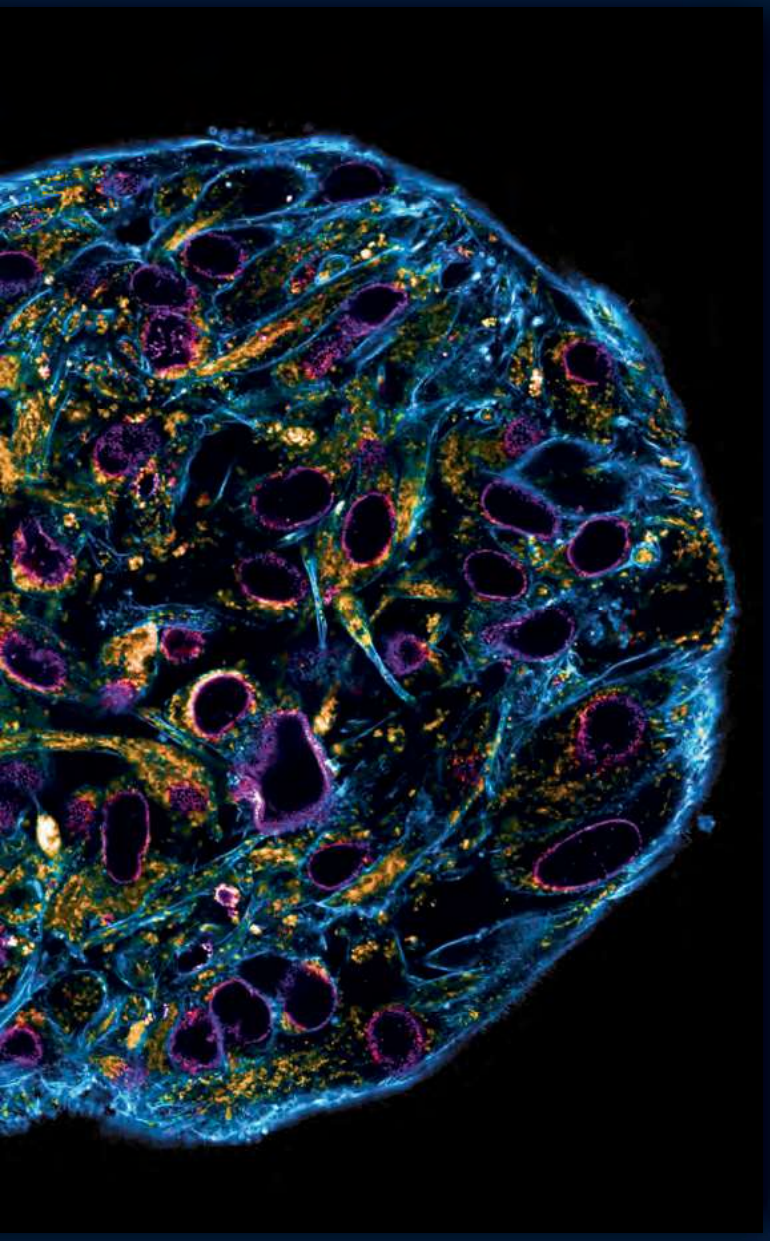
- GM-4



Specifications

Model	SMM-100C	SMM-200C	MDS-1	MD-OH-1
Product name	Stereotaxic manipulator		One-axis Motorized Stereotaxic Micromanipulator	Compact controller
				
Precision	XZ axes: Full rotation of knob : 4.2mm Minimum graduation: 0.1mm Y axis: Full rotation of knob : 1mm Minimum graduation: 0.01mm		MDS-1 Specifications Drive source: 5-phase Stepping Motor Movement range: 20mm Speed range: 0.1µm/s ~ 2,500µm/s (0.1µm/s increment) Distance range: 1µm ~ 20,000µm (1µm increment) Time range: 1s ~ 60min (0.1s increment)	
Movement range	XZ axes: Coarse 80mm Y axis: Fine 20mm			
Angles	<Non-simultaneous> Single angle, AP or ML	<Simultaneous> Double angles AP or ML		
Dimensions (mm) Weights	W85 x D162 x H256 1.75 kg	W85 x D162 x H286 2.0 kg	Drive unit: W56 x D60 x H122, 0.28kg Control unit: W180 x D260 x H95, 2.5kg	W40 x D81 x H36 112 g



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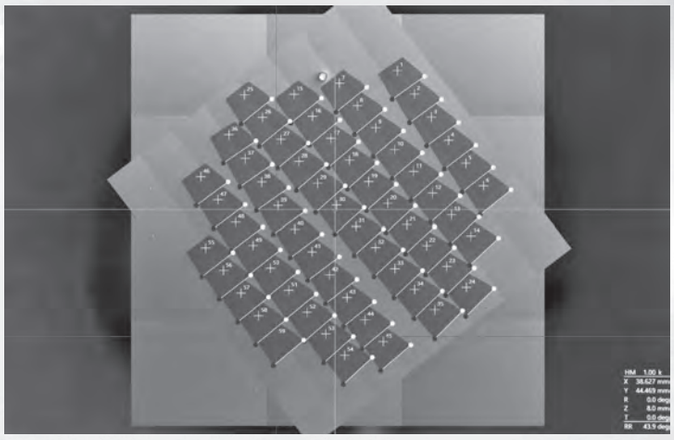

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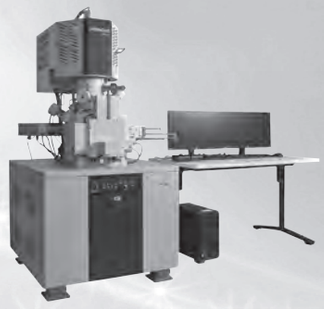

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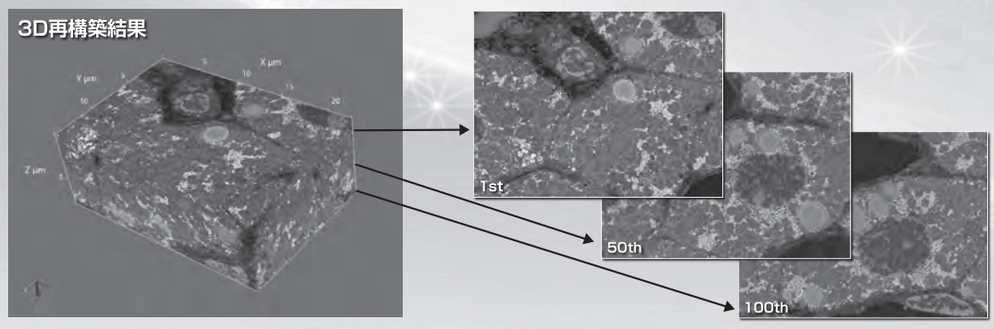

撮影枚数　　：117枚
スライスピッチ　：70 nm
3D再構成ソフト：Image Pro Premier 3D
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〒105-6409　東京都港区虎ノ門一丁目17番1号
虎ノ門ヒルズ ビジネスタワー
電話 03-3504-6111

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  Note: The high tilt specimen holder is required as option.

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Landing Voltage: 0.01 to 30 kV

JEOL JEOL Ltd.
3-1-2 Musashino Akishima Tokyo 196-8558 Japan Sales Division Tel. 81-3-6262-3561 Fax. 81-3-6262-3577
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