Centrioles and Cilia in Health and Brain Disease

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Abstract

The centriole is an essential component of the centrosome, which is required for the formation of the mitotic spindle, cilia, and flagella. Centriole duplication involves the growth of a procentriole (daughter centriole) from an existing centriole (mother centriole). During the past years, my laboratory has reported several key proteins, including CPAP (Nat Cell Biol 2009, Cell Rep 2016, J Cell Sci 2020, Front Cell Dev Biol 2022), STIL (EMBO J 2011), CEP135 (EMBO J 2013), CEP120 (J Cell Biol 2013, Sci Rep 2019, Genes & Development 2021), RTTN (Nat Commun 2017), and Myosin-Va (Nat Cell Biol 2019) that participate in centriole duplication and cilia formation. Primary microcephaly (MCPH) is a neurodevelopmental disorder characterized by small brain size with mild to severe intellectual disability, while Joubert syndrome is a hereditary autosomal-recessive ciliopathy, which exhibitscerebellum-brain stem malformation. Interestingly, mutations in many centriolar protein-encoding genes were reported to cause MCPH and Joubert syndrome,but their underlining mechanisms remain incomplete understood. To study the physiological roles of centriolar proteins in brain development and their pathological linkage with neurodevelopmental disorders, we have generated both microcephaly Cpapgene conditional knockout mice and Cpap-E1241Vknockin mice that phenocopy human microcephaly patients. We also used human iPS-derived brain organoidscarrying CPAP-E1235V disease-associated mutant protein and in vivo cerebellar electroporation to study neuronal cell proliferation and differentiation in MCPH and Joubert syndrome. The results from these promising experimental models for brain development and phenotypic features ofprimary microcephaly and Joubert syndromein humans will be discussed.and the mechanistic insight learned from our studies will be presented.

Selected recent publications:

1. Lin YN, Wu CT, Lin YC, Hsu WB, Tang CJC, Chang CW, Tang TK (2013) CEP120 interacts with CPAP and positively regulates centriole elongation. J. Cell Biol.202, 211-219.

2. Chen HY, Wu CT, Tang CJC, Lin YN, Wang WJ, Tang TK (2017) Human microcephaly protein RTTN interacts with STIL and is required to build full-length centrioles. Nat. Commun. 2017, 8:247.

3. Wu CT, Chen HY, Tang TK (2018) Myosin-Va is required for preciliary vesicle transportation to the mother centriole during ciliogenesis. Nat. Cell Biol. 20, 175–185.

4. Chang CH, Chen TY, Lu IL, Li RB, Tsai JJ, Lin PY, Tang TK (2021) CEP120-mediated KIAA0753 recruitmentonto centrioles is required for timelyneuronal differentiation and germinal zoneexit in the developing cerebellum. Genes & Development. 35:1445–1460.

5. An HL, Kuo HC, Tang TK (2022) Modeling human primary microcephaly with hiPSC-derived brain organoids carryingCPAP-E1235V disease-associated mutant protein. Front Cell Dev Biol. 10:830432.

Transient activation of Npas1 neurons recreates ensemble bursting in the basal forebrain

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Abstract

Recent studies from our group have shown that reward-predicting stimuli robustly activate a special subset of basal forebrain (BF) neurons, which are referred to as BF bursting neurons. BF bursting neurons are important for behavior because their responses are strongly associated with improved performance and faster decision speeds toward the reward-predicting stimuli. A central feature of BF bursting neurons is their highly synchronized excitatory responses to reward-predicting stimuli, creating BF ensemble bursting responses. Such BF ensemble bursting responses are robust irrespective of sensory modality of the stimulus. These observations highlight the importance for understanding how the BF ensemble bursting is generated, which will allow us to recreate the BF ensemble bursting response and test its causal role in modulating behaviors. Here we show that transient optogenetic activations in a subset of Npas1 BF neurons recreated the ensemble bursting response and improved behavioral performance in an auditory detection task. Based on BF single cell transcriptomics, we first identified Npas1 as a novel candidate marker for BF bursting neurons, which labels a special subset of GABAergic BF neurons. Brief optogenetic activation of Npas1 neurons elicited a BF ensemble bursting response after a short delay (30-40 msec latency). This Npas1-induced BF ensemble bursting selectively involved all BF bursting neurons in both hemispheres even when the optogenetic stimulation was unilaterally delivered. Furthermore, The bursting response amplitude in individual BF bursting neurons induced by Npas1 optogenetic stimulation was positively correlated with their response amplitude to reward-predicting stimuli. These properties of Npas1-induced BF ensemble bursting resemble the endogenous BF ensemble bursting responses elicited by reward-predicting stimuli. At the behavioral level, optogenetic activation of Npas1 neurons increased correct response probabilities and decision speeds in an auditory detection task, while their optogenetic inhibition had the opposite effects. Finally, the Npas1-induced BF ensemble bursting was completely abolished under anesthesia, suggesting that the delayed ensemble bursting response likely involved other brain regions. These results begin to reveal the circuit mechanisms in the BF that transform an excitatory input targeting a subset of Npas1 neurons into an BF ensemble bursting response, and establish its causal role in improving behavioral performance.

Decoding the focus of cross-modal selective attention in single trials via neuronal activity in the basal forebrain

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Abstract

Animals and humans have the ability to selectively focus their attention on one sensory modality while ignoring other irrelevant ones. This form of attention, referred to as cross-modal selective attention, is poorly understood because of the covert nature of attentional shift, and therefore the focus of attended sensory modality cannot be easily determined at any given moment. This makes it difficult to study cross-modal selective attention at the behavioral level as well as its implementations at the neural circuit level. Here we address this issue at both behavioral and neural activity levels to pinpoint the focus of cross-modal selective attention in single trials. At the behavioral level, we developed a novel behavioral task for rats that provided a clear readout of animals' attention focus. In this new cross-modal oddball task, auditory and visual stimuli were presented simultaneously once every two seconds. In each trial block, oddball targets in one of the two sensory modalities were task-relevant and predicted reward in either the left (auditory) or the right (visual) reward port. Behavioral responses toward the same multi-sensory stimulus were robustly different depending on the relevant modality in that trial block, and the behavioral response patterns rapidly switched across trial blocks. At the neuronal level, we showed that the activity of a special subset of neurons in the basal forebrain (BF), referred to as BF bursting neurons, can be used to decode animals' attention focus. BF bursting neurons preferentially responded to the oddball target in the attended sensory modality, while ignoring the same stimulus when the modality was not the focus of attention. Shifts of attention between auditory and visual modalities were also associated with significant shifts in BF response latencies. Moreover, shifts in BF neuronal activity were rapid and tightly coupled with behavioral switching at the trial block transitions. Such coordinated behavioral and BF activity shifts were also observed during occasional spontaneous shifts of attention initiated by the animal. Together, these results establish a new approach to study cross-modal selective attention and their dynamic shifts with fine temporal resolution. These results also highlight the important role of BF bursting neurons in cross-modal selective attention, which likely exert their influences through amplifying information processing in the prefrontal cortex.

Inhibitory Control of the Thalamic Reticular Nucleus by the Basal Forebrain

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Abstract

Thalamus is the central gatekeeper that controls the flow of information to the cerebral cortex. Activity in the thalamus, in turn, is controlled by a sheet of GABAergic neurons surrounding the thalamus, called the thalamic reticular nucleus (TRN). Because of its critical strategic position, the TRN has been implicated to play a key role in selective attention. Understanding how the TRN activity is controlled is therefore of great importance. A major input to the TRN comes from the basal forebrain (BF). However, the neurochemical identity and behavioral function of the BF-TRN projection has remained unclear. By combining cell-type specific viral tracing, slice physiology and in vivo multi-electrode recording across multiple brain regions in behaving rodents, here we describe a novel inhibitory control mechanism of the anterior TRN (aTRN) by BF Npr3 neurons. We first identified Npr3 as a novel marker for a subset of BF GABAergic neurons based on single cell RNA sequencing database. Anatomical characterization of BF Npr3 neurons' projection patterns revealed specific and dense innervations to the aTRN and the prefrontal cortex (PFC). Consistent with their GABAergic identity, optogenetic activations of BF Npr3 axon terminals in brain slices elicited strong inhibitory postsynaptic currents in aTRN neurons. To further determine the behavioral significance of this BF-aTRN projection, we simultaneously recorded neuronal activities of BF, aTRN and PFC in vivo. The activity of a subset of BF neurons, referred to as BF bursting neurons, was strongly coupled with local field potential (LFP) responses specifically in the aTRN in single trials, both in terms of amplitude and timing. Moreover, both the aTRN and BF bursting neurons responded to sensory stimuli that predicted reward, irrespective of their sensory modalities. Finally, aTRN and BF responses were both coupled with EEG responses in the PFC. Together, these results establish BF Npr3 neurons as a novel inhibitory control mechanism of the aTRN, which is engaged when animals attend to reward-predicting stimuli. This novel BF(Npr3)-TRN pathway may serve as an attention mechanism to enhance thalamocortical processing of reward-predicting stimuli through a disinhibition mechanism.

The subthreshold basis of spike synchrony between hippocampal parvalbumin interneurons

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Abstract

Inhibition is important for neural network functions. It can balance excitatory inputs and control the spiking outputs of downstream neurons. Furthermore, inhibition can even generate network oscillations critical for many cognitive functions. Inhibition in cortical areas is mediated by a small population of inhibitory interneurons. These neurons often coordinate the timing of their action potentials to produce precise inhibition of the network. One of the most striking examples of such coordination is the synchronous activity of parvalbumin (PV)-expressing interneurons, in which the action potentials of one neuron occur within just a few milliseconds from those of other cells. Such a precise synchrony is considered essential for the function of PV cells. However, how PV cells produce synchronous activity in vivo remains unclear. Several synaptic mechanisms have been proposed. For example, PV cells are coupled by gap junctions, which conduct action potentials into fast spikelets to facilitate synchrony. PV cells also share excitation from upstream excitatory neurons, which could drive their synchronous activity. Finally, PV cells are known to inhibit each other. This reciprocal inhibition has also been shown to transform irregular activity into synchronous network oscillations. To understand which of these mechanisms dominates the synchrony between PV cells in vivo, we simultaneously monitored membrane potentials in multiple PV cells using voltage imaging. This allows us to correlate the synchrony between pairs of PV cells with subthreshold signatures that provide information about the synaptic interaction between cells. We found that although a large fraction of the spikes in the PV cells occurred synchronously, there were also many spikes that occurred in isolation. Around these spikes, the membrane potentials of other PV cells showed slow depolarization. This ‘co-depolarization’ is not consistent with a dominant contribution of mutual inhibitory between PV cells. Furthermore, the slow kinetics of co-depolarization is also inconsistent with the dominant contribution of gap junctions, which produce a much faster ‘spikelet’ signal. Moreover, the amplitudes of these co-depolarizations correlate with the strength of synchrony between PV cells. Together, these results suggest that co-depolarization, possibly reflecting shared excitation, plays a dominant role in driving synchrony between PV cells in vivo.

γ-TuRC regulates neuronal migration during embryonic cortical

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Abstract

The γ-tubulin ring complex (γ-TuRC) is a multi-subunit protein complex composed of γ-tubulin and γ-tubulin complex proteins (GCPs). γ-TuRC promotes microtubule assembly by serving as a template that allows efficient nucleation and elongation of α/β-tubulins into microtubule filaments, thus playing a crucial role in various cellular processes including cell division, cell differentiation, cell polarization and cell migration. Recent studies revealed that mutations in the tubulin superfamily lead to cortical dysgenesis with a wide spectrum of neurodevelopmental defects, collectively termed tubulinopathies. In particular, mutations in the γ-TuRC core subunit γ-tubulin and its activator Cdk5Rap2 cause brain developmental disorders known as malformations of cortical development (MCD). However, it remains elusive how γ-TuRC regulates cerebral cortex formation during embryonic brain development. In this study, we set out to systematically dissect the roles of γ-TuRC in this process and illuminate the molecular mechanisms underlying clinical deficits using mouse model. Our preliminary data indicate that knockdown of individual γ-TuRC subunits by in utero electroporation severely delays neuronal migration in developing brain. In particular, GCP2-knockdown cells are stalled at the intermediate zone. Surprisingly, loss of GCP2 neither affects progenitor proliferation nor induces neuronal cell death. Rather interestingly, they fail to differentiate into the neuronal lineage. Furthermore, using live brain-slice imaging, we found that GCP2 knockdown compromises neuronal radial migration. These findings suggest that GCP2 is indispensable for establishing neuronal polarity that guides neuronal maturation and migration during cortical development.

The Role of ASIC Channels in the Response of N2a Cells to the Micropipette Guided Ultrasound Stimulation

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Abstract

Lines of compelling evidence have shown that low-intensity focused ultrasound has the capability of neuromodulation modality with exquisite spatial specificity and depth penetration. Although low-intensity focused ultrasound holds great promise as a novel approach to the potential clinical applications of neuron stimulation, the underlying mechanism at the cellular and molecular level remain unclear. In this study, we utilized a device of micropipette-guided ultrasound to dissect the involved channels in ultrasound-induced activation of somatosensory neurons and neuroblastoma N2a cells. The glass micropipette with an end-closed tip is a developed wave-guide device to transport the force of ultrasound. Ultrasound from the tip generates two forms of force: one is the acoustic pressure into cell solution with radiation force exerting on cells placed along its path, and the other is the streaming flow applying shear force on cells. These two force modalities could be fine-tuned by the input voltage and the duty factor. Our results demonstrated streaming force dominantly modulate intracellular calcium concentration. By pharmacological approaches through ASICs inhibitors and mechanosensitive channel blockers, ASIC1a has been identified as a vital mechanosensitive channel to mediate low-intensity ultrasound-induced activation of N2a and dorsal root ganglion cells. We also found the response to ultrasound is extracellular matrix dependent, suggesting the tethering model of mechanogating may be involved.

Genetically encoded tools applying in iPSC derived neurons and astrocytes for phenotypic/functional screening

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Abstract

Neurodegenerative disease or neurodegeneration caused by cognitive disturbance, progressive loss of functional neurons affects cognition, function, and behavior. Age-related dementia Alzheimer's Disease (AD) is among the most popular neurodegenerative disease that affect millions of people worldwide. It is an urgent need to identify effective drugs for prevention and treatment. However, majority of failure clinical trials for AD drug development is due to the lack of suitable models. Availability of primary mature neurons, on the other hand, is limited and insufficient, thus hinders application of human primary cell-based disease modelling in the study of AD. Disease-based human induced pluripotent stem cells (hiPSCs) provides a great hope for being used as "Clinical Trial on a Dish" Model for high throughput drug screening and testing. LumiSTAR has established "Clinical Trial on a Dish"-based iPSC technology generated either from blood samples of AD patients or through genetic editing by Crispr/Cas9. Using AD based iPSC model as an example, we demonstrated that AD iPSC -derived cortical neurons and -derived astrocytes recapture human disease phenotypes based on morphological analysis, ROS level, calcium activity and accumulation of Aβ42/Aβ40 ratio. Moreover, we can observe impaired mitochondrial morphology and dynamic in AD astrocytes when compared with healthy control. Finally, multi-parametric assessments using combinations of spectral and calcium affinity indicator variants (mNG-GECO, mtLAR-GECO, er-LAREX-GECO or Orai1-K-GECO) are restricted to different cellular compartments are also demonstrated in the cells.

The efficient induction of human retinal ganglion-like cells provides a platform for studying optic neuropathies

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Abstract

Retinal ganglion cells (RGCs) are essential for vision perception. In mammals, RGCs and their optic nerve axons undergo neurodegeneration and loss when glaucoma and other optic neuropathies are present; this can result in irreversible vision loss. Here we developed a rapid protocol for directly inducing RGC differentiation from human induced pluripotent stem cells (iPSCs) by the overexpression of ATOH7, BRN3B and SOX4. The hiPSC-derived RGC-like cells (iRGCs) show robust expression of various RGC-specific markers, such as BRN3A, EBF1, ISL1 and RBPMS. A functional assessment was also carried out and this demonstrated that these iRGCs display stimulus-induced neuronal activity, as well as spontaneous neuronal activity. Ethambutol (EMB), an effective first-line antituberculosis agent, is known to cause serious visual impairment and irreversible vision loss due to the RGC degeneration in a significant number of treated patients. Using our iRGCs, EMB was found to induce significant dose-dependent and time-dependent increases in cell death and neurite degeneration. Western blot analysis revealed that the expression levels of p62 and LC3-II were upregulated, and further investigations revealed that EMB caused a blockade of lysosome-autophagosome fusion; this indicates that impairment of autophagic flux is one of the adverse effects of that EMB has on iRGCs. In addition, EMB was found to elevate intracellular reactive oxygen species (ROS) levels increasing apoptotic cell death. This could be partially rescued by the co-treatment with the ROS scavenger NAC. Taken together, our findings suggest that this iRGC model, which achieves both high yield and high purity, is suitable for investigating optic neuropathies, as well as being useful when searching for potential drugs for therapeutic treatment and/or disease prevention.

Toward a novel strategy for optogenetic control of synaptic transmission

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Abstract

Optogenetics is an evolutionary technology for precise control of biological functions. With genetic and optical manipulations, we can modulate the neuron of interest with high spatial and temporal resolution. To date, optical control of neurotransmission, the fundamental process of neuronal communications, has mainly been achieved through light-sensitive neurotransmitter receptors. However, this approach may have constrained applicability because it heavily relies on the use of knock-in animals that carry the genetically-modified receptors. Here we explore a novel strategy to enable optogenetic control of native GABAA receptors, the major mediator of inhibitory transmission in the nervous system. We engineer a series of “Loading Dock” (LD) proteins for recruiting photoswitchable tethered ligands (PTLs) onto the neuronal surface, thereby enabling optical control of local GABAA receptors. By incorporating a specialized intracellular motif, we are able to enrich the LD protein at the inhibitory synapses. Moreover, we strategically tune the LD’s binding affinity to the postsynaptic scaffold, allowing it to enrich at inhibitory synapses without causing apparent electrophysiological perturbations. As synaptic and extrasynaptic GABAA receptors mediate distinct forms of neuronal inhibition (phasic and tonic, respectively), this approach may allow specific manipulations of endogenous phasic inhibition. To employ the tools in vivo, we generate bicistronic adeno-associated viruses (AAVs) that encode the LD genes with a fluorescent expression marker. We deliver the AAVs via neonatal injection and observe the punctate distribution of the LDs in the mouse neocortex, hippocampus, and cerebellum. In-depth characterizations are currently underway to verify the LD’s synaptic localization in vivo. Concurrently, we are developing LD-reactive photoswitchable antagonists for GABAA receptors. We expect that the LD-PTL toolkits will allow neuroscientists to control native GABAergic activities with high versatility and precision.

ExBrainable: An Open-Source GUI for EEG Decoding and Model Interpretation Based on Explainable Neural Networks

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Abstract

Recently, convolutional neural networks (CNN) are used to decode various types of electroencephalographic (EEG) sig- nals and have achieved improvement in the decoding accuracy. Yet, what CNN models learn from the EEG data remains unclear due to the lack of interpretability of models. In response to the need to explainable modeling tools for EEG data analysis, we introduce an open, compact, and easy- to-use tool for investigators in brain/neuroscience research to leverage the cutting-edge computational algorithms and functions for CNN-based EEG decoding and model interpretation. We have developed a graphic user interface (GUI), ExBrainable, dedicated to modeling, decoding, and visualization of electroencephalography (EEG) data based on explainable neural network models. Available functions include model training, evaluation, and parameter visualization. Demonstration on motor-imagery EEG data exhibits the spatial and temporal representations of EEG patterns associated with existing knowledge of neuroscience. As a growing open-source platform, ExBrainable offers fast, simplified, and user-friendly analysis of EEG data using cutting-edge computational approaches for brain/neuroscience research.

Nonlinear Dendritic Activity Drives Hippocampal Place-Field Forming Plasticity as A Function of Synaptic Input Dynamics And State

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Abstract

To achieve goals, it is a challenge for the animal's neural circuits to encode spatial and non-spatial features of the environments. Place cells in the hippocampus acquire these properties through experience. However, the mechanisms and algorithms of synaptic plasticity rules underlying place-field formation remain a fundamental problem. In light of in-vivo electrophysiology during mouse navigation behavior, we systematically investigated the properties of plasticity induction driven by dendritic calcium (Ca2+) plateau potentials. In acute hippocampal CA1 slices, an associative long-term potentiation (LTP) can be triggered by Ca2+ plateaus 1–2 seconds away from the to-be-potentiated synapses－recapturing the hallmark characteristics of the plasticity that rapidly produces place fields in vivo. Here, using patch-clamp recording in vitro, we found that presynaptic input frequency, existing synaptic weight, and temporal relationship of the presynaptic and postsynaptic activations jointly determined the magnitude and polarity of such behavioral timescale plasticity in CA1 pyramidal neurons. Interestingly, this is consistent with a latest theoretical prediction made by fitting in-vivo electrophysiological data to a hypothetical model. We posit that these mechanisms play an essential role in determining the transfer of spatial information to the CA1 in response to physiological dynamics of the upstream area. We attempt to analyze this possibility, in relation to changing rewards, using modeling techniques.

Investigation of the heterogeneity of calcium activity in the motor cortical and the striatal astrocytes

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Abstract

Astrocytic calcium signaling regulates the neuronal activity and various physiological functions. Aberrant astrocytic calcium signaling reduces motor function and is highly associated with movement disorders, such as Huntington's disease. This suggests that astrocytic calcium signaling plays a crucial role in the motor circuits. However, a comprehensive study of the properties of the astrocytic calcium activity in the motor circuit is still missing. Whether the astrocytic calcium activity exhibits regional heterogeneity, especially in the different layers of the primary motor cortex (M1) and the striatum, remains elusive. Here we monitored the astrocytic morphology and calcium activity in the layer 1, 2/3, 5, and 6 of the M1 (L1, L2/3, L5, and L6) and the striatum in acute brain slices of transgenic mice (Aldh1l1-CreERT2::lck-GCaMP6f or Aldh1l1-CreERT2::Salsa6f), in which the astrocytes express membrane-tethered GCaMP6f or GCaMP6f/tdTomato fusion proteins in an inducible manner. We used state-of-the-art software, Astrocyte Quantification and Analysis (AQuA), to conduct calcium event-based analysis and found that astrocytes show heterogeneity in both their morphology and calcium activity. The L1 astrocytes are comparatively smaller in their territory size but exhibit significantly higher calcium event frequency density than other regions. This is correlated with a higher immunostaining level of glial fibrillary acidic protein (GFAP), a marker for reactive astrocytes, in the L1. On the other hand, the L2/3 and the L5 astrocytes occupy a larger territory, and their processes often surround the neuronal somas. Furthermore, consistent with our previous findings, the calcium events are highly confined in fine local processes in all observed astrocytes. The L1, L2/3, and L5 astrocytic calcium events have a higher probability of spreading to the whole cell, whereas events in L6 and striatal astrocytes are restricted in propagation. In summary, our work provides a complete picture of the astrocytic morphology and calcium activity in the M1 and the striatum. This region-specific heterogeneity in astrocytic calcium activity might correlate directly to their diverse morphology, differential interaction with neuronal counterparts, and physiological functions.

Common Topological Properties and Self-similarity Shared by Neurons with Diverse Morphology in Drosophila melanogaster

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Abstract

Neuronal morphology directly influences the arrangement of synaptic inputs, outputs, intrinsic electrical properties, and, consequently, the computation performed by a neuron. Because of the extreme diversity of fruit fly's neuronal morphology, it is unclear whether the neurons share any morphological similarity with implies common computational characteristics. Thus, we aim to identify the structural patterns that are shared across diversified neurons and discover the existence of a universal building block of neurons. We analyze neuronal skeleton data from FlyCircuit and FlyEM databases using metrics including topological networks, branch lengths, and branch angles. To study the local bifurcating structures, we used the Balance Ratio to calculate the local symmetrical property within a neuron. We classified neurons with their structural levels evaluated by the Strahler Order System, which represents the symmetrical property and complexity in a whole neuron picture. This classification is found related to other neuronal properties including branch lengths, branching distribution, and fractals characteristics. This result reveals a crucial and interesting observation: even widely complex and diverse neurons share topological features which further imply a widely adapted neuronal computational principle. Finally, we aim to bridge the gap between our understanding of the neuronal structures and their computational abilities by studying how the fundamental features of a neuron's branching structure influence its ability to process diverse patterns of synaptic inputs. Our analysis suggests that the topological features of neurons in Drosophila represent balance between spatial and temporal signal processing.

Construction of forebrain projectome in adult zebrafish

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Abstract

Zebrafish has a nervous system that contains up to 10^7 neurons, an order of magnitude less than that in mice, and is an ideal system to study the neuronal projections, i.e. the projectome, throughout the brain. Previous studies focused on zebrafish larvae, which is small and transparent but exhibits limited cognitive functions. On the other hand, adult zebrafish has a fully developed brain which supports various cognitive functions such as associative learning and social behaviors. Here we developed a protocol for mapping the projections of sparsely labeled, cell type-specific neurons in adult zebrafish forebrain. We focused our investigation on glutamatergic and GABAergic neurons and injected plasmids encoding UAS: tdTomato-CAAX in the following transgenic lines: Tg[vglut1:gal4], Tg[vglut2a:gal4], and Tg[gad1b:gal4], all in the background of UAS:GFP. After removing a small piece of the skull at desired locations, plasmids were injected into the brain and electroporation was performed. By controlling the volume and concentration of plasmid injection, a sparse labeling of less than 30 neurons per animal can be achieved. 5 days after the injection, brain clearing was performed using a CUBIC protocol optimized for zebrafish. Then the entire forebrain was imaged using a confocal microscope to reveal the morphology of individual neurons expressing tdTomato. The neuronal projections were traced using a semi-automatic software to extract the 3-dimentional coordinates of the neurites. To combine data from different animals, we performed linear registrations on the contour of the brains and used the transformation matrix to pool the projectome data from different animals into a reference brain. Using this protocol, we aim to perform a comprehensive mapping of cell-typed specific neuronal projections throughout the forebrain in adult zebrafish. This structural investigation lays the basis for functional analysis of the forebrain in a small vertebrate model of cognitive functions.

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HIGH-RESOLUTION FUNCTIONAL MAPPING OF FOREBRAIN ACTIVITY IN BEHAVING ZEBRAFISH

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Abstract

The forebrain controls cognitive functions, emotions, hormone release, biological cycles and voluntary body movements. In the past, investigation of forebrain functions have been hampered by the difficulties to monitor a large portion of neurons in the brain at high resolution during behavior. In recent years, the zebrafish has become a popular animal model to study behavior and brain functions due to its small brain for optical recording of activities and dense reconstruction of neuronal circuits. Unlike the larval zebrafish, the adult zebrafish exhibit diverse social behaviors, including aggression, mating, shoaling and schooling. However, high-resolution activity measurements and functional mapping of the forebrain are still lacking in adult zebrafish. Here, we recorded movements of the tail, eyes and gills of a head-restrained adult zebrafish using a custom-built behavioral recording system and analysis pipeline. Simultaneously, the forebrain activity was non-invasively measured using two-photon calcium imaging in animals expressing GCaMP6f pan-neuronally. Currently, we are able to record ~200 neurons across 30% of forebrain in depth (200 μm) at a volume rate of 5Hz by using a resonant scanner and a piezo-controlled objective lens. First, we found that the movements of the eyes and the tail are highly correlated. Neurons in the forebrain region Dc (potential homologs of the isocortex) often exhibit positive or negative correlations to the eye and tail movements. On the other hand, a subset of neurons in Dl (potential homolog of hippocampus) exhibit activities that specifically correlate to the eye movements. In addition, neurons in the forebrain region Dm (homologous to the basolateral amygdala) tend to become active while the animal stopped moving. We are currently classifying and mapping these behavior-related neurons and other types of neurons across dorsal forebrain regions. This investigation of neuronal population activity could be combined with neuronal projectome data to establish the foundation for studying forebrain functions in a small vertebrate model.

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Large-scale and automated construction of multi-compartmental models for neurons in the FlyCircuit database

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Abstract

Understanding the functions of neural circuits is one of the most important topics in systems neuroscience. To study the detailed neural network functions at the whole-brain level, we propose to construct detailed computational models for each neuron in the FlyCircuit database, one of the largest neuronal imaging databases for Drosophila melanogaster. The proposed project can be divided into four phases. We first collaborate with the Brain Research Center at National Tsing Hua University and obtain detailed electrophysiological and neuronal structure information for several sample neurons. Second, we create multi-compartmental models for these neurons using the open-source NEURON simulator and use the SSO (simplified swarm optimization) algorithm for parameter search in order to find parameters that accurately reproduce the passive (subthreshold) properties of the neurons. We also add active zones (action-potential initiation sites) on the axon initial segments based on observations made in the Brain Research Center. Third, we will derive a set of algorithms that can translate the morphology of neurons into model parameters based on what we learned from modeling the sample neurons. Finally, we will create multi-compartment models for each neuron in the database using the algorithms and release the models in the FlyCircuit database. In this presentation we will describe our progress on the first two phases of the project.

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Hybrid network architecture of memory center in the Drosophila brain

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Abstract

Bio-signal encoding mechanisms are heavily determined by the architecture of underlying neural circuits. Mushroom body (MB) is the olfaction memory center of Drosophila. Previous studies support opposite perspectives to the upstream organization of MB, that is, completely random or stereotypic, based on experimental evidence of the connectivity at the mesoscopic level. Here we identify the hybrid network structure of Drosophila calyx that three Kenyon cell (KC) classes leverage different levels of input expansion by maintaining the spatial map across the olfactory system. We construct a simulation model of the MB tuning profile by integrating the response pattern of the receptor neurons with the connectome of olfactory system The model successfully predicts the odor-evoked activity of MB in the lobe region. The hybrid structure differentiates the chemical sensitivity of KCs and likely determines the innate tuning features of MB output neurons. Our results provide insights into the computational benefit of a calyceal hybrid network for translating molecular signals into higher-order perception.

Inhibition and stability in head-direction neural circuits

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Abstract

Navigation of insects is supported by the central complex which consists of extremely complex neural circuits. Previous studies of Drosophila central complex reported that the head-direction, essential information for navigation, is encoded by localized activity (termed activity bump) in two subregions, the ellipsoid body (EB) and the protocerebral bridge (PB). Moreover, detailed connectomic analysis of EB and PB revealed that they form attractor circuits, a network architecture that can support activity bumps based on theories of neural networks. These theories further suggest that feedback inhibition is crucial for the stability of activity bumps. However, several different sets of inhibitory neurons innervate the EB-PB circuits, their roles and relative contributions to the bump stabilization is still not fully understood. To address this issue, we constructed and systematically investigated several variants of biologically realistic neural circuit models based on the recently published EM (electronic microscopy) connectomic data. The circuit models share the basic EB-PB recurrent circuits, which maintain and update the active bump. The differences are the inhibitory mechanism, which is either by ring neurons (ER1) or by delta 7 neurons, and the connectomic databases the models based on. We further analyzed the differences in ring neuron and delta 7 neuron in different conditions. First, we tested the robustness of each model by scanning the available parameter in a large range. Second, we tested the maximum rotational speed that can be supported by the models. Last, we tested how multiple visual stimuli affect bump formation. Our study showed that the models using ring neurons as the inhibitory mechanism provides the best stability and robustness over other variants of models.

The Dynamical System and Application of Recurrent Neural Network

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Abstract

Recent development in connectomic research has enabled us to study complex neural circuit structures at the single-neuron levels. One of the most common features founds in almost all species under investigation is the motifs of recurrent connections at the micro-circuit levels. We hypothesize that these types of motifs may hold the key to the flexibility and multi-functionality of neural networks. To demonstrate how recurrent circuits work, we propose the Coupled Recurrent Inhibitatory and Recurrent Excitatory Loops (CRIRELs), which preserve the key features of the commonly observed neural motifs. CRIRELs contain two excitatory neurons and two inhibitory neurons. We found that by changing the biases of neurons, CRIRELs can perform different logic-gate-like functions. In the present study, we further explore the dynamics of CRIRELs. To analyze it mathematically, we replace the leaky integrate-and-fire model with the firing-rate model. Next, we use semi-analytical methods to study the detailed dynamics and bifurcation structure of CRIRELs. This analysis allows us to explain how we can rapidly switch CRIRELs between different functions simply by changing bias inputs. Finally, we found that such an “on-line” function switch has enormous applications in neuromorphic engineering. We demonstrate it by creating an “adder” using CRIRELs. Instead of using four logic gates as in the classical 1-bit full adder, using CRIRELs, we need only two gates. One gate acts as the carry-out and toggle between AND and OR gates, while the other gate acts as summation and toggle between XOR and XNOR gates. Add an excitatory neuron to the CRIRELs so that the loops can switch between the two logic-like functions in the same connection weight. Therefore, the new network can perform a full adder. This 1-bit full adder can be scaled up by connecting multiple adders in series to form a ripple-carry adder. By studying the dynamics of CRIRELs, we gain more insights into the multifunctionality of neural circuits. Moreover, our results show that CRIRELs have great potential in neuromorphic engineering as they can be used to create the lightweight and multifunctional artificial neural networks.

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Decision Making : Dynamical phase transition of meta-neurons

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Abstract

Meta-neurons are neuronal populations with internal synaptic connections, yet still can be captured by appropriate effective neuron models. Here we show that a meta-neuron undergoes a dynamical phase transition as internal synaptic connections strengthen. Similar to the magnetic phase transition for the spin systems, the synaptic strength connecting neurons plays the role as the exchange coupling between spins, while the external current stimulus mimics the magnetic field. It is rather remarkable the phase boundary of the transitions can be derived from the Legendre transform of the gain function relating the neuronal activity and the external stimulus. Despite its apparent similarity to the thermal phase transition, the dynamical phase transition includes competitions between all local minima and exhibits rich temporal evolutions, vital for information processing between neurons.

Proteomic and Transcriptomic Analysis of Gria3 Mutant Mice Suggests Dysregulation of Neuronal Pentraxins in Schizophrenia

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Abstract

The exact causes of schizophrenia, a chronic mental disorder mainly characterized by psychotic symptoms, are still unclear. Gria3 encodes AMPA glutamate receptor subunit 3 and has been found to be associated with schizophrenia. The mechanisms underlying Gria3 mutation contributes to schizophrenia progression remain little known. Here, we examined synaptosome proteomics of the cortex of the mice with a Gria3 mutation identified by the SCHEMA (SCHizophrenia Exome Meta-Analysis) project. We found downregulation of neuronal pentraxin (Nptx) 1 and 2 in the 1-month-old mutant mice. Transcriptome analysis on the somatosensory cortex also showed significantly decreased expression of Nptx2. Similarly, 3-month-old mutant mice have reduced expression of Nptx1 and 2. Our proteomic and transcriptomic analyses indicate Nptxs dysregulation in the brain of Gria3 mutant mice. Recent studies found that NPTXs were reduced in cerebrospinal fluid of individuals with schizophrenia and could activate the classical complement cascade. Our synaptosome proteomics showed significant downregulation of C1qa, b, and c levels in the 3-month-old mice, suggesting that Gria3 mutation might affect complement pathways in the brain. Overall, our study highlights a role of Nptx-complement signaling in the pathology of schizophrenia.

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CPEB3-downregulated Nr3c1 mRNA translation confers resilience to developing PTSD-like behavior in fear-conditioned mice

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Abstract

Posttraumatic stress disorder (PTSD) is a trauma-induced psychiatric disorder, which depends on not only the intensity of trauma but also genetic risk factors; the latter may result in enhanced fear memory formation and/or impaired fear extinction after exposure to trauma reminders. Susceptibility or resilience to PTSD depends on one's ability to appropriately adjust synaptic plasticity for coping with the traumatic experience. Activity-regulated mRNA translation synthesizes plasticity-related proteins to support long-term synaptic changes and memory. Hence, cytoplasmic polyadenylation element-binding protein 3-knockout (CPEB3-KO) mice, showing dysregulated translation-associated synaptic rigidity, may be susceptible to PTSD-like behavior. Here, using a context-dependent auditory fear conditioning and extinction paradigm, we found that CPEB3-KO mice exhibited traumatic intensity-dependent PTSD-like fear memory. A genome-wide screen of CPEB3-bound transcripts revealed that Nr3c1, encoding glucocorticoid receptor (GR), was translationally suppressed by CPEB3. Thus, CPEB3-KO neurons with elevated GR expression exhibited increased corticosterone-induced calcium influx and decreased mRNA and protein levels of brain-derived neurotrophic factor (Bdnf). Moreover, analysis of two GEO datasets revealed decreased transcriptomic expression of CPEB3 but not NR3C1 in peripheral blood mononuclear cells of humans with PTSD. Collectively, this study reveals that CPEB3, as a potential PTSD-risk gene, downregulates Nr3c1 translation to maintain proper GR-BDNF signaling for fear extinction.

Peroxiredoxin 6 Knockout Mice Demonstrate Anxiety Behavior and Attenuated Contextual Fear Memory after Receiving Acute Immobilization Stress

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Abstract

Stress can elicit glucocorticoid release to promote coping mechanisms and influence learning and memory performance. Individual memory performance varies in response to stress, and the underlying mechanism is not clear yet. Peroxiredoxin 6 (PRDX6) is a multifunctional enzyme participating in both physiological and pathological conditions. Several studies have demonstrated the correlation between PRDX6 expression levels and stress-related disorders. Our recent finding indicates that lack of the Prdx6 gene leads to enhanced fear memory. However, it is unknown whether PRDX6 is involved in changes in anxiety response and memory performance upon stress. The present study reveals that hippocampal PRDX6 level is downregulated 30 min after acute immobilization stress (AIS) and trace fear conditioning (TFC). In human retinal pigment epithelium (ARPE-19) cells, the PRDX6 expression level decreases after being treated with the stress hormone corticosterone. Lack of PRDX6 caused elevated basal H2O2 levels in the hippocampus, basolateral amygdala, and medial prefrontal cortex, brain regions involved in anxiety response and fear memory formation. Additionally, this H2O2 level was still high in the medial prefrontal cortex of the knockout mice under AIS. Anxiety behavior of Prdx6−/− mice was enhanced after immobilization for 30 min. After exposure to AIS before a contextual test, Prdx6−/− mice displayed a contextual fear memory deficit. Our results showed that the memory performance of Prdx6−/− mice were impaired when responding to AIS, accompanied by dysregulated H2O2 levels. The present study helps better understand the function of PRDX6 in memory performance after acute stress.

Attenuation of HECT-E3 ligase expression rescued memory deficits in 3xTg-AD mice

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Abstract

Alzheimer's disease (AD) is one of the most common progressive neurodegenerative disorders that cause deterioration of cognitive functions. Recent studies suggested that the accumulation of inflammatory molecules and impaired protein degradation mechanisms might both play a critical role in the progression of AD. Autophagy is a major protein degradation pathway that can be controlled by several HECT-E3 ligases, which then regulates the expression of inflammatory molecules. E3 ubiquitin ligases are known to be upregulated in several neurodegenerative diseases. Here, we studied the expressional change of HECT-E3 ligase using M01 on autophagy and inflammasome pathways in the context of AD pathogenesis. Our results demonstrated that the M01 treatment reversed the working memory deficits in 3xTg-AD mice when examined with the T-maze and reversal learning with the Morris water maze. Additionally, the electrophysiology recordings indicated that M01 treatment enhanced the long-term potentiation in the hippocampus of 3xTg-AD mice. Together with the improved memory performance, the expression levels of the NLRP3 inflammasome protein were decreased. On the other hand, autophagy-related molecules were increased in the hippocampus of 3xTg-AD mice. Furthermore, the protein docking analysis indicated that the binding affinity of M01 to the WWP1 and NEDD4 E3 ligases was the highest among the HECT family members. The western blot analysis also confirmed the decreased expression level of NEDD4 protein in the M01-treated 3xTg-AD mice. Overall, our results demonstrate that the modulation of HECT-E3 ligase expression level can be used as a strategy to treat early memory deficits in AD by decreasing NLRP3 inflammasome molecules and increasing the autophagy pathway.

Standardized Extract of IM01 Prevents Cued Fear Memory Deficit and Reduction of Hippocampal Long-Term Potentiation in 3xTg-AD Mice

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Abstract

Alzheimer's disease (AD) is the most common form of dementia with a progressive memory decline and synaptic dysfunction. Finding the drug that can prevent the development of such pathologies received more attentions in the field. A standardized extract IM01 isolated from the widely used Asian herb was recently reported to enhance memory and hippocampal long-term potentiation (LTP) in rats. Thus, it suggests the potential use of IM01 to prevent or attenuate the pathogenesis of AD. Our previous study reported that the triple transgenic AD (3xTg-AD) mice, an AD mouse model having both amyloid plaques and neurofibrillary tangles started to demonstrate impaired fear memory and synaptic dysfunction at the age of 6 months old. Administration of IM01 (doses; 10, 30 and 100 mg/kg) into 3xTg-AD mice from 5 months old for 30 consecutive days rescued impaired fear memory and enhanced hippocampal LTP in 3xTg- AD mice. Subsequent proteomic and western blot analyses showed that the major molecules in LTP induction and maintenance including brain-derived neurotrophic factor (BDNF), tyrosine receptor kinase B (TrkB) and its network proteins, extracellular signal-regulated kinase 1 and 2 (ERK1 and 2), were upregulated in the hippocampus and amygdala of 3xTg-AD mice after treatment of IM01. Our results indicate that IM01 is promising drug to help prevent cognitive decline and synaptic dysfunction in AD.

α6GABAAR-Selective Positive Allosteric Modulators Relieved Dental Pulp Injury-Induced Facial Allodynia in Mice via Enhancing GABA Currents in Trigeminal Ganglia

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Abstract

The α6 subunit-containing GABAA receptors (α6GABAARs) are highly expressed in trigeminal ganglia (TG), the hub of the trigeminal sensory system involved in the pathogenesis of migraine or orofacial pain. Previously, we have identified a series of pyrazoloquinolinones (PQ) to be α6GABAAR-selective positive allosteric modulators (PAMs), and substantiated that the Compound 6 and its deuterated derivative, DK-I-56-1, were effective in two rodent models of migraine. TG also play an important role in orofacial pain. Using dental pulp injury (DPI)-induced facial allodynia, we elucidated how PQ compounds exert TG inhibition to achieve their possible therapeutic effects on TG-related orofacial pain. Compound 6 (1, 3, 10 mg/kg, i.p.) significantly attenuated DPI-induced facial allodynia on post-surgical day1. The anti-allodynic effect of Compound 6 was significantly prevented by furosemide, a brain-impermeable α6GABAAR antagonist, given by either systemic administration (20 mg/kg, i.p.) or intra-TG microinjection (10 nmol/0.5 μl, i.tg.), suggesting the site of action of Compound 6 is the α6GABAARs in TG. DK-I-56-1, compared with Compound 6, displayed a similar efficacy but a longer action time (1.5hr vs. >3hrs). We further investigated the cellular mechanism of Compound 6 on isolated TG neurons by whole-cell and perforated patch clamp. The GABA currents (IGABA) induced by focal application of various concentrations of GABA obtained in whole-cell configuration showed an EC50 of GABA at 13.5±3.3 μM. Next, we assessed the potentiating effect of Compound 6 on GABA currents induced by EC50 of GABA (IGABA, EC50) in each neuron. On average, Compound 6 at 1 μM increased (IGABA, EC50) by 29.2±7.4 %. Importantly, this potentiating effect of Compound 6 was prevented by furosemide (100 μM). We further used perforated configuration to maintain the chloride gradient of TG neurons. Results showed that GABA induced membrane depolarization in TG neurons concentration dependently. Importantly, the anti-allodynic effect of Compound 6 can be mimicked by intra-TG injection of KCl, which can depolarize TG neurons. These results suggest that α6GABAAR-selective PAMs can potentiate the chloride conductance mediated by α6GABAARs in TG, which may induce depolarization block of the trigeminal sensory transmission, ultimately leading to the suppression of mechanical allodynia in mice with DPI.

The proton-sensing receptors, TDAG8 and OGR1 involved in CCI-induced neuropathic pain by modulating different neuron populations

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Abstract

Neuropathic pain caused by a lesion or disease of the somatosensory nervous system is usually accompanied by nerve degeneration, neuroinflammation, focal ischemia and acidosis of the injury site. However, it remains unclear when acute pain becomes chronic pain and which receptors are responsible for this transition. Given that proton-sensing G-protein coupled receptors (GPCRs) including GPR4, TDAG8, OGR1 and G2A, are fully activated in the range of pH6.4-6.8, these receptors could be involved in the early stage of neuropathic pain to initiate persistent pain. In this study, we used chronic constriction injury of sciatic nerve (CCI) as a model of neuropathic pain and found that CCI surgery in mice induces persistent pain (>14 weeks). Acid-induced calcium signals in dorsal root ganglia (DRG) neuron culture were observed at different time points after CCI surgery. In DRG neurons ranged <35 μm in diameter, calcium signals were increased after surgery and peaked at week 2; in DRG neurons >35μm in diameter calcium signals were peaked at week 8. We then injected shRNA plasmids intraplantarly to inhibit gene expression of proton-sensing GPCRs in peripheral afferents. After knockdown of TDAG8 and OGR1 genes, the mechanical allodynia was alleviated post CCI 1-4 weeks and 4-14 weeks, respectively. Calcium signals were also inhibited by TDAG8 knockout at week 2 in DRG neurons <20μm; calcium signals were inhibited by OGR1 knockdown at week 4 on DRG neurons ranged 20-35 μm and at week 8 on DRG neurons >35μm. The acute phase of mechanical allodynia from 1 to 4 weeks is mainly regulated by TDAG8 in DRG neurons <20μm, while the chronic phase from 4 to 14 weeks is modulated by OGR1 in DRG neurons of 20-35 μm at 4-8 weeks and in DRG neurons >35μm at 8-14 weeks. Accordingly, mechanical allodynia is mediated by more than one receptor and by distinct neuron populations.

投稿學會：台灣基礎神經科學學會	編號: P3-28

Acid sensing TDAG8 and ASIC1a are molecular determinants of acid-induced antinociceptive sngception in a mouse model of fibromyalgia.

Sitt Wai Fong, Cheng-Han Lee, Wei-Hsin Sun, Chih-Cheng Chen

Academia Sinica.

Abstract

For years, in human study, acid has been widely considered as the key for triggering chronic muscle pain and the cause of this involves two principal types of proton-sensing ion channels, namely, ASIC3 and TRPV1. In our previous study, we demonstrated for the first time acid not only respond to ASIC3 and TRPV1, but also trigger acid-induced antinociceptive effect via a non-ASIC3, non-TRPV1 neuron population. TDAG8 is a member of ORG family and it is a proton sensitive GPCR which exclusively found in small-diameter DRG neurons that are responsible for nociception. In the present study, two acid injection on TDAG8 KO prolonged chronic mechanical hyperalgesia for more than 10 wks, suggesting TDAG8 may play a role in modulating pain. BTB09089, a TDAG8 agonist, reversed acid-induced hyperalgesia in WT mice, but not in TDAG8 KO. SM-SP inverted the pain in both WT and TDAG8 KO. In TDAG8 KO, acid-induced pERK activity was dramatic increased and APETx2, a selective blocker of ASIC3, co-injected with CZP, a selective TRPV1 antagonist, reduced the acid-induced pERK induction. Collectively, these results strongly indicate TDAG8 modulates pain nociception probably via TDAG8-induced SP antinociception in non-ASIC3, non-TRPV1 signaling. ASIC1a, another specific type of proton-sensitive channels, has been shown recently to induce antinociceptive effect on dextrose-mediated antinociception in mouse model of fibromyalgia. In this present study, PcTx1, a selective ASIC1a antagonist, blocked the antinociceptive effect in non-ASIC3, non-TRPV1 pathway with a delay of transient effect development on second acid-injection. In contrast, in the absence of TDAG8, PcTx1 reversed the acid-induced antinociception with an early appearance of transient hyperalgesia. ASIC1a KO prolonged chronic muscle pain with only a single acid insult, suggesting ASIC1a, like TDAG8, may play a vital role in acid-induced antinociception. In situ hybridization revealed SP co-expressed with TDAG8 and ASIC1a in DRG neurons, indicating a possible role for antinociceptive pain modulation. Taken together, although acid-induced muscle chronic pain is not a new idea, the present study here show acid can also play a major role in antinociception via TDAG8/ASIC1a signaling in non-ASIC3, non-TRPV1 positive neuron. More importantly, this dual action induced by acid, is vital for pain nociceptive regulation in sensory ganglia and thus preventing further neuronal sensitization. In other words, this crucial action is to make sure and keep the pain threshold at bay without causing further increased sensitivity or damage to the acid-induced chronic muscle pain.

Investigating the role of Advillin in regulating neurite outgrowth on PDMS substrates of different stiffness levels

Yi-Ching Chen, Yu-Chia Chuang, Chih-Cheng Chen

Academia Sinica

Abstract

Advillin is an actin-binding protein strongly expressed in somatosensory neurons. It has been implicated in neurite growth, neuronal development, and cytoskeletal organization. Advillin is a key protein involved in neurite outgrowth, and colocalizes with the focal adhesion kinase, pFAK, at the tips of filopodia. Substrate stiffness has been previously shown to affect neurite outgrowth. However, the participation of Advillin in stiffness-dependent differential neurite growth is still unknown. Here, we aim to investigate whether Advillin has a role in coupling neurite outgrowth and cytoskeletal protein regulation to substrate stiffness of Neuro-2a (N2a) cells cultured on polydimethylsiloxane (PDMS) at three stiffness levels. Overexpressing advillin showed no phenotype in neurite length when compared to N2a with endogenous expression of Advillin in all stiffness levels. Overexpressing Advillin resulted in twice the linear density of filopodia along a neurite compared to control cells cultured on the 100 KPa and 1000 KPa PDMS substrates, demonstrating its role in regulating filopodia outgrowth on stiffer environments. Interestingly, when overexpressed, immunostaining suggests that Advillin accumulated at the filopodia roots 1000 times more than at the tips in all three substrates, despite different tip-to-root ratios in control expression levels.

Translocation of Paxillin to the Nucleus Supports Early Postnatal Neuron Maturation

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Abstract

Neuron maturation is a multiple-step process in which each step involves switches on/off sets of protein isoform, structure, and function. Whether and how neurotrophin factor instructs the timely maturation transitions reminds illusive. In this study, we will share our recent findings on a novel function of nuclear paxillin, which harbors a neuron-specific phosphorylation modification at Ser119 (p-paxillinS119) mediated by BDNF signaling or cdk5 activation and dephosphorylated by PP2A. The Ser119-phosphorylation of nuclear paxillin peaks on the seventh day in vitro (DIV) and forms nuclear sparkles with phosphorylated SR proteins till 10 DIV, covering a developmental transition when numerous maturation-promoting factors are undergoing isoforms switch. Blockade of the Ser119-phosphorylation or mutations in the PY-type NLS of paxillin significantly causes a reduction in the paxillin nuclear translocation and alters AIS location. Mass spectrometry-based proteomics of DIV4 neurons reveals that multiple splicing regulators associate with neuronal paxillin upon BDNF stimuli. By deploying a minigene splicing assay to assess exon skipping efficiency, we found that paxillinS119 phosphorylation modulates the neuronal, stage-specific splicing events. To gain more insight into the detailed mechanism underlying the timed, paxillin-regulated splicing program, we will analyze mRNA/protein isoform expression profiles of Ser119-phosphorylation-deficient neurons.

投稿學會：	編號: P3-31

Systematic Characterization of A Putative Novel Long Noncoding RNA in the Spinal Cord

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Abstract

Long non-coding RNAs (lncRNAs) are comprised of >200 nucleotides that are not translated into proteins. Accumulating evidence reveals that lncRNAs display more propensity in cell- or tissue-type specificity, thereby being regarded to contribute to specific cell-context dependent regulatory function. Although lncRNAs are traditionally considered to have no or little protein-coding potential, some recent reports indicated that lncRNAs could generate proteins. Here, we used spinal motor neurons (MNs) as a paradigm to investigate the functional role of a novel highly conserved MN-enriched lncRNA A730046J19Rik during MN development. To explore the role of A730046J19Rik during MN development, we utilized the mouse embryonic stem cell (ESC)-derived MN differentiation approach and established the A730046J19Rik knockout model to uncover several vital insights of this novel lncRNA. Interestingly, A730046J19Rik seems to only produce a protein at the postnatal stage albeit with already strong RNA expression in embryos. We are in the process to dissect the possible divergent role of A730046J19Rik RNA and protein at prenatal and postnatal stages respectively. We aimed to use A730046J19Rik as a proof of principle to shed light on the dual function of lncRNA during development, and this might open a new avenue of regulatory functional mode of lncRNA.

投稿學會：	編號: P3-32

m6A epitranscriptome: The role of RNA modification during motor neuron development and degeneration

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Abstract

Emerging studies have shown that N6-methyladenosine (m6A), the most prevalent and abundant RNA modification that occurs in the mRNA of most eukaryotes plays a critical role in various developmental processes. This modification is installed by the m6A methylation “writers” (Mettl3/Mettl14 methyltransferase complex) and can be reversed by demethylases “erasers” (Fto and Alkbh5). Depletion of m6A methylation writer Mettl14 via Mettl14 knockout in mouse embryonic nervous systems prolongs cell cycle progression of radial glia and extends cortical neurogenesis into postnatal stages. Although m6A mRNA methylation has long been recognized as a posttranscriptional modification in mammalian cells, the roles of this posttranscriptional process and the biological significance of m6A modification in mammalian neuronal development and disease, particularly motor neuron (MN) development and degeneration, are completely unknown. To decipher the role of the m6A modification during MN development and neurological disorders, we conditionally inactivating an essential m6A writer component Mettl14 specifically in the cells using a Mettl14 conditional (floxed) mouse line in combination with oligodendrocyte Cre driver lines (Olig2-Cre). We observed that Olig2-Cre-mediated knockout of Mettl14 induces significant reduction of MN numbers suggesting that m6A might serve as important roles during MN development. In the future, we will conduct m6A-sequencing (m6A-seq) of embryonic stem cell (ESC)-differentiated motor neurons (MNs) to assess the m6A distribution. Then we will be able to determine the biological significance of m6A RNA modification during mammalian MN development. Overall, this study will result in the first blueprint of epitranscriptional profiling of mammalian MNs and provide a new avenue for the MNs development.

Retinal Innervation Pattern in Central Clock, Suprachiasmatic Nucleus of Mice

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Abstract

Circadian rhythms modulate our daily activity patterns and other body mechanisms, such as metabolic and neuroendocrine rhythms. In mammals, circadian rhythms are controlled by the central clock, suprachiasmatic nuclei (SCN). The external light signal could entrain SCN through intrinsically photosensitive retinal ganglion cells (ipRGCs). SCN contains different neurons, while AVP and VIP neurons are critical for the networking of circadian rhythm. AVP neurons are mainly expressed in shell region of SCN, while VIP neurons are expressed in core region. In a previous study, VIP neurons are suggested as light signal receiving neurons, and AVP neurons are the primary output neurons for the SCN. However, in single ipRGC tracing study suggested that ipRGCs innervation does not limit to VIP neurons specifically but throughout the whole SCN. In addition, the mechanisms of how SCN neurons communicate with each other's remain unknown. To explore the route of SCN neurons, we will use expansion microscopy to observe the connection and retinal innervation of SCN neurons. Revealing the circuit within SCN will advance our understanding of circadian rhythms, thus finding new treatments for circadian arrhythmic diseases.

Light-induced spatiotemporal circuit from ipRGCs to the suprachiasmatic nucleus

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Abstract

The endogenous circadian clock exists in the organism. In the mammalian brain, the suprachiasmatic nucleus (SCN) is thought of as the central circadian clock, which can control the peripheral circadian rhythm of organs in the whole body. In the SCN, neurons are spatially divided into dorsal-medial (shell) and ventral-lateral (core) regions, which are enriched with arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) neurons respectively. According to previous studies in 2016, our group found that a single M1 ipRGC projects to either dorsal, medial, or ventral region in the SCN (Fernandez et al., 2016). Additionally, in hamsters, light-stimulating at different timing induced Fos expression in different regions of the SCN (Schöttner K, 2015; Samer Hattar, 2020). Therefore, the light-induced neural circuit in the SCN seems to contain both spatial and temporal cues. To test whether SCN could encode spatial or temporal information with distinct activation pattern, we used TRAP 2 mice and cFos immunostaining to identify the activated SCN neurons after different pattern of light exposure. Here we found that light source from above the animal and light source below the animal may activate different group of neurons in the SCN. Therefore, SCN may receive and compute spatial information in additional to brightness to control circadian photoentrainment.

Correlating locomotion behaviours with three-dimensional spatiotemporal dynamics of astrocytic Ca2+ signalling in the Motor Cortex in vivo

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Abstract

Astrocytes in the central nervous system define the brain environments and govern energy and metabolic support through neuron-astrocyte-blood vessel complex. Recent studies also found astrocytes regulate synaptogenesis, synaptic maintenance, and homeostasis of transmitters in neural circuits. Activation in astrocytic Ca2+ signalling is considered as the integrator linking neurovascular units and neuronal information to higher order physiological responses. Therefore, decoding astrocytic Ca2+ signalling is essential for the understandings of brain functions. Conventional method of studying calcium signals is based on only two-dimensional (2D) region-of-interest (ROI) analysis. However, highly divergent morphology of astrocytes and complex astrocytic Ca2+ dynamics make such conventional analysis a source of inconsistent results . Here we establish in vivo two-photon (2P) volumetric imaging on sparsely-labelled astrocytes using Aldh1l1-CreERT2::lck-GCaMP6f and Aldh1l1-CreERT2::Salsa6f transgenic mice. We monitor subcellular astrocytic Ca2+ dynamics in individual astrocytes in the primary motor cortex of awake mice. We developed a three-dimension (3D) analysis and tracking method to identify splitting and merging of Ca2+ events in the astrocytic territory. The event properties such as duration and maximum propagation detected in 3D are higher than that in 2D, which is consistent with our expectation that 3D analysis can reveal more insights. Furthermore, along with 2P Ca2+ imaging, we also recorded the animal locomotion behaviours simultaneously for animal pose estimations by DeepLabCut. By using these experimental methods and analysis pipeline, we aimed to decode the intricate astrocytic Ca2+ signals integrate from small subcellular microdomains to global compartments that affecting cortical mantle and coupling to behaviours .

Interactive dynamics of the somatosensory and motor cortices during forelimb movement in mice

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Abstract

How neural signals in various brain regions coordinate to generate behavioral movement is an important question in understanding the brain function. It's been shown that the neural activities from primary motor cortex (M1), the final station before sending signals to spinal cord, is highly influenced by signals from other brain areas such as the somatosensory cortex (S1) and the pre-motor cortex (M2). However, how these cross-cortical activities interact with each other to initiate and control movement is not fully understood. We established a CMOS-multielectrode array (CMOS-MEA) to simultaneously record M1, M2, and S1 spike activities on mice during a forelimb food-pallet reaching task. After spike sorting, signals from more than a thousand of single- or multi-unit clusters are successfully obtained. Latent Factor Analysis via Dynamical Systems (LFADS) is applied to extract the denoised spike rates from single trials and to map neural signals to a low dimensional latent factor space. We showed the mice paw position can be successfully decoded with high precision ($R2 > 0.95$). Moreover, 38 low dimensional latent factors could also result in similar high performance of decoding ($R2 > 0.89$). It's also found that the dynamics of some latent factors corresponds to different functional roles of brain areas, such as preparational signals before motion in M2. In addition, comparing with the case of dropping S1 signals, the decoding performance decreases substantially (6%). This indicated that the interactive dynamics between motor cortices and S1 might be crucial in generating movement. These results demonstrated the different roles of different brain areas and their contribution in motion generation.

Neuronal responses under ultrahigh frequency stimulation

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Department of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, Taipei, Taiwan Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan Institute of Electronics Engineering, National Tsing Hua University, Hsinchu, Taiwan Neuroscience Program in Academia Sinica (NPAS), Academia Sinica, Taipei, Taiwan Department of Life Science, College of Life Science, National Taiwan University, Taipei, Taiwan

Abstract

Advancing fabrication of implantable multichannel-electrode arrays (MEAs) for in vivo chronic large-scale electrophysiology

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Abstract

Deciphering neural information with single-neuron resolution requires implantable electrodes to record their action potentials. Bundled parallel microelectrode arrays have been demonstrated for in vivo large-scale cortical recording of spiking activity (Obaid et al., 2020). We further verified that spike recoding with microwire bundle implanted into cerebral cortex is chronically stable and caused minor tissue damage with wire diameter is smaller than 20 µm (Obaid & Wu et al., 2020). However, the fabrication of the microwire bundle is still not optimized. Arranging the microscopic and fragile wires into bundle format with an ideal pitch or a specific pattern is still challenging. Here, we developed scalable fabrication procedures for bundled microwire arrays. Platinum Iridium (PtIr) microwires with a diameter of 13 µm are coated with high dielectric constant material Parylene C (PaC) to create a sacrificial layer to reach a diameter of 100 to 150 µm for maintaining the straightness of the wires and defining the pitch between wires. A Perfluoroalkoxy alkane (PFA) heat-shrink tube is used to bundle the PaC-coated microwires in a hexagonal-close-packed manner. We further designed a patternable alignment system utilizing metal-guide plates and a semi-automatic wire-loading design. This fabrication procedure enables the arrangement of individual wires to a specific location and forms the desired patterns, i.e., an 8-by-8 square array or multiple square arrays. The bundled microwires can target neuronal populations of different cortical layers by shaping the wires into different lengths with an angled-polishing procedure to yield 3-dimensional microwire bundles. Finally, our in vivo implant demonstrated that the chronic stability of spike recording could reach more than six months, suggesting our microwire bundles are ideal neural interfacing for chronic recording in 3-dimensional brain tissue.

投稿學會：	編號: P3-39

Circuit mechanisms underlying CB1R mediated suppression of dentate granule cell recruitment by cortical input

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Abstract

The neuromodulatory system plays an important role in regulating synaptic plasticity, signaling environmental cues and modulating cognitive functions. The cannabinoid type 1 receptors (CB1Rs) in the dentate gyrus (DG) have been implicated in cognition and emotion, and are highly expressed in GABAergic cholecystokinin-expressing interneurons (CCK-INs) and glutamatergic hilar mossy cells. Endocannabinoids released from the post-synaptic dendrites retrogradely target the pre-synaptic CB1Rs in an activity-dependent manner, and thereby lead to a reduction of neurotransmitter release. The DG, the first station of the hippocampus, receives multimodal inputs from the cortex and processes the information to downstream hippocampal CA regions. However, how the endocannabinoid system (ECS) modulates the DG input-output transformation remains unclear. Using ex vivo electrophysiological recording and pharmacological approaches, we found that activating endocannabinoid signaling by the CB1R agonist WIN 55,212-2 (5 μM) attenuated the perforant path (PP)-mediated granule cell population spikes (GC pSpikes) without affecting synaptic transmission of the PP. Moreover, CCK-INs appear to be essential for CB1R-induced suppression of GC activity because either blockade of GABAAR or chemogenetic inactivation of CCK-INs abolished the reduction of GC pSpikes after CB1R activation. The neural mechanism by which CB1R activation at CCK-INs contributes to suppression of GC responses to the cortical inputs remains unclear and awaits to be explored in the near future.

投稿學會：台灣基礎神經科學學會 | 編號: P3-40

Regulation of Hippocampal Dynamics by Hilar Mossy Cells

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Abstract

The hippocampus is one of the critical brain regions for learning and memory. The dentate gyrus (DG), the first relay station of the hippocampus, receives multimodal sensory inputs from cortical areas and participates in pattern separation and contextual fear memory. The DG is composed of two types of glutamatergic neurons, the granule cells (GCs) and the hilar mossy cells (MCs), as well as several types of GABAergic interneurons (INs). The axons of MCs project to both local and distal lamellae of the DG, and differentially modulate GC and IN activity in the local and distal DG. Activation of ventral MCs primarily excites GCs in the dorsal DG via longitudinal axonal projections whereas excitation of MC commissural projections (COM) preferentially recruits INs, thereby suppressing GC activity via feedforward inhibition. Long-term potential (LTP) is a synaptic substrate underlying learning and memory. Repetitive stimulation of MC axons induces LTP at MC-to-GC synapse via increasing excitation/inhibition balance in GCs, thereby enhancing GC output. Preliminary data from our lab showed that activation of MC COM projections enhances the performance of contextual fear memory.

Mapping the inputs and outputs of the paraventricular nucleus of the thalamus

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Abstract

The paraventricular nucleus of the thalamus (PVT) is known to encode salience of reinforcing stimuli and regulate associative learning. How the PVT neurons acquire and relay valence to initiate proper responding remains elusive. To address this question, we first employed retrograde viral tracing in anterior and posterior parts of the PVT respectively to map their afferent inputs. We found that, comparing to anterior part of the PVT (aPVT), posterior part of the PVT (pPVT) received stronger innervations from cortical regions, such as medial prefrontal cortex (mPFC), insular cortex, anterior cingulate cortex (ACC), somatosensory cortex and entorhinal cortex. On the contrary, aPVT received stronger innervations from the subcortical regions, such as parabrachial nucleus and retromammiliary nucleus. Interestingly, we found that it was aPVT, but not pPVT, that received dense afferent input selectively from the ventral rather than dorsal CA1 (vCA1). We then focused on vCA1-to-aPVT input and employed anterograde viral tracing to examine its downstream projections. We detected axonal projections of vCA1-innervated aPVT cells across the brain, such as mPFC, ACC, nucleus accumbens, bed nucleus of the stria terminalis, amygdala and hypothalamus. Given that vCA1 is involved in social memory and regulates affection, we are currently employing optogenetic approaches to investigate the behavioral functions of vCA1-to-aPVT connection.

Functional characterization of afferent inputs from the ventral midbrain to the zona incerta

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Abstract

In nature, when animals perceive reward-related or danger stimuli, they show corresponding responses to retrieve the reward or avoid the threat. Recent studies have shown that the ventral tegmental area (VTA) and substantia nigra (SN) in the ventral midbrain can regulate defensive behaviors. Although both regions send projections to the ZI, which is shown to regulate defensive behaviors, the functional roles of midbrain-to-ZI connections remain elusive. As the first step to investigate the circuit function, we combined dual viral retrograde targeting approach with in situ hybridization (RNAscope) technique to study the neurochemical phenotypes of midbrain cells projecting to the ZI. We found that ZI-projecting VTA neurons consisted mostly of glutamatergic and a small population of GABAergic neurons, whereas ZI-projecting SN neurons consisted mostly of GABAergic and some dopaminergic neurons. We further characterized the behavioral involvement of ZI-projecting midbrain neurons in a mouse model of stress and performed neural activity-dependent c-Fos immunostaining assay. We found that ZI-projecting midbrain neurons were significantly involved in restraint stress. Moreover, we found that ZI-projecting SN neurons were significantly activated by TMT presentation, which mimics nature threat. We further employed excitatory optogenetic approach to causally examine behavior functions of this connection. We found that activation of SN-to-ZI input resulted in aversion in real time conditioned place preference assay. We then further developed a defensive behavioral paradigm and found that activation of the SN-to-ZI input significantly increased defensive behavior induced by TMT presentation. To sum up, our research has demonstrated a novel function of the SN-to-ZI input in regulating defensive behavior.

投稿學會：台灣基礎神經科學學會 | 編號: P3-43

MActivity-dependent feedback regulation of thalamocortical axon development by Lhx2 in cortical layer 4 neurons

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Abstract

The development of neuronal circuits requires interactions between the pre- and postsynaptic neurons. To illuminate the mechanisms under circuit formation, we study the development of rodent barrel cortex, the largest component in the primary somatosensory cortex (S1). The development of barrel cortex is instructed by presynaptic thalamocortical axons (TCAs). In the first postnatal weeks, TCA terminals arborize in layer (L) 4 to fill in the barrel center, but it is unclear how TCA development is regulated. We previously demonstrated that the deletion of Lhx2 in the postmitotic cortical neurons in the Lhx2 conditional knockout (cKO) leads to TCA arborization defects, which is accompanied with deficits in sensory-evoked and spontaneous cortical activities and impaired lesion-induced plasticity following early whisker follicle ablation. Reintroducing Lhx2 back in L4 neurons in cKO ameliorated TCA arborization and plasticity defects. By manipulating L4 neuronal activity, we further demonstrated that Lhx2 induces TCA arborization via an activity-dependent mechanism. Additionally, we identified the extracellular signaling protein Sema7a as an activity-dependent downstream target of Lhx2 in regulating TCA branching. Thus, we discovered a bottom-up feedback mechanism for the L4 neurons to regulate TCA development and this process is important for the barrel cortex plasticity.

投稿學會：國立台灣大學醫療器材研發中心	編號: P3-44

Mechanoresponsive phosphorylation and subcellular redistribution of septin-2 upon low-intensity pulsed ultrasound (LIPUS) stimulation

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Abstract

Septins are newly categorized as the fourth component of the cytoskeleton, which conventionally comprises microtubule, microfilament, and intermediate filament. Recent studies have suggested that septins interact with phosphoinositides(PIPs) to initiate exocytosis (Collins et al., 2020), guide microtubules (Short, 2011), and are often found close to mechanosensitive compartments, such as primary cilia and plasma membranes (Lam & Calvo, 2019). Although septins are correlated to mechanosensitive behaviors, for instance, the formation of membrane protrusions in cell migration and angiogenic invasion of endothelial cells, septins are mechanoresponsive has not been demonstrated. We aim to test the protein phosphorylation and subcellular re-distributions of septin-2 upon mechano-stimulation by application of ultrasound. To reveal the network among these diverse features of septins, we utilized LIPUS as non-invasive, mechanical stress to induce the phosphorylation of septin-2 and to further observe the corresponding subcellular localization in cells. By immunoblot analysis of the septin-2 phosphorylation in ultrasound-stimulated (600mVpp, 1MHz, 5min) chinese hamster ovary (CHO) cells, we discover that septin-2 phosphorylation increased dose-dependently as ultrasound's duty factor was elevated from 1% to 3%. Furthermore, such stimulation also induces clustering of septin-2 at the cortical actin-enriched sites of the cell periphery while the resting cells predominantly exhibit a microtubule pattern of septin-2. Since ultrasound has been a promising technology for neuronal modulations in the brain for therapeutic purposes, our findings provide a molecular basis for the considerations of how ultrasound should be administered. In short, our study provides a deeper understanding of septin dynamics in response to mechano-stimulation.

Mechanoresponsive of NMDAR2B and CamKIIa phosphorylation in mouse hippocampus stimulated by ultrasound

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Abstract

Ultrasound stimulation is a promising approach to modulate neuronal activities for therapeutic purposes.Our lab previously identified Acid-Sensing Ion Channel 1a (ASIC1a) as a mechanoreceptor of ultrasound in the mouse brain (Lim et al., 2021). We also found that phosphorylated Extracellular signal-Regulated Kinase (p-ERK) responses to ultrasound in a dose dependent manner in isolated hippocampal tissues of mice (Lim et al., 2022). Therefore, we are interested in investigating the overall phosphorylation signals in mouse hippocampus. Using the Mass spectrometry method, we have performed an analysis of phospho-proteomics of mouse hippocampus stimulated by ultrasound. In this poster, we report the characterization of ultrasound induced phosphorylation of Ca2 +/calmodulin-dependent protein kinase II(CamKIIa) and N-methyl-D-aspartate receptor(NMDAR2B). CamKIIa is a kinase that can phosphorylate NMDAR2B ,which plays important roles in learning,memory, and depression. CamKIIa has been reported to phosphorylate S1303 of NMDAR2B (Tullis et al., 2021). The phosphorylation of S1303 alters the long term depression but not the long term potentiation of hippocampus (Tullis et al., 2021). On the other hand, NMDAR2B Y1070 phosphorylation inhibition has been associated with the resilience of mice suffering from the forced swimming test that causes depression (shi et al.,2021). In this study, 1Mhz ultrasound with input voltage of 900mVpp and duty factor of 5% is applied to the hippocampus dissected from postnatal day 7 ICR pups. Hippocampi are then homogenized and lysed in RIPA buffer and subsequently subjected to Western Blot Analysis to evaluate whether NMDAR2B (Grin2b, GluN2B) and CamKIIa are phosphorylated upon ultrasound. We discover that NMDAR2B is phosphorylated at both S1303 and Y1070 sites upon ultrasound stimulations. The phosphorylation is dose-dependently enhanced by increasing ultrasound input voltage. In addition, the phosphorylation is temporally regulated by ultrasound stimulation. Moreover, the dynamics of NMDAR2B phosphorylation are different from the phosphorylation of CamKIIa. We will further study whether these phosphorylation can be detected in ultrasound transcranial stimulation of the mouse brain. Our findings should alert a cautiousness of transcranial ultrasound for therapeutic applications.

投稿學會：	編號: P3-46

Developmental abnormalities of the nigrostriatal pathway in mice with dopamine synthetic defect

Pei-Chun Hsu, Tzu-I Chen, Ni-Chung Lee,Yu-Han Liu, Hao-Chun Wang, Yen-Hsu Lu, Yin-Hsiu Chien, Wuh-Liang Hwu

Department of Pediatrics and Medical Genetics

Abstract

The development of dopaminergic neurons is a complex process, and abnormalities in dopaminergic neuron development may be involved in diseases of dopamine deficiency. In the current study, single-nucleus RNA sequencing was employed to analyze midbrain cells of DdcKI mice, a disease model of dopamine synthetic defect, at postnatal day 0, 7, and 14. Two-dimensional t-distributed stochastic neighbor embedding of merged data from the wild-type and DdcKI mice identified cell clusters containing dopaminergic neurons (Th+) or DA neural precursors (Th-, Lmx1a+). Gene ontology analysis of differentially expressed genes revealed a delay in dopaminergic neuron axonogenesis and synapse formation in the DdcKI mice. Pseudotime analyses demonstrated an activation of dopaminergic neural precursors at postnatal day 7 in the DdcKI mice, with an increased expression of dopaminergic neuron development-related genes Otx2 and Pax5. Immunohistochemical staining of brain sections and cleared whole brain in the DdcKI mice further revealed dispersed dopaminergic nerve bundles and decreased dopaminergic innervation in the putamen. Therefore, dopamine deficiency may cause structural abnormalities in dopaminergic neuron exon extension and innervation, which could limit the treatment efficacy of those diseases.

Interaction between reward learning and punishment learning

Wen-Wei Lin Ming-Tsung Tseng Pei-Yu Lee

Graduate Institute of Brain and Mind Sciences, NTU

Abstract

Reward and punishment often act as important factors that modulate human behavior through learning to maximize the former, and minimizing the latter. Although much is known about how reward and punishment contribute to guiding our behavior independently, how these two types of learning interact with each other remains largely unclear. Here, we used a probabilistic instrumental learning task with binary choice options in combination with functional magnetic resonance imaging to address this issue. Healthy participants were required to try their best to earn money and to avoid losing money or avoid painful stimulation throughout the learning task. Preliminary behavioral results from the first experiment suggest that when an option was simultaneously associated with rewarding and punishing outcomes, representing the interaction between the two types of learning, only the performance of reward learning was interfered by punishment learning, but not vice versa. Our second experiment was conducted to clarify the mechanism of the interference effect of punishment learning on reward learning. Results from the two experiments together provided better knowledge for understanding the asymmetry between reward learning and punishment learning with an interaction relationship and also the underlying mechanism of this behavior phenomenon.

投稿學會：	編號: P3-48

Haptic perception and motor function ability with or without musician

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Abstract

Musicians have been found to show increased fine motor skills through extensive piano practice. Numerous studies have reported that proprioception is increased in musicians who regularly play musical instruments. However, little is known about haptic function, the combination of proprioception and touch perception, is improved in musicians. The purpose of this study was to systematically investigate haptic function and how it is linked to different domains of motor skills in musicians. Twenty-two musicians (age 21.91±3.05 years) and 22 controls without previous experience of music (age 21.77±3.09 years) participated. All participants performed two haptic tasks: 1) a haptic detection task and 2) a haptic discrimination task. The haptic block system consists of 18 plastic blocks with different curvatures on the top of block surfaces. During the detection task, participants touched a single haptic block with their dominant index fingers and were asked to judge whether the block was curved or not. In contrast, during the haptic discrimination task, participants explored two haptic blocks and identified which of the two blocks was more curved. The haptic sensitivity (measured by haptic detection thresholds) and haptic acuity (measured by discrimination thresholds) were obtained to measure haptic function. Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Long Form (BOT-2-LF) was used to assess different domains of motor functions. The independent t-test revealed that the musician group demonstrated a higher haptic sensitivity (decreased haptic detection thresholds) when compared to their controls ($p = .049$). However, haptic acuity was not significantly different between the two groups ($p = .108$). The Pearson product-moment correlation coefficient showed that the haptic detection thresholds significantly correlated with manual coordination measured by BOT-2-LF ($r = -.582$, $p < .01$). This study documented that musicians have higher haptic sensitivity, which is linked to their greater manual coordination.

Meta-analytic Neuroimaging Evidence of the Association between Orofacial Pain and Mastication

Chia-Shu Lin (1,2,3) and Ta-Chung Chen (4)

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Abstract

Temporomandibular disorders, characterized by pain and impaired masticatory functions, are common chronic orofacial pain in adults. The Integrated Pain Adaptation Model (IPAM) predicts that the reduction in jaw movement is associated with increased pain and such an association varies between patients because of the inter-individual differences in pain. Critically, evidence from clinical, animal, and neuroimaging research has convergently revealed the brain mechanisms in both mastication and pain processing. The IPAM predicts the sensorimotor network of the brain may contribute to the pain-mastication association, a hypothesis not been fully investigated. We here provide meta-analytic evidence of potential brain mechanisms of the association between mastication and orofacial pain. An imaging meta-analysis was conducted for neuroimaging studies on the following three topics: Group A-chewing movement of healthy adults (13 studies), Group B-orofacial pain in patients with temporomandibular disorders (4 studies), and Group C-muscle pain in healthy subjects (3 studies). Consistent loci of brain activation were synthesized using Activation Likelihood Estimation (ALE) for the chewing studies (i.e., Group A, 111 foci from 13 studies, 160 subjects) and orofacial pain-related studies (i.e., Group B+C, 84 foci from 7 studies, 100 subjects). All the ALE results were thresholded by intensity ($p<0.05$, uncorrected) and cluster size ($p<0.05$, familywise error-corrected). The chewing studies consistently revealed consistent activation at the primary somatosensory cortex, the primary and secondary motor cortices, and the insula (predominantly the mid-posterior insula), as shown in our previous study (Lin, 2018). In contrast, the pain-related studies revealed consistent activation at the anterior cingulate cortex and the anterior insula. Notably, a conjunctional analysis of chewing and pain-related studies showed consistent activation at the bilateral anterior insula. The meta-analytical evidence suggests that the anterior insula, which has been widely conceived as a key region in pain, interoception, and salience processing, may contribute to the pain-mastication association. The findings provide an additional neural basis to the IPAM and suggest a focus on the insula in future research in mastication and orofacial pain.

Evaluation of age-related development of executive function by using the Conners K–CPT 2 and event-related potential component in a three-stimulus auditory oddball task

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1 Research Center for Education and Mind Sciences, National Tsing Hua University, 2 PhD Program in Cognitive Sciences, National Chung Cheng University, 3 Institute of Behavioral Medicine, National Cheng Kung University 4 Interdisciplinary Program of Education, National Tsing Hua University 5 Department of Early Childhood Education, National Tsing Hua University 6 Department of Early Childhood Education, University of Taipei 7 Department of Education and Learning Technology, National Tsing Hua University 8 Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital Hsin-ChuBranch * Corresponding author.

Abstract

Objective: Human frontal lobe development is strongly linked to the development of executive functions, which are among the last mental processes to mature. In comparison to young adults, children have lower levels of executive function due to their unfully-developed frontal lobes. The P300 ERPs are regarded as an effective method of identifying changes in the frontal-parietal connection that are associated with executive dysfunction. On the other hand, the continuous performance tests measure impulsivity associated with inhibitory control, a key component of executive function. The purpose of this study is to evaluate the children's executive functions by using auditory oddball event-related potentials and the K-CPT2 test. Methods: The three-stimulus auditory oddball task is comprised of 240 frequent non-target tones (1 KHz, P=0.80), 30 rare target tones (2 KHz, P=0.10), and 30 rare novel non-target tones (0.5 KHz, P=0.10) given randomly one at a time with inter-trial intervals of 1500ms. An auditory oddball task was recorded from the midline sites (Fz, Cz, and Pz) of 18 aged 48 months to 97 months (M=69.33, SD=12.64) children. Participants were instructed to respond quickly to each target tone while inhibiting their responses to novel and non-target tones. After getting ERP data, K-CPT2 software was used to run a computerized continuous performance test. Results: Behavioral data showed that oddball hit rates increase with age. Further investigation of K-CPT 2 performance revealed that both the error rates of omission and hit response time were correlated with oddball task performance negatively. In terms of ERP analysis, for the target tones, the mean corrected amplitude of late positive components (adjusted by subtracting the ERP wave of the frequent tones) was increased linearly with age in Cz and Pz, but not in Fz channels. The mean corrected N2 amplitude in the Fz and CZ channels, which were triggered by rare novel tones, went down in a straight line with the number of commission errors made on the KCPT-2 task. Conclusion: The results suggest that combining the Conners K-CPT 2 and the three-stimulus auditory oddball task may be a feasible index for neuropsychological examinations of preschool children's executive function development.

The human orbitofrontal cortex represents the subjective value of the present, and the past food rewards

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Abstract

Electrophysiological studies in monkeys and functional imaging in humans have shown that activity in the orbitofrontal cortex (OFC) encodes the subjective value (SV) of an option while making economic choices. Mounting evidences have suggested that OFC dynamically compute current value based on the recent experience of decision makers. However, these findings were mainly based on single-unit electrophysiology in non-human primates and have not been widely reported in humans. In this study, subjects indicated their subjective value for a variety of snack foods in a Becker-DeGroot-Marschack (BDM) auction task during stereo-electroencephalography (sEEG) recording. The event-related spectral perturbation for different frequency bands were extracted and regressed against the SV in the current trial and the SV in the previous trial. We found that the high frequency power (gamma and high-gamma, 30-150 Hz) in the OFC positively correlated with the current SV and negatively correlated with the previous SV. The low frequency power (theta and alpha, 4-12 Hz) also represented SV, but in opposite encoding directions. Furthermore, the significant results primarily came from electrodes in the central and medial OFC, but not lateral OFC.

投稿學會：	編號: P3-52

Attention related changes in aperiodic neural activity with time-on-task

Lin-Yuan Tseng, Niall Duncan

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Abstract

Attentional state fluctuates from moment to moment, with sustained attention requiring dynamic patterns of brain network activity that are formed and dissolved to support this function. These patterns can be measured through electroencephalography (EEG). Such electrophysiological signals exhibit periodic, oscillatory, characteristics that are thought to exist in tandem with aperiodic fluctuations. This aperiodic activity has a 1/f-like distribution, the parameters of which appear to be influenced by age, task demands and cognitive state (He, 2014; Voytek et al., 2015). The steepness of this 1/f distribution has been suggested to represent the balance between excitatory and inhibitory neural activity (E:I balance; Gao et al., 2017). Previous studies have demonstrated the effect of attentional control on the oscillatory component of EEG signals with time-on-task (Shalev et al., 2019; Reteig et al. 2019). However, less is known about how attention affects their aperiodic component. As such, the aim of the current study was to investigate attention effects on the aperiodic component and how it is changed with time-on-task. The current study found that changes in aperiodic activity, as well as its behavioural relevance, may be linked to changes in the E:I balance and mean neural population spiking within underlying neural populations. The findings provide new insights into neural correlates of sustained attention in humans and point to the potential importance of changes in local excitation and inhibition balances to this process.

投稿學會：	編號: P3-53

TStability of the heartbeat counting task for measuting interoception

Evgeny A. Parfenov, Niall W. Duncan

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Abstract

Objective. Interoceptive awareness (IA) is the ability to perceive signals from the visceral organs of our body. One common task for evaluating IA is the heartbeat counting task (HCT) during which participants need to count their heartbeats over a period of time. It has been argued recently, however, that this task may not measure stable trait features and that it may involve non-interoceptive processes. This study therefore aimed to: 1) observe the HCT performance changes across multiple repetitions of the task; and 2) compare performance in the HCT with a visual counting task (VCT) to investigate generalized propensities of underreporting ambiguous stimuli. Methods. The study sampled 46 healthy subjects (25 females, mean age = 27.5 ± 4.2) with no history of neurological, psychiatric, or cardiac disorders; with normal or corrected-to-normal vision; and with a BMI < 30. Participants performed multiple repetitions of the HCT and the VCT designed to mirror the HCT. During the VCT participants were asked to count Gabors presented beneath variable noise. The frequency of the VCT stimulus presentation was matched to the individual's heart rate. Results. A one-way repeated measures ANOVA showed that IA did not change over the seven blocks of the HCT ($F = 1.3$, $p = 0.256$). In contrast, changes in visual accuracy derived from the VCT did differ across blocks ($F = 15.27$, $p < 0.001$), with performance degrading over time. No correlation was observed between participant's performance in the HCT and the VCT ($r = 0.28$, $p = 0.056$). Conclusion. Performance of the HCT is stable across repetitions of the task. This suggests an absence of a training effect or changing performance with increasing task's familiarity. The lack of correlation between the HCT and the VCT may point to different mechanisms underlying in exteroceptive and interoceptive processes or may reflect an inherent difference in their difficulty.

投稿學會：	編號: P3-54

Relating interneuron populations to spontaneous neural activity properties across the human cortex

Chien-Ming Lo, Niall Duncan.

Graduate Institute of Mind, Brain, and Consciousness

Abstract

The brain is built from complex networks of different neuron subtypes. The specific mix of types varies systematically across the brain according to regional function. This is particularly true of inhibitory interneurons, where there is significantly greater morphological variation than is seen for excitatory cells. Exactly how this microstructural variation is related to differences in overall network activity has not, however, been studied in humans. To begin outlining this microstructure-function relationship we used a combination of gene expression data and MEG recordings from across the cortical sheet. A manifold representing variation in inhibitory interneuron subtype marker genes was first calculated (the “gradient”), giving summary information at each vertex on what mix of cell types are present. The spatial arrangement of these cell markers was then related to the spatial layout of different features of resting-state MEG recordings from 100 healthy participants. This showed that the intrinsic timescale of this activity was correlated with the interneuron gradient. In addition, the functional inhibition/excitation balance of gamma band activity specifically was also correlated with this gradient. Finally, looking at local activity contributions to global avalanches, we found a dissociation with the interneuron gradient. A vertex’s contribution to global avalanches was instead determined by its anterior-posterior location. These results help advance our understanding of the structure-function relationship in the human brain. They show how local neural network properties are connected to the mass activity features revealed through neuroimaging techniques, linking these to specific biological substrates.

投稿學會：台灣認知神經科學學會	編號: P3-55

Musical Training Shapes the Processing of Degraded Speech in Noisy Environment

Yu-Jyun Guo and I-Hui Hsieh

Institute of Cognitive Neuroscience, National Central University

Abstract

Many neurophysiological and behavioral studies show that musical training benefits the encoding of speech in noisy environment. One putative explanation is that musicians can track the fundamental frequency (F0) information in speech better than non-musicians. Recent studies reported that flattening the F0 contours of Mandarin speech reduced speech intelligibility in noise for normal listeners. However, it is presently unknown whether musician advantage for speech-in-noise persists under conditions of degraded F0 speech contours. The current study investigates the effects of different levels of degraded F0 contour (i.e., conveying lexical tone or intonation information) on speech-in-noise performance in musicians. A cohort of twenty non-musicians and sixteen trained musicians were tested on the intelligibility of Mandarin Chinese sentences with natural, flattened-tone, flattened-intonation and flattened-all F0 contours (created via speech synthesizer) embedded in background noise masker under four signal-to-noise ratios (silence, 0, -5 and -9 dB). F0 pitch discrimination threshold was examined using an adaptive tracking procedure. Results showed that musicians outperformed non-musicians at encoding all types of flattened-F0 speech in noise. Speech intelligibility score declined with increasing signal-to-noise level, with the musicians more resilient to the detrimental effects of noise particularly for identifying flat-intonation and flat-F0 sentences. Compared to non-musicians, musicians relied more on tone-level than intonation-level F0 contour information at comprehending speech under difficult listening conditions. Smaller F0 pitch discrimination limen was found in musicians and correlated with higher intelligibility for understanding speech with degraded F0 information. Collectively, these results suggest that an advantage in tracking tone-level F0 pitch contour in musicians contributes to comprehending speech in noisy backgrounds. Our findings implicate that the potential use of music training to improve speech perception in complex listening environment may be contingent on an enhanced sensitivity to F0 pitch contours.

The Role of Amyloid in Alzheimer Disease

Chaur-Jong Hu, M.D.

In this presentation, I will discuss the evidences of the pathophysiological role of amyloid in Alzheimer disease (AD). Amyloid accumulation is the crucial pathology findings in AD. All the proteins encoded by familial AD genes are involved in amyloid metabolism. High risk of developing AD occurs in Down's syndrome (trisomy 21). The behavioral and pathological changes appear in transgenic animals. The success of aducanumab in AD clinical trial further strengthens the amyloid theory. However, there are challenges of amyloid-clearing therapy, including patient selection, outcome measurement, heterogeneity of disease trajectory and pathophysiology beyond amyloid.

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Reference
1. Spinraza 核准仿單
2. Hagenacker, Tim, et al. The Lancet Neurology, 2020, 19.4: 317-325.

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特別的警語和使用注意事項：腰椎穿刺步驟：腰椎穿刺步驟的部分存在發生不良反應的風險（例如頭痛，背痛，嘔吐）。這種給藥途徑在年紀非常小的病患和脊柱側彎的病患中可能有潛在的困難性。血小板減少和凝血異常：在投與其他皮下或靜脈內給藥之反義寡核苷酸後，曾經觀察到凝血異常和血小板減少，包括急性嚴重血小板減少。如果有臨床上的須要，在 Spinraza 給藥之前，建議進行血小板和凝血實驗室檢測。
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演講主題

機械手臂下的神經外科手術

摘要

隨著科技演進，醫療需求在治療原有疾病之上，更希望能夠增進治療的精準度以微創的方式達到目標。立體定位技術和影像融合、導航技術的發展和成熟，更加推動了精準手術的推廣和應用。在神經外科領域，不管是腦部或是脊髓都是極為精密的構造，在治療方面尤其要求細緻與精準。林口長庚醫院為提升醫療品質於 2020 年引進全國第二台 ROSA ® (Medtech）機械手臂，神經外科醫師可以在手術前於工作站先行做好完整規劃，手術中再輔以機器手臂自動導引至預設位置，並透過機器手臂比人體穩定的優點，將手術儀器架設於機器手臂上來執行手術，大幅增加準確性與降低手術風險。

一般機械手臂於神經外科手術大多使用於脊椎手術，但由於機械手臂的改良與進步，精準度也越來越高，林口長庚神外團隊即利用此優勢，結合機械手臂的精準與微創，創新應用在疼痛治療，腦瘤近接治療，內視鏡輔助手術等，目前是全台唯一將機械手臂應用最廣泛的神外團隊。我們將分享這兩年的機械手臂經驗與特殊案例分享，神經外科醫師如何與機械手臂相互學習，開拓神經外科傳統手術以外更加精準又安全的治療方式。

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Dendrite Arborization and Pruning

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Abstract

One way to characterize different types of neurons isby their distinct morphology, mainly the dendritic trees. One fascinating research direction is how neurons grow such exuberant and distinct patterns of dendrites after their birth. We have been using Drosophila dendritic arborization (da) neurons as the model system to study dendrite growth and pruning during development. There are four types of da neurons (classes I-IV) with class IV da (C4da) neurons being the most complex in morphology. We study cellular machineries underlying endocytosis and exocytosis that are highly active during dendrite elaboration. Golgi outposts are dynamic in dendrites and are regulated in their transport during growth and pruning. Dendrites of C4da neurons innervate epithelial cells that support growth and prevent fasciculation. Protein glycosylation that modifies cell surface receptors that phagocytoses fragmentated dendrites during pruning.

Selected recent publications:

1. 1. Yang, W.-K., Peng, Y.-H., Li, H., Lin, H.-C., Lin, Y.-J., Lai, T.-T., Suo, H., Wang, C.-H. Lin, W.-H., Ou, C.-Y., Zhou, X., Pi, H., Chang, H. C, Chien, C.-T.* (2011) Nak regulates localization of clathrin sites in higher-order dendrites to promote local dendrite growth. Neuron, 72(2) 285-299.
2. 2. Lin, C.-H., Li, H., Lee, Y.-N., Cheng, Y.-J., Wu, R.-M., and Chien, C.-T.* (2015) Lrrk regulates the dynamic profile of dendritic Golgi outposts through the golgin Lava lamp.J. Cell Biol., 210(3) 471-483. (The first two contribute equally).
3. 3. Nithianandam, V. and Chien, C.-T.*, (2018) Actin blobs prefigure dendrite branching sites. J. Cell Biol., 217(10) 3731-3746.
4. 4. Yang, W.-K., Chueh, Y.-R., Cheng, Y.-J., Siegenthaler, D., Pielage, J. and Chien, C. -T.* (2019) Epidermis-derived L1CAM homolog Neuroglianmediates dendrite enclosure and blocksheteroneuronaldendrite bundling. Curr. Biol., 29(9), 1445-1459.
5. 5. Hsun, H., Sung,H.-H., Cheng, Y.-J., Yeh, H.-F., Pi, H., Giniger, E., Chien,C.-T.*Fringe-positive Golgi outposts converge temporal Furin 2 convertase activity and spatial Delta signal to promote dendrite pruning(in revision).

From Biomarkers to Clinical Trials: Lessons of Translational Brain Cancer Stem Cell Biology

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Chair Professor, Graduate Institute of Biomedical Sciences
Director, Neuroscience and Brain Disease Center
China Medical University
Yu Shan Scholar, Ministry of Education, Taiwan
Professor, The University of Texas at Austin.

Ph.D.,MIT (Whitehead Institute for Biomedical Research)
M.D.,Harvard Medical School (Harvard-MIT Division of Health Sciences and Technology)

Abstract

Patients diagnosed with malignant brain tumors such as brain metastases or the primary brain cancer, glioblastoma (GBM), carry a poor prognosis for long term survival and suffer a significantly diminished quality of life. The challenges of tumor heterogeneity, rapid recurrence and therapeutic resistance will be discussed in the context of translational biology studies using patient-derived cancer stem cells and xenograft models. Discovery of new clinically relevant biomarkers from developmental neurobiology approaches, ion channel studies and immuno-screening discovery strategies lead to new perspectives on GBM molecular diagnosis and therapeutics. Preclinical and clinical trial studies of novel cancer alkylphosphocholine analogs for diagnostic detection, fluorescence visualization and therapeutic strategies will also be presented as the foundation of new theranostic strategy for many different cancers.

Selected recent publications:

1. Grudzinski JJ, Hall LT, Cho S, Liu G, Traynor A, Lee MH, Longino M, Pinchuk A, Jaskowiak C, Bednarz B, Weichert J, **Kuo JS**(2022) "Clinical imaging and dosimetry of a pan-cancer targeting alkylphosphocholine analog, ^{124}I-NM404." *Radiation* 2: 215-227.

2. Kukreja L, Li C, Ezhilan S, Iyer V, **Kuo JS**(2022)"Emerging epigenetic therapies for brain tumors." *NeuroMolecular Medicine* 24 (1): 41-49.

3. Umlauf BJ, Clark PA, Lajoie JM, Georgieva JV, Bremner S, Herrin BR, **Kuo JS*,** Shusta EV* (2019) "Identification of variable lymphocyte receptor antibodies that can target therapeutics to pathologically exposed brain extracellular matrix." *Science Advances* 5 (5): eaau4245.

4. Pointer KB, Clark PA, Eliceiri KW, Robertson G*, **Kuo JS***(2017) "Administration of non-torsadogenic human Ether-à-go-go Related Gene (hERG) inhibitors is associated with better survival for high hERG-expressing glioblastoma patients." *Clinical Cancer Research* 23 (1): 73-80.

5. Zhang RR, Schroeder AB, Grudzinski JJ, Rosenthal EL, Warram JM, Pinchuk AN, Eliceiri KW, **Kuo JS***, Weichert JP* (2017) "Beyond the margins: Real time detection of cancer using targeted fluorophores." *Nature Reviews Clinical Oncology* 14 (6): 347-364.

On the neural language of the cerebellum

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Abstract

A slow sensory system presents major problems for movement control. Yet, despite this shortcoming the healthy brain composes exquisite movements. Textbooks posit that this remarkable ability is due to the cerebellum, a structure that learns to predict sensory consequences, thus overcoming time delays. However, cerebellar neurons fire in patterns that do not correspond well with movements. For example, neuronal activity is modulated long after the movement has ended. Thus, the language with which the cerebellum expresses its predictions has remained a mystery.

The idea that we have explored is that in the cerebellum, the fundamental unit of computation may not be a single neuron, but a group of neurons that share the same teacher. In this analogy, the teacher is the inferior olive, organizing the students (Purkinje cells) into groups. To test this idea, we have measured activity of neurons in macaques and marmosets and found that while activity of individual neurons is difficult to decipher, activity of a group of neurons that shares the same teacher is a rather precise predictor of the ongoing movement, particularly during deceleration and stopping.

Selected recent publications:

1. Herzfeld DJ, Vaswani PA, Marko MK, and Shadmehr R (2014) A memory of errors in sensorimotor learning. Science 345:1349-135.

2. Herzfeld DJ, Kojima Y, Soetedjo R, and Shadmehr R (2015) Encoding of action by the Purkinje cells of the cerebellum. Nature 526:439-442.

3. Herzfeld DJ, Kojima Y, Soetedjo R, and Shadmehr R (2018) Encoding of error and learning to correct for that error by the Purkinje cells of the cerebellum. Nature Neuroscience 21:736-743.

4. Sedaghat-Nejad E, Pi JS, Hage P, Fakharian MA, Shadmehr R (2022) Synchronous spiking of cerebellar Purkinje cells during control of movements. Proc. National Academy of Sciences (USA)119:e2118954119.

5. Shadmehr R (2020) Population coding in the cerebellum: a machine learning perspective. Journal of Neurophysiology 124:2022-2051.

Effects of equilibrative nucleoside transporter 1 (ENT1) inhibitor on cognitive deficits and sleep disruptions in sporadic Alzheimer's mice

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Abstract

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases in the elderly and there is no adequate medicine for the treatment. We employs the intracerebroventricular (icv) injection of streptozotocin (STZ; 3 mg/kg, the total injection volume is 1 μl) and intrahippocampal (ih) injection of amyloid-beta (Aβ1-42;1 μg/μl, the total volume is 1 μl) in consecutive 4 days to establish a reliable animal model of sporadic AD (sAD) and determined the efficacy of equilibrative nucleoside transporter (ENT)1 inhibitor on sAD treatment. The expression of pathological hallmarks of amyloid-beta plaques and phosphorylated tau proteins, the indicator of apoptosis, the marker of broken DNA double-strand, the nitrite levels of oxidative stress, the cell number of cholinergic, the Morris water maze (MWM) and novel object recognition (NOR) task were evaluated after oral administration of the ENT1 inhibitor. A 24h sleep-wake activity was acquired by analyzing electroencephalogram (EEG) and electromyogram (EMG). Our results indicated that the ENT1 inhibitor blocked the increases of nitric oxide, caspase 3 and phosphorylated γ-H2AX, increased activities of nuclear DNA-dependent serine/threonine protein kinase (DNA-PKcs) through the non-homologous end joining (NHEJ) pathway to repair DNA double-strand breaks and alleviated cholinergic neuronal loss in sAD mice. The ENT1 inhibitor also improved the cognitive deficits in the MWM and NOR tasks. Furthermore, sAD mice increased non-rapid eye movement (NREM) sleep during dark period and decreased NREM and REM sleep during light period, while the elevation of extracellular adenosine by ENT1 inhibitor exhibited beneficial for recovering the homeostatic sleep. In conclusion, our results indicated that the ENT1 inhibitor could be potential for sAD treatment.

Selected recent publications:

1. Yun Lo, Pei-Lu Yi, Yi-Tse Hsiao, **Fang-Chia Chang***. Hypocretin in locus coeruleus and dorsal raphe nucleus mediates inescapable footshock stimulation (IFS)-induced REM sleep alteration. *Sleep* 2021; https://doi.org/10.1093/sleep/zsab301.
2. I-Chen Li, Ting-Wei Lin, Tung-Yen Lee, Yun Lo, Yih-Min Jiang, Yu-Hsuan Kuo, Chin-Chu Chen, **Fang-Chia Chang***. Oral delivered Armillaria mellea promotes non-rapid eye movement and rapid eye movement sleep in rats. *Journal of Fungi* 2021; 7(5): 371.
3. Yi-Tse Hsiao, Yun Lo, Pei-Lu Yi, **Fang-Chia Chang***. Hypocretin in median raphe nucleus modulates footshock stimuli-induced REM sleep alteration. *Scientific Reports* 2019; 9: 8198.
4. Pei-Lu Yi, Ying-Ju Chen, Chung-Tien Lin, **Fang-Chia Chang***. Occurrence of epilepsy at different zeitgeber times alters sleep homeostasis differently in rats. *Sleep* 2012; 35(12):1651-1665.
5. Yi-Tse Hsiao, Pei-Lu Yi, Chia-Ling Li, **Fang-Chia Chang***. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology* 2012; 62:373-384.

Sleep and restless leg syndrome: perspectives beyond dopaminergic pathway

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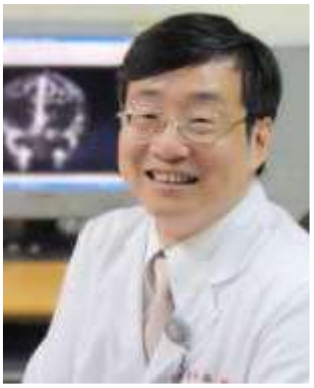

Abstract

Restless legs syndrome (RLS) belongs to sleep-related movement disorder but the underlying pathogenesis is not completely clarified. There is a breakthrough change regarding the treatment of RLS. The dopamine agonists, which have been the evidence-based first choice treatment of RLS, leadto a severe “augmentation” of RLS symptoms. This big change comes from a new concept that RLS is basically a dopamine “hyperactivity” instead of “hypoactivity” state. We started from the dopamine-related “reward system”, coming up with an experimental design using the stimuli based on the idea of “novelty seeking” and “risk taking” behavior, to investigate changes of dopaminergic and opioidreceptor genes, circadian rhythm-related melatonin and clock genes, sleep homeostasis-related cytokines and alpha-2/delta-1 calcium channel receptor gene before and after the stimuli. We chose iron deficiency anemia model of RLS to control the severity and step-wise progression of anemia and conduct a two-axis interventional study in terms of human “full-spectrum light exposure” via retino-thalamic tract and animal low frequency “deep brain stimulation” via bilateral A11 subthalamic nuclei. We analyzed the sleep microstructure, the clock genes expression and changes of melatonin concentration in both humans and animals. We also measured “cognition and balance“related with “sleep deprivation and degree of “impulsivity” and “novelty” related with “dopamine hyperactivity”. We quantified the changes of neurotransmitters and localize the changes using immunohistochemistry in the hypothalamus and basal ganglia-related brain regions. The goal of our study is trying to find out a “point-of-no-return” to promote the pathogenesis of RLS and its interaction with “circadian rhythm”, “homeostasis” and “extra-dopaminergic pathways”.

Selected recent publications:

1. WC Yeh, YC Chuang, CW Yen, MC Liu, MN Wu, LM Liou, CFang Hsieh, CF Chien, CY Hsu*. Static Postural Stability and Neuropsychological Performance After Awakening From REM and NREM Sleep in Patients With Chronic Insomnia: A Randomized, Crossover, Overnight Polysomnography Study. Journal of Clinical SleepMedicine, https://doi.org/10.5664/jcsm.10052, 2022 (SCIE, 69/208, CLINICAL NEUROLOGY).

2. WC Yeh, HL, YS Li, CF Chien, MN Wu, LM Liou, CF Hsieh, CY Hsu*. Non-rapid eye movement (NREM) sleep instability in adults with epilepsy: a systematic review and meta-analysis of cyclic alternating pattern (CAP). SLEEP 45(4), 2022. (SCI, 33/208, CLINICAL NEUROLOGY).

3. CY Hsu, YC Chuang, FC Chang, HY Chuang, TY Chiou, CT Lee*. Disrupted Sleep Homeostasis and Altered Expressions of Clock Genes in Rats with Chronic Lead Exposure. Toxics, 9(9):217, 2021. (SCIE, 30/93, TOXICOLOGY).

4. WC Yeh, PJ Lin, YC Chuang, CY Hsu*. Quantitative evaluation of the microstructure of rapid eye movement sleep in refractory epilepsy: a preliminary study using electroencephalography and heart rate variability analysis. Sleep Medicine, 85:239-245, 2021. (SCIE, 94/208, CLINICAL NEUROLOGY).

5. HJ Lin, JH Yeh, MT Hsieh, CY Hsu*. Continuous positive airway pressure with good adherence can reduce risk of stroke in patients with moderate to severe obstructive sleep apnea: An updated systematic review and meta-analysis. Sleep Medicine Reviews, 54:101354, 2020. (SCI, 8/204, CLINICAL NEUROLOGY).

Brain Functional Reorganizations in Light Sleep

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Joint-Appointment Professor, Ph.D. Program in Neuroscience of Cognition and Consciousness, Taipei Medical University

Ph.D. in Electrical Engineering, National Taiwan University

Abstract

Compared with the rapid-eye-movement (REM) sleep, non-REM (NREM) sleep is associated with fading consciousness and memory consolidation. A decade ago, neuroimaging literature has demonstrated the spatiotemporal alterations of the brain functional connectivity (FC) in NREM sleep, especially in the deep sleep (NREM sleep stage 3, *N3 sleep*) or slow-wave sleep (SWS). In contrast, the light sleep (NREM sleep stage 2, *N2 sleep*), over 50% of total sleep time, does not draw lots of attention in sleep neuroimaging. Recently, we measured the sleeping brain using simultaneous EEG-fMRI recordings at midnight. Beyond the FC changes, we adopted multiverse analytical indices to probe the brain functional alterations across NREM sleep stages, such as complexity to FC variability across distinct spatial scales. Interestingly, we found that the intrinsic brain networks, such as default-mode network (DMN) and attention networks, would experience an extremely unstable long-range connection with enhanced entropy in the N2 sleep. Around the local regional space, the brain in the N2 sleep comes with the elevated local connectivity with reduced local entropy. Altogether, these phenomena indicate that, in contrast to the general inactive brain functions in N3 sleep, the brain in the N2 sleep is undergoing a series of unstable information exchange without the constraints of network boundaries, which relates to an intensive functional reorganizations and implies why we fall into the unresponsive consciousness dissipation every night.

Selected recent publications:

1. Kung, Y.-C., Li, C.-W., Hsiao, F.-C., Tsai, P.-J., Chen, S., Li, M.-K., Lee, H.-C., Chang, C.-Y., **Wu, C.W.**, Lin, C.- P., May 17 2022, Cross-Scale Dynamicity of Entropy and Connectivity in the Sleeping Brain, In: *Brain Connectivity* (In press).

2. Wu, H., Qi, Z., Wu, X., Zhang, J., **Wu, C.**, Huang, Z., Zang, D., Fogel, S., Tanabe, S., Hudetz, A. G., Northoff, G., Mao, Y. & Qin, P., Jan 2022, Anterior precuneus related to the recovery of consciousness, In: *NeuroImage: Clinical*. 33, 102951.

3. Qin, P., Wu, X., **Wu, C., Wu**, H., Zhang, J., Huang, Z., Weng, X., Zang, D., Qi, Z., Tang, W., Hiromi, T., Tan, J., Tanabe, S., Fogel, S., Hudetz, A. G., Yang, Y., Stamatakis, E. A., Mao, Y. & Northoff, G., May 1 2021, Higher-order sensorimotor circuit of the brain's global network supports human consciousness, In: *NeuroImage*. 231, 117850.

4. **Wu, C.W.**, Tsai, P.-J., Chen, C.-J., Li, C.-W., Hsu, A.-L., Wu, H.-Y., Ko, Y.-T., Hung, P.-C., Chang, C.-Y., Lin, C.- P., Lane, T.J., Chen, C.-Y., Aug 2 2019, Indication of Dynamic Neurovascular Coupling from Inconsistency between EEG and fMRI Indices across Sleep-wake States, In: *Sleep and Biological Rhythms*. 17, 423.

5. Kung, Y.-C., Li, C.-W., Chen, S., Chen, C.-J., Lo, C.-Y., Ko, Y.-T., Biswal, B.B., Chang, C.-Y., **Wu, C.W.**, Lin, C.- P., Aug 1 2019, Instability of Brain Connectivity during NREM Sleep Reflects Altered Properties of Information Integration, In: *Human Brain Mapping*. 40, 3192.

Resting state brain oscillatory dynamics in people with varying degree of anxiety and mindfulness

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Ph.D. in Dept. of Physics, National Taiwan University

Abstract

Anxiety and mindfulness are two inversely linked traits shown to be involved in various physiological domains. We used resting state electroencephalography (EEG) to explore differences between people with low mindfulness-high anxiety (LMHA) and high mindfulness-low anxiety (HMLA). The resting EEG was collected for a total of 6 minutes, with a randomized sequence of eyes closed and eyes opened conditions. Two advanced EEG analysis methods, Holo-Hilbert Spectral Analysis and Holo-Hilbert cross-frequency phase clustering (HHCFPC), were employed to estimate the power-based amplitude modulation of brain oscillations, and cross-frequency coupling between low and high frequencies, respectively. The unique advantage of Holo-based methods is that they can reveal the nonlinear and nonstationary characteristics of EEG signals. The presence of higher oscillation power across the delta and theta frequencies in the LMHA group than the HMLA group might have been due to the similarity between the resting state and situations of uncertainty, which reportedly triggers motivational and emotional arousal. Additionally, a higher δ-β and δ-γ CFC in LMHA suggested greater local-global neural integration, consequently a greater functional association between cortex and limbic system than in the HMLA group. The present cross-sectional study may guide future longitudinal studies on anxiety aiming with interventions such as mindfulness to characterize the individuals based on their resting state physiology.

Selected recent publications:

1. **Wei-Kuang Liang***, Philip Tseng, Jia-Rong Yeh, Norden E Huang, Chi-Hung Juan, 2021/04, Frontoparietal beta amplitude modulation and its interareal cross-frequency coupling in visual working memory, NEUROSCIENCE, 460 69-87.
2. Chong-Chih Tsai, **Wei-Kuang Liang***, 2021/03, Event-related components are structurally represented by intrinsic event-related potentials, Scientific Reports, 11 1 5670.
3. Satish Jaiswal, Shao-Yang Tsai, Chi-Hung Juan, Neil G Muggleton, **Wei-Kuang Liang*** (2019, Jun). Low delta and high alpha power are associated with better conflict control and working memory in high mindfulness, low anxiety individuals. *Social Cognitive and Affective Neuroscience*, 14 (6), 645-655
4. Andrew J. Quinn, Vítor Lopes-dos-Santos, Norden Huang, **Wei-Kuang Liang**, Chi-Hung Juan, Jia-Rong Yeh, Anna C. Nobre, David Dupret, and Mark W. Woolrich, 2021/09, Within-cycle instantaneous frequency profiles report oscillatory waveform dynamics, Journal of Neurophysiology, 2021 126:4, 1190-1208
5. Chun-Hao Wang*, **Wei-Kuang Liang***, David Moreau, 2020/01, Differential Modulation of Brain SignalVariability During Cognitive Control in Athletes with Different Domains of Expertise, NEUROSCIENCE, 425 267-279

Automatic sleep staging using intrinsic multi-scale entropy features of five-channel EEG recordings

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Abstract

Sleep is an interesting research topic with growing applications in neuroscience and sleep medicine. This present works proposes a systemic method named as intrinsic multi-scale entropy (iMSE) to quantify a scale-sensitive entropy of electroencephalography (EEG) over two dimensions of filtering and coarse-graining timescales, which performs as a good measure for monitoring sleep status. Methods: A database of polysomnography (PSG) downloaded from PhysioNet with clear notations of sleep stages was used as the material of this study. The five-channels EEG recordings were analyzedby iMSE using 20 filtering and 60 coarse-graining timescales. Two intrinsic entropies sensitively correlated to consciousness level in sleep were defined as indicators for monitoring sleep cycles. Different specific intrinsic entropies perform well in different classifications among six sleep stages (the average of area under ROC curve is 0.925). The dimensionless and objective physical measure of entropy is a good biomarker for monitoring consciousness level in sleep. Entropies calculated from the filtered and coarse-grained time series using specific filtering and coarse-graining timescales work well for automatic sleep staging. A systemic approaching method for determining specific timescales in entropy analysis is the most important contribution in this study. Entropy measure can be a candidate with high scale resolution and high time resolution for investigating the dynamic properties in sleep.

Selected recent publications:

How Dendrites and Spine Layouts can Increase Storage Capacity for Episodic Memory

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Abstract

In order to record the stream of autobiographical information that defines our unique personal history, our brains must form durable memories from single brief exposures to the patterned stimuli that impinge on them continuously throughout life. However, little is known about the computational strategies or neural mechanisms that underlie the brain's ability to perform this type of one-shot "episodic" learning. We present findings at two levels. First, based on evidence that dendrites can act as both signaling and learning units in the brain, we developed a model that relates memory capacity to numerous dendritic, network, pattern, and task-related parameters. We used the model to determine what dendrite size maximizes storage capacity under various conditions. We show that over a several-fold range of both of these parameters and multiple orders-of-magnitude of memory size, capacity is maximized when dendrites contain a few hundred synapses—roughly the natural number found in memory-related areas of the brain. Thus, in comparison to entire neurons, dendrites increase storage capacity by providing a larger number of better-sized learning units (Wu et al. 2019). Second, at a more fine-grained level of analysis, we show that the spine density profile strongly influences a dendrite's nonlinear signaling behavior. In particular, when spine density declines moving outward along individual dendrites – as seen both in the hippocampus and the neocortex – individual dendrites function as more reliable binary-valued thresholding devices which, coming full circle, benefits one-shot learning (Ramdas and Mel, 2021).

Selected recent publications:

1. Mel, B.W., Schiller, J., and Poirazi, P. (2017). Synaptic plasticity in dendrites: complications and coping strategies. *CurrOpinNeurobiol*, 43:177-186, PMID: 28453975.

2. Kumar, A., Schiff, O., Barkai, E., Mel, B.W., Poleg-Polsky, A. and Schiller, J. (2018). NMDA spikes mediate amplification of inputs in the rat pyriform cortex. *eLife, 7:e38446 DOI: 10.7554/elife.38446*

3. Wu, X.E., Strouse, D.J., Mel, G.C., and Mel, B.W. (2019). How dendrites affect online recognition memory. *PLoSComput Biol, 15(5): e1006892. DOI: https://doi.org/10.1371/journal.pcbi.1006892*

4. Jin, L., Behabadi, B. F., Jadi, M. P., Ramachandra, C. A., & Mel, B. W. (2022). Classical-contextual interactions in V1 may rely on dendritic computations. *Neuroscience*, S0306452222001038. *DOI*:https://doi.org/10.1016/j.neuroscience.2022.02.033.

5. Ramdas, T. and Mel, B.W. (2021) Optimizing a neuron for reliable dendritic subunit pooling. Neuroscience, Oct 26;S0306-4522(21)00526-1. *DOI*: https://doi.org/10.1016/j.neuroscience.2021.10.017.

Deep Exposure: hidden behind natural images

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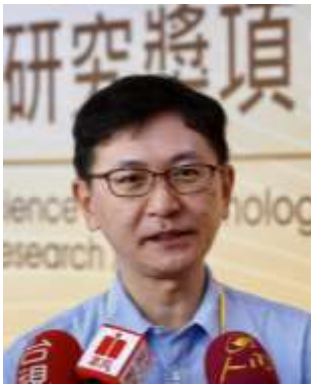

Abstract

Human vision is a powerful sensory system for detecting environmental information. However, its efficiency comes along with built-in fallacies often neglected. Utilizing a machine-learning approach, we reveal a universal hidden structures embedded in most natural images and show that 2D natural images can be compressed and thus encoded faithfully by vorticities along 1D boundaries. In addition, a hierarchy of visual information can be constructed according to the human-eye sensitivity. By projecting out the principal components for human vision, the invisible textures of the natural images emerge, providing a promising tool for medical image analysis in the future.

Selected recent publications:

1. U(1) dynamics in neuronal activities. CY Lin, PH Chen, HH Lin, WM Huang. arXiv:2109.12608 (2021)
2. Manipulating exchange bias by spin–orbit torque. PH Lin, BY Yang, MH Tsai, PC Chen, KF Huang, HH Lin, CH Lai. *Nature Materials* 18, 335-341 (2019).
3. Initialization-free multilevel states driven by spin-orbit torque switching. KF Huang, DS Wang, MH Tsai, HH Lin, CH Lai. *Advanced Materials* 29, 1601575 (2017).
4. Pairing mechanism in multiband superconductors. WM Huang, HH Lin. *Scientific Reports* 10, 7439 (2020).
5. Anomalous isotope effect in iron-based superconductors. WM Huang and HH Lin. *Scientific Reports* 9, 5547 (2019).

Seeking Thermodynamics in Computing Networks of Neurons

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Ph.D. University of Washington

Abstract

Computing networks in intelligent machines and animals alike consist of large numbers of neurons. While the states of these constituent neurons are relatively simple, their collective dynamics gives rise to a very rich repertoire of functional dynamics. With the large degrees of freedom, statistical approaches are desirable in sifting through the voluminous of data for relevant insights into the mechanisms these networks deploy to serve their functional requirements. By matching the statistical properties of the observed data from the dynamics of the neural systems, we can solve for simplified model networks that reproduce the observed statistics. Through these uncovered models, increased possibilities of theoretical and computational analysis from statistical thermodynamics and complex networks can be applied for various characterizations of their states. Similar to statistical physics for understanding the phase behavior of materials, these quantitative descriptions can hopefully lead to better understanding of functional behavior of the neural systems.

Selected recent publications:

1. Yi-Ling Chen, **Chun-Chung Chen**, Yu-Ying Mei, Ning Zhou, Dongchuan Wu, and Ting-Kuo Lee. Ubiquitous proximity to a critical state for collective neural activity in the CA1 region of freely moving mice. Chinese Journal of Physics, 77:497–510, 2022.

2. Kevin Sean Chen, **Chun-Chung Chen**, and C. K. Chan. Characterization of Predictive Behavior of a Retina by Mutual Information. Frontiers in Computational Neuroscience, 11:66, 2017.

3. Chih-Hsu Huang, Yu-Ting Huang, **Chun-Chung Chen**, and C. K. Chan. Propagation and synchronization of reverberatory bursts in developing cultured networks. Journal of Computational Neuroscience, 42(2):177–185, 2017.

4. Yu-Ting Huang, Yu-Lin Chang, **Chun-Chung Chen**, Pik-Yin Lai, and C. K. Chan. Positive feedback and synchronized bursts in neuronal cultures. PLoS ONE, 12(11):e0187276, November 2017.

5. Kai-Yi Wang, Jei-Wei Wu, Jen-Kun Cheng, **Chun-Chung Chen**, Wai-Yi Wong, Robert G. Averkin, Gábor Tamás, Kazu Nakazawa, and Cheng-Chang Lien. Elevation of hilar mossy cell activity suppresses hippocampal excitability and avoidance behavior. Cell Reports, 36(11):109702, 2021.

Worms in maze:
Spatial learning and decision making in a structured environment

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Abstract

Mazes are broadly used to investigate animal decision-making and spatial learning. However, they have been sparsely employed to explore *C. elegans* behavior and training-improved performance. We have developed a highly reproducible, low-cost maze platform, made of the standard, agar-based, nematode culturing material. Using this"Worm-Maze" platform, we show that *C. elegans* nematodes learn to associate food with a combination of proprioceptive cues and information on the structure of their surroundings (maze), perceived through mechanosensation. We demonstrated that *C. elegans* young adults can locate food in T-shaped mazes and, following that experience, learn to reach a specific maze arm.*C. elegans* learning inside the maze is possible after a single training session, it resembles working memory, and it prevails over conflicting environmental cues. We provide evidence that the observed learning is a food-triggered multisensory behavior, which requires mechanosensory and proprioceptive input, and utilizes cues about the structural features of nematodes' environment and their body actions. The CREB-like transcription factor and dopamine signaling are also involved in maze performance. Lastly, we show that the observed aging-driven decline of *C. elegans* learning ability in the maze can be reversed by starvation.

Selected recent publications:

1. Lim CY, Lin HT, Kumsta C, Lu TC, Kang YH, Hansen M, Ching TT*, Hsu AL*. (2022) "SAMS-1 coordinates HLH-30/TFEB and PHA-4/FOXA activities through histone methylation to regulate autophagy and longevity." ***Autophagy.****in press*.

2. Gourgou E, Adiga K, Goettemoeller A, Chen C, Hsu AL*.(2021)"*C. elegans* learning in a structured maze is a multisensory behavior." ***iScience.*** 24(4): 102284.

3. Lin JL, Kuo WL, Huang YH, Jong TL, Hsu AL*****, Hsu WH*. (2021) "Using convolutional neural network to measure the physiological age of *C. elegans*." ***IEEE/ACM Trans. Comput. Biol. Bioinform.*** 18(6): 2724-2732. doi: 10.1109/TCBB.2020.2971992.

4. Sural S, Liang CY, Wang FY, Ching TT*, Hsu AL*. (2020) "HSB-1/HSF-1 pathway modulates histone H4 in mitochondria to control mtDNA transcription and longevity."***Science Advances***. 6(43): eaaz4452.

5. Li G, Gond JK, Liu J, Liu JZ, Li HH, Hsu AL, Liu J, Xu XZS. (2019) "Genetic and pharmacological interventions in the aging motor nervous system slow motor aging and extend lifespan in *C. elegans*." ***Science Advances***. 5(1): eaau5041.

Why burst-dependent synaptic plasticity is relevant for neuromorphic computing

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Abstract

Synaptic plasticity is believed to be a key physiological mechanism for learning. It is well established that it depends on pre- and postsynaptic activity. However, models that rely solely on pre- and postsynaptic activity for synaptic changes have, so far, not been able to account for learning complex tasks that demand credit assignment in hierarchical networks. Here we show that if synaptic plasticity is regulated by high-frequency bursts of spikes, then pyramidal neurons higher in a hierarchical circuit can coordinate the plasticity of lower-level connections. Using simulations and mathematical analyses, we demonstrate that, when paired with short-term synaptic dynamics, regenerative activity in the apical dendrites and synaptic plasticity in feedback pathways, a burst-dependent learning rule can solve challenging tasks that require deep network architectures. Our results demonstrate that well-known properties of dendrites, synapses and synaptic plasticity are sufficient to enable sophisticated learning in hierarchical circuits. We discuss the implications for neuromorphic computing.

Selected recent publications:

1. Payeur, Alexandre, et al. "Burst-dependent synaptic plasticity can coordinate learning in hierarchical circuits." *Nature neuroscience* 24.7 (2021): 1010-1019.
2. Doron, Guy, et al. "Perirhinal input to neocortical layer 1 controls learning." *Science* 370.6523 (2020): eaaz3136.

Blood-based biomarkers for Alzheimer's disease: current status of their clinical implementation in diagnosis, treatment and prevention

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Abstract

Neurodegenerative disorders such as Alzheimer's disease (AD) represent a mounting public health challenge. As these diseases are difficult to diagnose clinically, biomarkers of underlying pathophysiology are playing an ever-increasing role in research, clinical trials, and in the clinical work-up of patients. Though cerebrospinal fluid (CSF) and positron emission tomography (PET)-based measures are available, their use is not widespread due to limitations, including high costs and perceived invasiveness. As a result of rapid advances in the development of ultra-sensitive assays, the levels of pathological brain- and AD-related proteins can now be measured in blood, with recent work showing promising results. To date, several biomarkers have been established that, to a different extent, allow researchers and clinicians to evaluate, diagnose, and more specially exclude other related pathologies. In this talk, we will extensively review data on the currently explored biomarkers in terms of AD pathology-specific and non-specific biomarkers and highlighted the recent developments in the diagnostic and theragnostic domains.

Selected recent publications:

1. Lin SY, Lin PC, Lin YC, Lee YJ, Wang CY, Peng SW, Wang PN*. The Clinical Course of Early and Late Mild Cognitive Impairment. Front Neurol. 2022 May 16;13:685636.

2. Huang YL, Lin CH, Tsai TH, Huang H, Li JL, Chen LK, Li CH, Tsai TF, Wang PN*. Discovery of a Metabolic Signature Predisposing High Risk Patients with Mild Cognitive Impairment to Converting to Alzheimer's Disease. International Journal of Molecular Sciences. 2021 Oct; 22(20):10903.

3. Chen TB, Lin KJ, Lin SY, Lee YJ, Lin YC, Wang CY, Chen JP, Wang PN*. Prediction of Cerebral Amyloid Pathology Based on Plasma Amyloid and Tau Related Markers. Front Neurol.2021 Oct 4;12:619388

4. Wang PN, Lin KJ, Liu HC, Andreasson U, Blennow K, Zetterberg H, Yang SY. Plasma pyroglutamate-modified amyloid beta differentiates amyloid pathology. Alzheimers Dement (Amst). 2020 Apr 30;12(1):e12029.

5. Lin SY, Lin KJ, Lin PC, Huang CC, Chang CC, Lee YC, Hsiao IT, Yen TC, Huang WS, Yang BH, Wang PN*. Plasma amyloid assay as a pre-screening tool for amyloid positron emission tomography imaging in early stage Alzheimer's disease. Alzheimers Res Ther. 2019 Dec 27;11(1):11.

Mild Behavioral Impairment—Novel Prodromal Phenotype of Dementia

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Abstract

Dementia has become a public health priority in aging societies. The limited effects of current treatments for dementia are partly attributable to late diagnoses; therefore, methods for the early identification of dementia must be developed. In addition to cognitive impairment, patients with dementia often experience various neuropsychiatric symptoms before the diagnosis of dementia. A longitudinal study demonstrated that individuals with normal cognition who had neuropsychiatric symptoms exhibited more rapid cognitive decline compared with those without these symptoms. A population-based prospective cohort study reported that the symptoms of irritability, agitation, depression, anxiety, and apathy increased the risk of mild cognitive impairment (MCI) in individuals with normal cognition. Neuropsychiatric symptoms that are observed by clinicians, patients, or informants and persistently occur in middle-aged and older individuals without dementia are named as mild behavioral impairment (MBI), and these symptoms might indicate the prodrome of dementia.

It is a big issue for early detection of dementia. Besides mild cognitive impairment (MCI), diagnosis of mild behavioral impairment (MBI) has been developing recently. Aspects of MBI include decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception or thought content. MBI-checklist (MBI-C) is developed for assessment of MBI. However, the prevalence and biological etiologies of MBI are still unclear. The learning objects of this talk are 1) to understand how to assess MBI using MBI-C in use in Taiwan, 2) to realize the association between MBI and MCI; 3) to learn the biological markers of MBI.

Selected recent publications:

1.

The Discovery of Novel Therapeutic Targets for Alzheimer's Disease

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Ph.D., University of Georgia, Athens, GA, USA.

Abstract

Alzheimer's disease (AD) is characterized by a chronic decline in cognitive functionand is pathologically typified by cerebral deposition of amyloid-β peptide (Aβ). Theproduction of Aβ is mediated by sequential proteolysis of amyloid precursor protein(APP) by β- and γ-secretases, which has been regarded as the amyloidogenic pathway of AD pathogenesis. An RNA interference-based screen has led us to identify an ErbB2-centered signaling network that preferentially govern the proteostasis of APP-C99, a direct substrate of γ-secretases. Down-regulation of ErbB2 by CL-387,785 decreases the levels ofC99 and secreted amyloid-β in cellular, zebrafish, and mouse modelsof AD, through the activation of autophagy. Oral administration of CL-387,785 for 3 wk significantly improves the cognitivefunctions of APP/PS1 transgenic mice, establishing ErbB2 as a novel therapeutic target for AD. A previous report documents the significant correlation between lipid metabolism and incipient AD by using microarray correlation analyses. Given that the level of phosphatidylinositol-4,5-bisphosphate [PI(4,5)P2] in the membrane has been implicated to modulateAβ production, we then investigate whether PIP5Ktype Iα (PIP5K1A) can affect Aβ production by modulating the PIP2 content of the membrane. Our data show that overexpression ofPIP5K1A results in significant enhancement of non-amyloidogenic APP processing, leading to a markeddecrease in secreted Aβ and a concomitant redistribution of APP from endosomal compartments to the cell surface. These results suggesting that PIP5K1A may bea valuable therapeutic target for AD through its effect on promoting non-amyloidogenic processing of APP.

Selected recent publications:

1. B.-J. Wang, G. M. Her, M.-K. Hu, Y.-W. Chen, Y.-T. Tung, P.-Y. Wu, W.-M. Hsu, H. Lee, L.-W. Jin, S.-P. L. Hwang, R. P.-Y. Chen, C.-J. Huang, and **Y.-F. Liao*.** (2017) ErbB2 regulates autophagic flux to modulate the proteostasis of APP-CTFs in Alzheimer's disease. *Proc. Natl. Acad. Sci. U.S.A., 114: E3129-E3138*.

2. P.-Y. Wu, P.-Y. Chuang, G.-D. Chang, Y.-Y. Chan, T.-C. Tsai, B.-J. Wang, K.-H. Lin, W.-M. Hsu*, **Y.-F. Liao***, and H. Lee*. (2019) Novel Endogenous Ligands of Aryl Hydrocarbon Receptor Mediate Neural Development and Differentiation of Neuroblastoma. *ACS Chem. Neurosci., 10: 4031-4042*.

3. P.-Y. Wu, I-S. Yu, Y.-C. Lin, Y.-T. Chang, C.-C. Chen, K.-H. Lin, T.-H. Tseng, M. Kargren, Y.-L. Tai, T.-L. Shen, Y.-L. Liu, B.-J. Wang, C.-H. Chang, W.-M. Chen, H.-F. Juan, S.-F. Huang, Y.-Y. Chan, **Y.-F. Liao***, W.-M. Hsu*, and H. Lee*. (2019) Activation of Aryl Hydrocarbon Receptor by Kynurenine Impairs Progression and Metastasis of Neuroblastoma. *Cancer Res., 79: 5550-5562*.

4. P.-F. Wu, N. Bhore, Y.-L. Lee, J.-Y. Chou, Y.-W. Chen, P.-Y. Wu, W.-M. Hsu, H. Lee, Y.-S. Huang, P.-J. Lu, **Y.-F. Liao***. (2020) Phosphatidylinositol-4-Phosphate 5-Kinase Type 1α Attenuates Aβ Production by Promoting Non-amyloidogenic Processing of Amyloid Precursor Protein. *FASEB J., 34: 12127-12146*.

5. N. Bhore, B.-J. Wang, P.-F. Wu, Y.-L. Lee, Y.-W. Chen, W.- M. Hsu, H. Lee, Y.-S. Huang, D.-I Yang, and **Y.-F. Liao***. (2021) Dual-specificity phosphatase 15 (DUSP15) modulates Notch signaling by enhancing the stability of Notch protein. *Mol. Neurobiol., 58: 2204-2214*.

Investigation of TDP-43 in Alzheimer's disease and the therapeutic development

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Abstract

TDP-43 is an RNA binding protein normally resided in the nucleus. Since 2006, TDP-43 inclusions are found in brain and/or spinal cord tissue of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD) patients. The inclusions were also found in nearly 57% Alzheimer's disease (AD) patients who present faster disease progression and greater brain atrophy. In 2014, we found that recombinant full-length human TDP-43 forms toxic spherical oligomers and perturbs amyloid-β (Aβ) fibrillization. We generated TDP-43 oligomer-specific antibody, TDP-O, and identified the species in FTLD patients by immunostaining and immunoprecipitation. In this talk, I will first present our study to investigate the role of TDP-43 in AD. We identified the interaction of TDP-43 and Aβ and examined the effect of TDP-43 in Aβ fibrillization and in AD mouse models. We also showed that TDP-43 oligomers mostly colocalized with intraneuronal Aβ in the brain of AD patients. Together, we demonstrated that TDP-43 inhibits Aβ fibrillization through its Aβ interaction and exacerbates AD pathology3. In addition, I will discuss our latest results on the therapeutic and diagnostic potential of TDP-43 oligomer-specific monoclonal antibody for neurodegenerative diseases.

Selected recent publications:

1. Fang YS, Tsai KJ, Chang YJ, Kao P, Woods R, Kuo PH, Wu CC, Liao JY, Chou SC, Lin V, Jin LW, Yuan H, Cheng IH, Tu PH, and **Chen YR***."Full-Length TDP-43 Forms Toxic Amyloid Oligomers that are Present in Frontotemporal Lobar Dementia-TDP Patients." **Nature Communications,** 5:4824**(2014)**

2. Tu LH, Tseng NH, Tsai YR, Lin, Lo YW, Charng JL, Hsu HT, Chen YS, Chen RJ, WuYD, Chan YT, Chen CS, Fang JM*, and**Chen YR***.Rationally Designed Divalent Caffeic Amides Inhibit Amyloid-β Fibrillization, Induce Fibril Dissociation, and Ameliorate Cytotoxicity. **European Journal of Medicinal Chemistry**. 158: 393-404 **(2018)**

3. Lee MC, Yu WC, Shih YH, Chen CY, Guo ZH, Huang SJ, Chan JCC, and **Chen YR***. Zinc ion rapidly induces toxic, off-pathway amyloid-β oligomers distinct from amyloid-β derived diffusible ligands in Alzheimer's disease. **Scientific Reports** 8, Article number: 4772 **(2018)**

4. Shih YH§, Tu LH§, Chang TY, Ganesan K, Chang WW,Chang PS, Fang YS, Lin YT, Jin LW, and **Chen YR***.TDP-43 interacts with amyloid-β, inhibits fibrillization, and worsens pathology in a model of Alzheimer's disease. **Nature Communications**. 11: 5950 **(2020)**

5. Chiang WC§, Fang YS§, Lye YS, Wong TY, Ganesan K, Chou SC, **Chen YR***.Hyperphosphorylation-mimetic TDP-43 Drives Amyloid Formation and Possesses Neuronal Toxicity at the Oligomeric Stage. **ACS Chemical Neuroscience**. In revision. **(2022)**

IGF-1 as a Potential Therapy for Spinocerebellar Ataxia Type 3

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Ph.D National Yang-Ming University Institute of Clinical Medicine, Taipei, Taiwan

Abstract

Although the effects of growth hormone (GH) therapy on spinocerebellar ataxia type 3 (SCA3) have been examined in transgenic SCA3 mice, it still poses a nonnegligible risk of cancer when used for a long term. This study investigated the efficacy of IGF-1, a downstream mediator of GH, in vivo for SCA3 treatment. IGF-1 (50 mg/kg) or saline, once a week, was intraperitoneally injected to SCA3 84Q transgenic mice harboring a human ATXN3 gene with a pathogenic expanded 84 cytosine-adenine-guanine (CAG) repeat motif at 9 months of age. Compared with the control mice harboring a 15 CAG repeat motif, the SCA3 84Q mice treated with IGF-1 for 9 months exhibited the improvement only in locomotor function and minimized degeneration of the cerebellar cortex as indicated by the survival of more Purkinje cells with a more favorable mitochondrial function along with a decrease in oxidative stress caused by DNA damage. These findings could be attributable to the inhibition of mitochondrial fission, resulting in mitochondrial fusion, and decreased immunofluorescence staining in aggresome formation and ataxin-3 mutant protein levels, possibly through the enhancement of autophagy. The findings of this study show the therapeutic potential effect of IGF-1 injection for SCA3 to prevent the exacerbation of disease progress.

Selected recent publications:

1. Wu SL, Liu KH, Cheng WL, Su SL, Lin YS, Lin TS, Cheng YS, Chang JC, Wu YL, **Liu CS***. Growth hormone rescue cerebellar degeneration in SCA3 transgenic mice. Biochem Biophys Res Commun. 2020 Aug 20;529(2):467-473.

2. Lin YT, Lin YS, Cheng WL, Chang JC, Chao YC, **Liu CS***, Wei AC*. Transcriptomic and Metabolic Network Analysis of Metabolic Reprogramming and IGF-1 Modulation in SCA3 Transgenic Mice. Int J Mol Sci. 2021 Jul 26;22(15):7974. doi: 10.3390/ijms22157974. PMID: 34360740; PMCID: PMC8348158.

3. Chang JC, Chao YC, Chang HS, Wu YL, Chang HJ, Lin YS, Cheng WL, Lin TT, **Liu CS**. Intranasal delivery of mitochondria for treatment of Parkinson's Disease model rats lesioned with 6-hydroxydopamine. Sci Rep. 2021 May 19;11(1):10597. doi: 10.1038/ s41598-021- 90094-w. PMID: 34011937; PMCID: PMC8136477.

4. .Chang CC, Chen PS, Lin JR, Chen YA, **Liu CS**, Lin TT, Chang HH. Mitochondrial DNA copy number is associated with treatment response and cognitive function in euthymic bipolar patients receiving valproate. Int J Neuropsychopharmacol. 2022 Jan 3:pyab095.

5. .Lin YS, Cheng WL, Chang JC, Lin TT, Chao YC, **Liu CS***. IGF-1 as a Potential Therapy for Spinocerebellar Ataxia Type 3. Biomedicines 2022, 10(2), 505.

Two independent mechanisms that lower mutant ATXN3 expression

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Abstract

Spinocerebellar ataxia type 3 (SCA3), also known as Machado–Joseph disease, is an autosomal dominant neurological disorder caused by an expansion of CAG repeats in the coding sequence of ATXN3 gene. Synthesis together with accumulation of mutant ATXN3 is detrimental to neurons, and accumulated evidence have indicated that a delay or even prevention of SCA3 onset and progression in animals is achievable by lowering the mutated gene expression. In our recent studies, we found that cellular proteins SUPT4H and PIAS1 via two distinct molecular mechanisms to modulate the production of mutant ATXN3. Genetic knockdown of SUPT4H impairs RNA polymerase II transcription machinery elongating over DNA templates containing pathogenic-length of CAG repeats, including SCA3 mutant gene, whereas a decreased ATXN3 protein abundance by a change in its protein stability and post-translational modification is observed in PIAS1 deficient cells. More intriguingly, a PIAS1 genetic variant identified from clinical samples of SCA3 patients with late onset of disease, exhibits a biochemical characteristic that drives mutant but not wild-type normal ATXN3 protein turnover. SUPT4H and PIAS1 thus enable to modulate mutant ATXN3 at the transcriptional and post-transcriptional level respectively and by targeting these cellular proteins individually or in a combinational manner might serve as a practical approach for treatment of SCA3.

Selected recent publications:

1. CR Liu, CR Chang, Y Chern, TH Wang, WC Hsieh, WC Shen, CY Chang, IC Chu, N Deng, SN Cohen*, and **TH Cheng*** (2012). Spt4 is Selectively Required for Transcription of Extended Trinucleotide Repeats. *Cell* 148, 690-701.

2. HM Cheng, Y Chern, IH Chen, CR Liu, SH Li, S Chun, F Rigo,CF Bennett, N Deng, Y Feng, CS Lin, YT Yan*, SN Cohen*, and **TH Cheng*** (2015). Effects on Murine Behavior and Lifespan by Selectively Decreasing Expression of Mutant Huntingtin Allele by Supt4h knockdown. *PLoS Genetics*11, e1005043.

3. CR Liu and **TH Cheng*** (2015). Allele-selective Suppression of Mutant Genes in Polyglutamine Diseases. *Journal of neurogenetics* 29 (2-3): 41-49.

4. NJ Kramer, Y Carlomagno, YJ Zhang, S Almeida, CN Cook, TF Gendron, M Prudencio, MV Blitterswijk, V Belzil, J Couthouis, JW Paul III, LD Goodman, L Daughrity, J Chew, A Garrett, L Pregent, K Jansen-West, LJ Tabassian, R Rademakers, K Boylan, NR Graff-Radford, KA Josephs, JE Parisi, DS Knopman, RC Petersen, BF Boeve, N Deng, Y Feng, **TH Cheng**, DW Dickson, SN Cohen, NM Bonini, CD Link, FB Gao, L Petrucelli*,AD Gitler* (2016). Spt4 selectively regulates the expression of C9orf72 sense and antisense mutant transcripts. *Science* 353, 708-712.

5. YH Lee, YS Tsai, CC Chang, CC Ho, HM Shih, HM Chen, HL Lai, CW Lee, YC Lee, YC Liao, UC Yang*, **TH Cheng***, YJ Chern*, BW Soong* (2021). A PIAS1 protective variant S510G delays polyQ disease onset by modifying protein homeostasis. *Movement Disorders* (in press)

mRNA capping regulates cerebellar development and motor function

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Abstract

Eukaryotic mRNAs have 7-methylguanosine (m7GpppNN, N: any nucleotide) at the 5' end and poly(A) at the 3' end, both of which are important for mRNA stability and translation. In recent years, several chemical modifications in mRNA have been mapped to a transcriptome-wide scale. However, in contrast to epigenetic regulation, mechanisms underlying epitranscriptome-controlled gene expression remain largely unexplored.Therefore, we began to study molecular and physiological functions of cap methyltransferase 1 (CMTR1) and CMTR2, which catalyze 2'-O-ribose methylation (2'-O-Me) of the first (N1) and second (N2) nucleotides in mRNA, respectively. Addition of 2'-O-Me to the 5'-end nucleotides generates cap1 (m7GpppNmN) and cap2 (m7GpppNmNm) structures that have been identified for almost 50 years, but how cells recognize these chemical moieties to control gene expression for physiological functionsremains a mystery. Thus, we generated conditional knockout (cKO) of CMTR2 mice by crossing with *Nestin*-Cre mice whoseCreexpression begins at E10.5 in pan neuron progenitors. CMTR2-cKO mice showed impaired motor coordination and balance in rotarod and beam walking tests. Anatomical and electrophysiological analyses revealed abnormal axonal and dendritic structures and impaired synaptic transmission in CMTR2-deficient Purkinje cells. Which transcripts are N2 2'-O-Me by CMTR2 to support the development and function of Purkinje cells and whether such a modification is perturbed under pathological conditions are currently under investigation.

Selected recent publications:

1. Lu WH, Chao HW, Lin PY, Lin SH, Liu TH, **Huang YS** (2021) CPEB3-downregulated *Nr3c1* mRNA translation confers resilience to developing posttraumatic stress disorder-like behavior in fear-conditioned mice. *Neuropsychopharmacology* 46:1669-1679

2. Lee YL, Kung FC, Lin CH, **Huang YS** (2020) CMTR1-catalyzed 2'-O-ribose methylation controls neuronal development by regulating *Camk2α* expression independent of RIG-I signaling. *Cell Reports* 33:108269

3. Chen HF, Hsu CM, **Huang YS** (2018) CPEB2-dependent translation of long 3'-UTR Ucp1 mRNA promotes thermogenesis in brown adipose tissue. *EMBO Journal*37: e99071

4. Tseng CS, Chao HW, Huang HS, **Huang YS** (2017) Olfactory experience- and developmental stage-dependent control of CPEB4 regulates c-*Fos* mRNA translation for granule cell survival. *Cell Reports* 21: 2264-2276

5. Lu WH, Yeh NH, **Huang YS** (2017)CPEB2 activates GRASP1 mRNA translation and promotes AMPA receptor surface expression, long-term potentiation and memory. *Cell Reports* 21: 1783-1794

Activation of TrkB signaling reverses *Rbm4* knockout induced cerebellar malformation

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Ph.D.National TsingHua University

Abstract

A multifunctional splicing regulator, RBM4 is involved in neuronal differentiation of mouse P19 cells *in vitro* and radial migration of cortical progenitors *in utero* by altering splice isoform expression of critical signaling genes. To gain insights into the function of RBM4 during development, we recently generated conventional *Rbm4* double gene knockout (dKO) mice. *Rbm4*dKO showed rather normal cortical morphology but a foliation defect at cerebellar lobules VI and VII, which is clinically reminiscent of a group of individuals with autism spectrum disorder (ASD). These mice exhibited hyperactive exploratory behavior in the open-field test. The absence of RBM4delayed cell cycle exit of granule cell (GC) precursors and radial migration of postmitotic GCs in the developing cerebellum. The mutant mice also exhibited stunted dendritic arborization of Purkinje cells. These features are reminiscent of neurotrophin deficiency. Strikingly, *Rbm4* knockout reduced the level of brain-derived neurotrophic factor (BDNF)-TrkB signaling. Treatment of pregnant *Rbm4*dOK mice with a TrkB agonist restored cerebellar development and reversed hypoplasia of lobules VI-VII. We further demonstrated that RBM4 promotes BDNF expression. This study provides evidence that prenatal activation of the BDNF-TrkB signaling may ameliorate the defects of cerebellar development caused by *Rbm4* deficiency.

Selected recent publications:

1. Su CH, Hung KY, Hung SC,**Tarn, WY** (2017) RBM4 regulates neuronal differentiation of mesenchymal stem cells by modulating alternative splicing of pyruvate kinase M. *Mol. Cell. Biol*. 37: e00466-16

2. D D, Hung KY,**Tarn, WY** (2018) RBM4 modulates radial migration via alternative splicing of Dab1 during cortex development. *Mol. Cell. Biol*. 38: e00007-18

3. Chuang TW, Lu CC, Su CH, Wu PY,Easwvaran S, Lee CC, Kuo HC, Hung KY, Lee KM, Tsai CY,**Tarn WY** (2019) The RNA processing factor Y14 participates in DNA damage response and repair. *iScience*13: 402-415

4. Chen HH, Yu HI, Rudy R, Lim SL, Chen YF, Wu SH, Lin SC, Yang MH,**Tarn, WY** (2021) DDX3 modulates the tumor microenvironment via its role in endoplasmic reticulum-associated translation. *iScience* 24: 103086

5. Su CH, Liao WJ, Ke WC, Yang RB,**Tarn WY** (2021) The Y14-p53 regulatory circuit in megakaryocyte differentiation and thrombocytopenia. *iScience* 24: 103368

Keynote speech

心智問題的時代特性：以科學與藝術對話為例

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National Taiwan University

Ph.D. National Taiwan University

Abstract

每個時代都有其特殊的心智問題。先以Molyneux question、潛意識因果力量、與自由意志三類歷史上的科學驗證予以說明。其中最關鍵的是完整有效的心智生物學，需要包含哪些部分，需要多久才能發展出來？1880年代，已有測量腦部血流以了解心智活動的19 世紀版本腦部造影系統，1980年代才建立可用的PET與1990年代的fMRI及BOLD訊號，但神經影像與神經元激發量之間具有線性關聯的直接證據，一直到2000年才建立起來，花了120年。Eric Kandel (2012)在其「啟示的年代」(The age of insight)書中，指出腦部的掃描可能發現了憂鬱的神經訊號，但貝多芬交響樂(與梵谷的畫)則展現了對該一憂鬱狀態的真正感覺。1980年代心智與腦部的關係才變得比較清楚，2000年對情緒與同理心才有較廣泛了解，而視知覺重要問題的全盤了解花了50年，所以他樂觀期望對有關情緒共感、社會性大腦運作、無意識與創意歷程、以及主觀內在經驗(含第三與第一人稱經驗)，能做知性了解的心智生物學，可能還需50年。這也是他判斷真正可以處理科學與藝術對話的時間，但現在已經過了十年。最後則依同樣理路，分析如何在現實經驗中判斷精神力量是否介入神經活動，以及小孩如何懷疑Santa Claus是否存在之測試方式。

Selected recent publications:

1. Chiu, Y. C., Lin, C. H., *Huang, J. T., Lin, S., Lee, P.L., & Hsieh, J. C. (2008). Immediate gain is long-term loss: Are there foresighted decision makers in the Iowa Gambling Task? Behavioral and Brain Functions, 4(13), 1-10.

2. Lin, C. H. Chiu, Y. C., *Huang, J. T. (2009). Gain-loss frequency and final outcome in the Soochow Gambling Task: A reassessment. Behavioral and Brain Functions, 5(45), 1-9.

3. 黃榮村、唐大崙、袁之琦、黃淑麗、櫻井正二郎 (2011)。立體視覺之低階運算與高階調控。中華心理學刊，53卷，1期，1-20。

4. Lin, C. Y., Tien, Y. M., Huang, J. T., Tsai, C. H., & Hsu, L. C. (2016). Degraded impairment of emotion recognition in Parkinson's disease extends from negative to positive emotions. Behavioural Neurology, Volume 2016, Article ID 9287092.

5. Chiu, Y. C., Huang, J. T., Lee, W. K., Lin, C. J., & Lin, C. H. (2022). Reanalyzing the Maia and McClelland (2004) empirical data: How do participants really behave in the Iowa Gambling Task? Frontiers in Psychiatry, 13: 788456.

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