International Symposium on Brain Structure and Function

July 1st - July 2nd, 2024

Organizers：Michel Thiebaut de Schotten (CNRS and University of Bordeaux, France / Editor-in-Chief of Brain Structure and Function)
Hiromasa Takemura (National Institute for Physiological Sciences, Japan / Section Editor of Brain Structure and Function)

Host: National Institute for Physiological Sciences
Co-Host: MEXT Promotion of Development of a Joint Usage/ Research System Project: Coalition of Universities for Research Excellence Program (CURE), Frontiers of Spin Life Sciences [Spin-L]
Sponsor: Neuroscience Alliance, Bcblab

Hybrid
Onsite Venue：Main Conference Room
Myodaiji Area, 1st floor, National Institute for Physiological Sciences

Program

Day 1: July 1st, 2024 (Monday)

8:30 Registration is Open

9:00 Opening Remark and Introduction of Brain Structure and Function
Michel Thiebaut de Schotten (Editor-in-Chief of Brain Structure and Function)

Session 1: Neurotransmitter Systems
Chair: Laszlo Zaborszky (Rutgers University)

9:10- 9:50 Susan Sesack (University of Pittsburgh, USA)
Astrocytic Ensheathment of Glutamate Synapses in the Accumbens is Highly Variable

9:50-10:30 Nicola Palomero-Gallagher (Research Centre Jülich, Germany)
Receptor architectonic mapping as a tool to understand the link between the structural and functional segregation of the brain

10:30-10:50 Coffee break

Session 2: Visual System, #1
Chair: Franco Pestilli (University of Texas at Austin)

10:50-11:30 Mayu Takahashi (Tokyo Medical and Dental University, Japan)
Neural circuits for triggering saccadic eye movements by inhibiting eye fixation circuits

11:30-12:10 Marcello Rosa (Monash University, Australia)
The anatomical and physiological consequences of striate cortex lesions in primates of different ages

12:10-13:30 Lunchtime break and poster viewing

Session 3: Basal Ganglia
Chair: Noritaka Ichinohe (National Center for Neurology and Psychiatry)

13:30-14:10 Hiromi Sano (Fujita Health University, Japan)
Pathophysiological Changes in a Mouse Model of Parkinson's Disease and Novel Therapeutic Approach through Activation of the PKA/Rap1 Cascade

14:10-14:50 Thomas Boraud (CNRS and University of Bordeaux, France)
A distributed architecture for Actor and Critics in the primate cortex basal ganglia loop (CBG loop)

14:50-15:10 Coffee break

Session 4: Neuroinformatics
Chair: Stephanie Forkel (Donders Institute of Brain, Cognition and Behavior)
15:10-15:50 Ariel Rokem (University of Washington, USA)
What should we do with Big Data?
15:50-16:30 Noritaka Ichinohe (National Center for Neurology and Psychiatry, Japan)
Understanding Cortical Layer Inputs in Marmoset Neuroanatomy

16:30-16:40 Photo Taking Session

16:40-18:00 Poster Session (onsite only)

18:00-20:00 Banquet (registered attendees only)

Day 2: July 2nd, 2024 (Tuesday)

8:30 Registration is Open

Session 5: Functional Mapping and White Matter
Chair: Ariel Rokem (University of Washington)
9:00- 9:40 Riho Nakajima (Kanazawa University, Japan)
Functional brain network study using awake brain mapping and neuroimaging analysis in patients with brain tumor
9:40-10:20 Michel Thiebaut de Schotten (CNRS and University of Bordeaux, France)
Mapping Functions on the White Matter

10:20-10:40 Coffee break

Session 6: Visual System, #2
Chair: Mayu Takahashi (Tokyo Medical and Dental University)
10:40-11:20 Yumiko Yoshimura (National Institute for Physiological Sciences, Japan)

Experience-dependent circuit development in the mouse visual cortex

11:20-12:00 Franco Pestilli (University of Texas at Austin, USA)
A connectivity correlate of visual perceptual asymmetries

12:00-13:30 Lunchtime break and poster viewing

Session 7: Cognition and Evolution
Chair: Nicola Palomero-Gallagher (Research Centre Jülich)

13:30-14:10 Stephanie Forkel (Donders Institute of Brain, Cognition and Behavior, Netherlands)
Exploring Neurovariability: Unraveling the Complexities of Brain Structure and Function

14:10-14:50 Hiromasa Takemura (National Institute for Physiological Sciences, Japan)
Comparative study on white matter pathway connecting dorsal and ventral visual cortex

14:50-15:10 Coffee break

Session 8: Connectomics
Chair: Michel Thiebaut de Schotten (CNRS and University of Bordeaux)

15:10-15:50 Denis Le Bihan (Neurospin, France)
The dimensions of the brain connectome

15:50-16:00 Coffee break

Session 9: Forebrain and Cholinergic System
Chair: Susan Sesack (University of Pittburgh)

16:00-16:40 Toshihiko Momiyama (Jikei University School of Medicine, Japan)
Serotonin receptor-mediated modulation of excitatory transmission onto cholinergic neurons in the rat basal forebrain

16:40-17:20 Laszlo Zaborszky (Rutgers University, USA)
Hierarchical Organization of the Forebrain Cholinergic System in Rat

17:20 Closing Remark
Hiromasa Takemura (National Institue for Physiological Sciences, Japan)

Astrocytic Ensheathment of Glutamate Synapses in the Accumbens is Highly Variable

Susan R. Sesack, PhD (Departments of Neuroscience and Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA)

The concept of the tripartite synapse poses that pre- and postsynaptic structures in excitatory axospinous contacts are closely apposed by a third astrocytic element participating in communication and plasticity with both sides of the junction. Since the pioneering reconstructions by Kristen Harris, it has been known that over 40% of excitatory synapses on spines in the hippocampus are without such astrocytic contacts, and those that are contacted are covered on only 40% of the available synaptic surface. Given that astrocytes clear extracellular glutamate, these observations have profound implications for understanding how excitatory synapses are regulated and therefore how they may operate as independent computational elements. Despite such importance, these parameters have not been investigated within the striatal complex where cortical afferents critically regulate goal-directed behavior.

We have been examining astrocytic ensheathment of axospinous synapses in the nucleus accumbens core, a ventral striatal region for which glutamate homeostasis vitally contributes to and is shaped by drugs of abuse. First, we investigated naïve rats and mice using electron microscopy and 3D reconstruction of excitatory-type axospinous synapses: over 300 from rats and over 100 from mice. Roughly one-third of synapses exhibited no astrocytic contact. Of the synapses showing some ensheathment, only one-third of the available synaptic surface was contacted. The findings were consistent across the two species and comparable to those reported for the hippocampus. In a second study done in collaboration with Dr. Yan Dong, four rats were examined, two each self-administering saline or cocaine for 5 days. Reconstruction of 72 synapses from saline animals and 77 synapses from cocaine rats showed no significant differences in any morphological measure or the proportion of astrocytic contact with synapses. This is the first such electron microscopic investigation of animals chronically self-administering cocaine. Several dependent measures show considerable underlying variation, both in treated and naïve animals. Hence, the drug investigation is underpowered, and a larger sample size is needed if any significant impact of cocaine is to be uncovered.

Receptor architectonic mapping as a tool to understand the link between the structural and functional segregation of the brain

Nicola Palomero-Gallagher (Research Centre Jülich, Germany)

Neurotransmitters and their receptors mediate signal transduction at the synaptic level and thus play a fundamental role in enabling information transmission within the nervous system. Receptors for classical neurotransmitters are proteins or protein complexes located on the surface of the neuronal membrane. However, their heterogeneous distribution throughout the brain should not be interpreted as merely reflecting differences in cell packing densities. Rather, as highlighted in this talk, analysis of the regional and laminar distribution patterns or neurotransmitter receptors sheds light on the link between the cytoarchitectonic (structural) and functional segregation patterns of the brain. Each cortical area or subcortical nucleus is characterized by a unique co-distribution pattern of multiple receptor types, which has been described as the "receptor fingerprint" of the brain entity in question. Differences in the size and/or shape of receptor fingerprints segregate areas from different phylogenetic origins (paleo- archi-, periallo- proiso- and neocortex), functional systems (e.g., motor, visual, somatosensory, auditory) and cortical types (unimodal vs. multimodal association areas). Within a given functional system, receptor fingerprints also differ between hierarchical processing levels. E.g., the density of muscarinic M_2 receptors decreases progressively when moving from primary sensory areas through unimodal areas of increasing hierarchy and is lowest in association areas, and the opposite sequence is observed for the adrenergic α_1 receptor. Similarities in the size and/or shape of receptor fingerprints, on the other hand, constitute the molecular underpinning of functional networks, since areas with a similar receptor architecture are more likely to respond to similar signals, thus facilitating coordinated responses within a network that subserves a specific brain function. Importantly for translational neuroscience, these organizational principles could be demonstrated for both the human and the macaque monkey brain. Concluding, a comprehensive characterization of the brain’s receptor architecture is essential to decipher its intricate signaling networks and to acquire a better understanding of the relationship between the structural and functional segregation patterns of the brain.

Neural circuits for triggering saccadic eye movements by inhibiting eye fixation circuits

Mayu Takahashi
(Dept. of Neuroanatomy & Cellular Neurobiology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University)
(Dept. of Physiology, Graduate School of Medicine, The University of Tokyo)

Saccadic eye movements are the fastest and most accurate movement among all kinds of body movements, and are vital for vision and represented in wide areas of the central nervous system. Saccades shift gaze to objects of interest in the visual field, moving their image to the central retina, where it is maintained for detailed examination (eye fixation). During such fixation, all eye movements to other targets are suppressed.

From clinical observations, it has been generally believed that saccade driving circuits are composed of horizontal and vertical systems. Later animal experimentations revealed that saccade driving signals arising from the cortical frontal eye field are conveyed via the midbrain superior colliculus (SC) and the brainstem lower centers to ocular motoneurons. However, the detailed neural circuits from the SC to ocular motoneurons have not been understood well, especially neural circuits for vertical saccades.

We analyzed the neural circuits for generating horizontal and vertical saccades using intracellular recording (electrophysiology) and staining (anatomy) methods in anesthetized cats.

We revealed that the output pathways from the SC to ocular motoneurons are composed of horizontal, upward-torsional and downward-torsional systems, and are very similar to those of the well-known vestibuloocular reflex pathways, and concluded that the saccade system uses 3D semicircular canal coordinates rather than 2D horizontal and vertical coordinates.

It is known that neurons in the raphe interpositus have tonic activity that suppress high gain saccade burst neurons during fixation, and that is inhibited before and during saccades, but the neural mechanisms for triggering saccades by suppressing raphe neurons have not been analyzed. Recently, we identified the neural mechanisms for suppressing saccades (fixation) and triggering saccades, using the same methods. In this presentation, I'd like to discuss the neural mechanisms for triggering saccades, and the presumed common coordinate system in various eye movement systems.

The anatomical and physiological consequences of striate cortex lesions in primates of different ages

Marcello Rosa (Department of Physiology, Neuroscience Program, Biomedicine Discovery Institute, Monash University, Australia)

Primates are unique with respect to the development of the geniculostriate system, and other areas of the visual cortex. This evolutionary gain endows us with the ability to see and comprehend sharp, colourful images in 3 dimensions, and to guide precise actions. However, there is also a price to pay: The position of V1 (striate cortex) as a key node in the distribution of information, from the retina and thalamus to the rest of the cortex, means that damage to this single area is sufficient to render us blind. But not all is lost; studies over decades have documented that some visual abilities, largely subconscious, survive V1 lesions, and that there is some room for improving them using behavioural techniques. Our research program is focused on understanding the changes to the visual system triggered by V1 lesions, both in early life and in adulthood, using the marmoset monkey as an animal model. Whereas most studies have focused on the role of the superior colliculus and its efferent connections in mediating residual vision following V1 damage, we have found that there is also significant preservation of function in the lateral geniculate nucleus, and that projections from this complex to extrastriate areas are not only preserved, but enhanced after V1 lesions. These results indicate that recovery of function following V1 lesions may involve multiple neural pathways, and that the lateral geniculate nucleus can play a significant role in this process.

Pathophysiological Changes in a Mouse Model of Parkinson's Disease and Novel Therapeutic Approach through Activation of the PKA/Rap1 Cascade

Hiromi Sano (International Center for Brain Science, Fujita Health University)

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of nigrostriatal dopaminergic neurons that exhibits severe motor symptoms. Supplementation of reduced dopamine with L-DOPA improves PD symptoms, but long-term L-DOPA treatment induces involuntary movements known as L-DOPA-induced dyskinesia (LID). The striatum is one of the input nuclei of the basal ganglia (BG) and receives corticostriatal and nigrostriatal inputs. The projection neurons in the striatum are divided into striatonigral medium spiny neurons (MSNs) and striatopallidal MSNs. Striatonigral and striatopallidal MSNs express dopamine D1 receptor (D1R) and dopamine D2 receptor (D2R), respectively. D1R activates protein kinase A (PKA), whereas D2R inhibits PKA. Dopamine is supposed to exert an excitatory effect on D1R-MSNs and an inhibitory control on D2R-MSNs. Activation of D1R controls the PKA/Rap1 cascade and modulates the membrane excitability of D1R-MSNs. D1R-MSNs send information directly to the output nuclei of the BG, the substantia nigra pars reticulata (SNr). D2R-MSNs send information to the SNr via the *indirect* striato-pallido-subthalamo-SNr pathway. In the standard model of the BG, D1R-MSNs (the *direct* pathway) suppress the activity of SNr neurons and increase motor activity. In contrast, D2R-MSNs increase the activity of SNr neurons through the *indirect* pathway and suppress motor activity. In PD, the loss of dopamine is predicted to cause an imbalance between the *direct* and *indirect* pathways, and the neuronal activity in the SNr is thought to be increased in PD and decreased in LID. However, the actual pathophysiological changes are not well understood.

In this symposium, we will show and discuss the relationship between cortico-BG pathway information flow and motor symptoms in PD and LID mouse models. In addition, we will present our recent data that activation of the PKA/Rap1 cascade in D1R-MSNs ameliorates PD symptoms and discuss the therapeutic opportunities based on this signaling system.

A distributed architecture for Actor and Critics in the primate cortex basal ganglia loop (CBG loop)

Thomas Boraud (CNRS, University of Bordeaux)

The cortex of mammals makes a loop circuit with the basal ganglia and the thalamus, known to control and adapt behaviour. However, the Who's Who of the functional roles of these structures and their dynamic properties are still debated. We previously proposed a minimal computational framework in which dopaminergic-dependent operant learning relies upon reward-biased competition processes inside the whole CBG loop, while habits rely on cortical-only competition processes. Based on new electrophysiological data recorded in Monkeys performing an economic task, we developed our model to encompass the architecture of the critics.

What should we do with Big Data?

Ariel Rokem (University of Washington, USA)

Thanks to advances in data collection technologies, and in the technologies to store and compute on data, and thanks to sociotechnical trends towards increased reproducibility and transparency, researchers in many fields are increasingly gaining access to large, diverse and complex datasets. Through a range of centralized data collection efforts, researchers in neuroscience are now also able to access datasets of unprecedented size and diversity. But the question is: what should we do with these datasets to maximize their utility? What do these datasets enable that was not possible with smaller focused studies? This talk will discuss a few of the challenges that large neuroscience datasets present and discuss some of their promise. The talk will revolve around a set of open-source software tools that we developed for data-driven analysis of major brain white matter pathways. The tools that we have developed address a range of issues: research procedures that are routine for small experimental datasets are close to impossible in large datasets, and we have developed scalable computing tools, as well as tools that crowd-source research procedures. These datasets present remarkable opportunities to harness data-driven methods, such as machine learning algorithms, to study the brain basis of individual differences, but care needs to be taken so that these methods are not led astray by confounding information or become too opaque to provide useful information. We have addressed this by creating tightly-matched sub-samples from large datasets, and by harnessing interpretable machine learning methods. Finally, I will discuss the challenges of training the next generation of researchers to judiciously combine neuroscience knowledge with data science methods. I will focus on the NeuroHackademy summer institute for neuroimaging and data science that we have established in order to provide such training.

Understanding Cortical Layer Inputs in Marmoset Neuroanatomy

Noritaka Ichinohe (Department of Ultrastructural Research, National Institute of Neurology and Psychiatry, Kodaira, Tokyo, Japan)

The dynamic and intricate circuits interconnecting the cortical regions form the foundation of complex functions within the brain. The neocortex is composed of distinct layers, each characterized by unique cell types and processes that vary in connectivity and functionality. These layers form specific channels to their respective domains, and it is known that connections between neocortical areas target characteristic layers. This targeting is not random; it reflects the brain's evolutionary strategy to optimize information flow, ensuring efficient and effective neural processing across different cortical areas. Traditionally, the interpretation of layer-specific inputs has been limited to comparatively basic schemes, specifically within the context of hierarchical models like feedforward, feedback, and lateral connections. However, the interactions in cortical systems and neural circuits likely follow various logics and computations, suggesting the existence of categories more complex than currently recognized. The key to systematically understanding this complexity lies in having access to a sizeable and representative dataset under consistent conditions. Japan's Brain/Minds project is an initiative aimed at elucidating the neural circuits of primate brains, using the marmoset as a model organism. Within this project, we have injected AAV vectors coding for fluorescent proteins, which serve as anterograde tracers, into over 100 cortical areas of the marmoset brain. These injections spanned the frontal, temporal, occipital, parietal lobes, cingulate cortex, and insular cortex, covering functional modules such as the visual, auditory, somatosensory, and motor cortices. All injection conditions, survival times, and fixation methods were standardized. The fluorescent signals were detected and reconstructed easily while brain sectioning using two-photon microscopy. Data from these signals were segmented using AI, allowing for specific and low-noise detection, and processed through a sophisticated pipeline. The presentation will explore the significance of findings in relation to current models of cortical processing, emphasizing the novel complexities uncovered in marmoset brain circuits.

Functional brain network study using awake brain mapping and neuroimaging analysis in patients with brain tumor

Riho Nakajima (Department of Occupational Therapy, Faculty of Health Science, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan)

We have investigated functional network in patients with brain tumor using awake brain mapping and neuroimaging analysis. Awake brain mapping is a surgical procedure in which the patient remains conscious while functional areas are examined by direct electrical stimulation and functional task to preserve brain function and maximize lesion resection. These methods provide a unique opportunity to know changes in the human brain network directly following brain injury, which could not be known in a healthy brain. If the brain is damaged by lesions, a “functional shift” can occur, in which brain functions dynamically move toward outside of lesioned area to maintain own functional constancy. Because of this functional shift, brain function is often normal despite the extension of the lesion into functional areas. Although patients experience loss of brain function, recovery remains possible. We found that the functional shift does not occur randomly, rather it occurs under a certain rule and condition. Here, I will present a study of functional brain networks and functional shifts in motor, language, visuospatial cognition, and other higher brain functions from the standpoint of rehabilitation medicine. I hope that this study will contribute not only to the progress of neuroscience but also to the quality of life of patients with brain tumor.

Mapping Functions on the White Matter

Michel Thiebaut de Schotten (CNRS and University of Bordeaux, France)

Significant strides have been made in delineating the white matter architecture in the living human brain in the last two decades. These pathways have been identified as pivotal in supporting cognitive functions, with their variability closely associated with differences in cognitive performance, psychiatric conditions, and neurological manifestations. This underscores a hypothesis that brain functionality is not isolated within regions but emerges from the interaction facilitated by white matter connections. In our presentation, we will unveil cutting-edge methodologies developed recently in our lab – namely, the functionnectome and emuse – to explore these emergent properties. We will discuss their implications for understanding complex neuroscientific phenomena, such as consciousness and neuropsychological recovery post-stroke. We aim to engage the Brain Structure and Function community in a dialogue that challenges prevailing paradigms and fosters new insights into the integrative nature of brain function.

Experience-dependent circuit development in the mouse visual cortex

Yumiko Yoshimura (Division of Visual Information Processing, National Institute for Physiological Sciences)

The shift of ocular dominance in the primary visual cortex following monocular deprivation has been studied intensively to elucidate the mechanisms of experience-dependent cortical development. It has been reported that ocular dominance plasticity during the critical periods occurs in layer 2-5 neurons of the mouse visual cortex. This study aimed to characterize the experience-dependent functional plasticity of layer 6b (L6b) neurons in the mouse primary visual cortex during the critical periods. Chronic two-photon Ca^{2+} imaging revealed that L6b neurons exhibited ocular dominance plasticity following monocular deprivation similar to other layer neurons. The ocular dominance shift to the open eye depended on the response strength to the stimulation of the eye to be deprived before starting monocular deprivation. L6b neurons showed broader tunings for orientation, direction, and spatial frequency than did layer 2/3 neurons. There were no significant differences in these visual response selectivities prior to monocular deprivation between the ocular dominance changed and unchanged L6b neuron groups. These results suggest that the plasticity can occur in L6b neurons showing any response features. In this symposium, we will discuss the properties and mechanisms of experience-dependent functional development in the postnatal visual cortex.

A connectivity correlate of visual perceptual asymmetries

Bradley Caron and Franco Pestilli (The University of Texas, Austin)

Visual performance and properties in humans are asymmetrically dependent on visual field location and persist across many aspects of human vision including visual acuity, contrast sensitivity, spatial resolution, and visual short-term memory to name a few. This manifests as better performance on visual behavioral tasks when responding to iso-eccentric locations along the horizontal axis as compared to the vertical axis (horizontal-vertical asymmetry), and when responding to iso-eccentric locations along the lower vertical meridian as compared to the upper vertical meridian (vertical-meridian asymmetry). In addition, structural morphometric and functional activation in visual regions during visual tasks show the same pattern of asymmetry. However, little is known regarding whether these asymmetries exist in the structural connectivity of the visual white matter using diffusion magnetic resonance imaging. Here we report the existence of the HVA and VMA in the structural connectivity of the human white matter of over 1500 participants. These asymmetries are not dependent on the morphometry of the visual areas nor influenced by the known gyral bias of diffusion tractography. They are also highly reliable across visual areas and participant demographics, including age. These findings are indicative of a natural hard-wiring of the visual white matter tuned to visual behavior asymmetries.

Exploring Neurovariability: Unraveling the Complexities of Brain Structure and Function

Stephanie Forkel (Donders Institute of Brain, Cognition and Behavior, Netherlands)

In this talk, I will explore the complexities of neurovariability and its influence on human cognition and behaviour. Integrating advanced neuroimaging techniques and pioneering research in lesion-symptom mapping. I will discuss the role of brain structure and connectivity in understanding neurological disorders and predicting clinical outcomes. My work, which intersects clinical neuropsychology with neuroscience, offers insights into individual differences in cognitive abilities and recovery processes, highlighting the significance of precision neuroscience in both research and clinical applications.

Comparative study on white matter pathway connecting dorsal and ventral visual cortex

Hiromasa Takemura[1,2,3)]

1) Division of Sensory and Cognitive Brain Mapping, Department of System Neuroscience, National Institute for Physiological Sciences, Okazaki, Japan
2) Graduate Institute for Advanced Studies, SOKENDAI, Hayama, Japan
3) Center for Information and Neural Networks (CiNet), Advanced ICT Research Institute, National Institute of Information and Communications Technology, Suita, Japan

Vision is a sensory system crucial for humans and animals, aiding survival and daily activities. Neuroscientists have long explored parallel processing streams in the dorsal and ventral visual cortex for spatial and categorical processing, respectively (Ungerleider and Mishkin 1982; Goodale and Milner 1992). Recent diffusion-weighted MRI (dMRI) studies in humans have renewed interest in the vertical occipital fasciculus (VOF), connecting these cortical regions (Yeatman et al., 2013; 2014; Takemura et al., 2016), although its functional significance remains unclear. This presentation describes investigations for the evolution of the VOF across mammalian species. Using dMRI, we compared VOF similarities and differences in humans and two representative non-human primates, rhesus macaque and common marmoset (Takemura et al., 2017; Kaneko et al., 2020). We also analyzed micrometer-resolution polarized light imaging (PLI) data to study the VOF in the vervet monkey brain (Takemura et al., 2020). Additionally, we analyzed dMRI data from various mammalian species, including primates, tree shrews, rodents, and carnivores. In all primate species examined, the VOF was identifiable, but not in non-primate species from the same superorder. These results suggest a significant expansion or emergence of the VOF in primates, likely influencing their unique visually guided spatial behaviors, including manual object manipulation, social interactions, and arboreal locomotion.

The dimensions of the brain connectome

Denis Le Bihan[1,2,3]

[1]NeuroSpin, Frédéric Joliot Institute for Life Sciences (Commissariat à l'Energie Atomique, CEA), Centre d'études de Saclay, Paris-Saclay University, Bâtiment 145, 91191 Gif-sur-Yvette, France

[2]Human Brain Research Center, Kyoto University, Kyoto, Japan

[3]Department of System Neuroscience, National Institutes for Physiological Sciences, Okazaki, Japan

There is an upper limit on the action potential propagation speed in the brain. Functional "distances" between neural nodes (geodesics), thus, depend on both the spatial distances between nodes and the time to propagate between them, through a connectome spacetime with four intricated dimensions, a view common to the relativity theory. Furthermore, propagation speed depends on axonal length: longer fibers carry faster speeds because they are surrounded by a thicker myelin sheath. The density of functional connections is known to decrease in patients in minimally conscious states, with the disappearance of the short (slow) connections to the benefit of long-range (fast) connections. This suggests that conscious activity must be associated to a slowdown of the overall propagation speed, in as similar way a gravitational field slows the speed of light according to general relativity. Neural nodes act as "masses" which, depending on their degree of activation, curve the connectome spacetime and the flow of action potentials (brainlines) around them. This curvature may be estimated from MRI, providing a quantitative signature of consciousness. Furthermore, a clue to bridge the apparent gap between the microscopic and macroscopic connectome scales may be found in the AdS/CFT correspondence. Applied to the relativistic brain connectome, this means that consciousness is the emergence in a 5D spacetime of the neural activity present as its boundaries, the 4D cortical spacetime. Consciousness would, thus, be a holographic 5D construction by our inner brain emerging from connections between events present at the surface of its material 4D connectome. In other words, the conflict between 'consciousness and matter' could be resolved by considering that the spacetime of our cerebral connectome has five dimensions, the fifth dimension allowing the natural, immaterial emergence of consciousness as a dual form of the 4D spacetime embedded in our material cerebral cortex.

Serotonin receptor-mediated modulation of excitatory transmission onto cholinergic neurons in the rat basal forebrain

Toshihiko Momiyama (Department of Pharmacology, Jikei University School of Medicine
Tokyo 105-8461, Japan)

Cholinergic neurons in the basal forebrain (BF) project to various brain regions and receive excitatory inputs, as well as receiving serotonergic fibers from the dorsal raphe nuclei. This study investigated serotonin (5-HT)-induced modulation of glutamatergic transmission onto BF cholinergic neurons using rat brain slice preparations. BF cholinergic neurons were identified with Cy3-192IgG. Excitatory postsynaptic currents (EPSCs) were evoked by focal stimulation. A 5-HT_{1A} receptor agonist or a 5-HT_{1B} receptor agonist inhibited the amplitude of EPSCs. The inhibition was antagonized in the presence of both 5-HT_{1A} and 5-HT_{1B} receptor antagonists. Paired-pulse ratio (PPR) and coefficient of variation (CV) of the EPSCs were increased by the 5-HT_{1B} receptor agonist, whereas the 5-HT_{1A} receptor agonist had no effect on PPR or CV. The 5-HT_{1A} receptor agonist inhibited the inward currents induced by puff application of L-glutamate, which were unaffected by the 5-HT_{1B} receptor agonist. The 5-HT_{1A} receptor agonist suppressed the amplitude of miniature EPSCs (mEPSCs) without affecting their frequency. The frequency of mEPSCs was decreased by the 5-HT_{1B} receptor agonist in more than half of the neurons examined, whereas the amplitude was unaffected. The 5-HT_{1A} receptor agonist or the 5-HT_{1B} receptor agonist alone inhibited the NMDA receptor-mediated currents. 5-HT-induced inhibition was smaller in the presence of ω-agatoxin TK (Aga), a P/Q-type C^{2+} channel blocker than that without Aga. Furthermore, the 5-HT_{1B} receptor agonist-induced inhibition of EPSCs was eliminated in the presence of Aga, whereas the 5-HT_{1A} receptor agonist still inhibited the EPSCs in the presence of Aga. These results suggest that activation of 5-HT_{1A} receptors reduces the sensitivity of postsynaptic glutamate receptors to glutamate, whereas activation 5-HT_{1B} receptors presynaptically inhibits glutamate release by blocking P/Q-type calcium channels.

Hierarchical Organization of the Forebrain Cholinergic System in Rat

Laszlo Zaborszky (Rutgers, The State University of New Jersey, Newark, NJ, USA)

The basal forebrain (BF) cholinergic system (BFCS) is a Janus-faced network, which can participate in both global (sleep-wake) and more selective functions like specific sensory perception. However, anatomical data are lacking on how this system is organized. Patients with Alzheimer's disease (AD) have a significant decrease of acetylcholine in the cerebral cortex and show pathological changes in cholinergic neurons in the BF.

Cholinergic neurons (n=7,400) were assessed in a common 3D reference coordinate space for spatial correlation from 73 rat brains with 107 retrograde tracer injections into various cortical targets. The correlation matrices revealed that the BFCS is organized into three principal networks: somatosensory-motor, auditory, and visual. Within each of these networks, clusters of cholinergic cells with increasing complexity innervate cortical targets. These networks represent hierarchically organized building blocks that may enable the BFCS to coordinate spatially selective signaling, including parallel modulation of multiple functionally interconnected yet diverse groups of cortical areas. This is a novel working hypothesis, challenging ideas that cholinergic projections are part of diffuse modulatory systems that affect globally cortical regions. Our data provide a unified conceptual framework of a hierarchically organized network of nodes to furnish testing of various functional hypotheses.

Evidence suggests that degeneration of BF neurons may precede, predict, and even potentiate cortical degeneration (Schmitz and Zaborszky, 2021). Using canonical correlation analysis of ADNI patients, our preliminary analysis shows that only a subgroup of patients has serious memory symptoms, but another group of persons who were also diagnosed with AD, showed better than average memory tests, but poor language symptoms (Ardekani and Zaborszky, 2022, AAIC Abstract). In the light of results in rodents, it would be important to re-investigate the pathology affecting the human BF, if progression of degeneration in the BF follow a trend that may be surmised from a hierarchic organization of the cholinergic system.