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Program Book

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Keynote speech

Sailing into the Neglected Sea of Cerebellum: A Brand New Two-Brain Theory of Human Cognition

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Date: 9/2 (Fri) 09:45~10:55
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Abstract

Cerebral lateralization of cognitive functions had been recognized for a long time. Convincing clinical evidences for the hemispheric asymmetry in language processing appeared 150 years ago by medical doctors Broca (1861) in France and Wernicke (1876) in Germany. Experimental results from the split-brain patients and from normal subjects with visual-half field as well as dichotic listening paradigms in the 60's and 70's provided further support for the two-brain for one consciousness description of cerebral asymmetry. Tzeng and Wang (1984) characterized the dominant function of the left and right hemispheres in terms of superior temporal and spatial coding, respectively. With more and more specific cognitive functions being identified and localized in the two hemispheres, an architecture of functional lateralization and its relationship to callosal connectivity in the human brain was constructed (Kaloris, et al., 2019). However, in retrospect, an unfortunate misgiving in constructing a brain architecture regarding the various specific cognitive functions is its obvious neglect of the cerebellum, which sits at the back and bottom of the brain, behind the brainstem, and had long been recognized as responsible for several function relating only to fine movements and coordination, including maintaining balance, controlling eye movements, and facilitating motor learning. Since late 90's, our laboratory studies have consistently found the cerebellum is engaged during reading and differentially activates in response to phonologic and semantic tasks, indicating that it contributes to the cognitive processes integral to reading (Fulbright, et al., 1999). Lately, more and more recent studies, which focus on scanning the cerebellum, have clearly shown that it appears to play a critical role in cognitive functions such as working memory, cognitive control, action observation, language, decision making, emotion, and social cognition like daily planning. But so far, no theory has been provided to identify the functional role the cerebellum plays in its coordination with the cerebral cortex, which of course is the major player in performing the cognitive tasks. In this talk, I will present a new two-brain theory which specify the critical role of the cerebellum as the professional construction management (PCM) unit, setting up an internal model of the cognitive task at hand and monitoring the performing operations of the cerebral cortex with respect to the temporal and spatial bindings at the neuro-cellular level. It is speculated that the PCM-like control processor allows the cerebellum to provide a scaffolding role for the emergence of an efficient information processing architecture (Encoding, Organized Storage, Fast Retrieval) and make it possible for human being to be good at focus attention, divided attention and selective attention, in performing sophisticated poblem solving, innovation, and creativity. In sum, the new two-brain theory articulates the vital role of the cerebellum in transforming the cognitive operations of the whole brain from a simple shop (柑仔店) to become a complex corporate (e.g., 7/Eleven Super Market)

Selected recent publications:

1.Rueckl, J. G., Paz-Alonso Molfese, P. M., Kuo, W.-J., Bick, A., Frost, S., J., Hancock, R., Wu, D. H., Mencl, W. E., Duñabeitia, J. P., Andoni, J. Lee, J.-R., Oliver, M., Zevin, J. D., Hoeft, F., Carreiras, M., Tzeng, O. J. L., Pugh, K. R. and Frost, R. (2015). Universal brain signature of proficient reading: Evidence from four contrasting languages, Proceedings of the National Academy of Sciences of the United States of America (PNAS), 112(50), 15510-15515.

2.Tzeng, O. J.-L., Lee, C. Y., Lee, J. R., Wu, D. H., Lee, R. R.-W., & Hung, D. L. (2017) Neurolinguistic studies of reading in Chinese. New Directions for Child and Adolescent Development, 158, 55-168.

3.Yu, A., Chen, M, Hung, D., Tzeng, O., Cherodath, S., & Wu, D. H. (2019). Neuroimaging evidence for sensitivity to orthography-to-phonology conversion in native readers and foreign learners of Chinese. Journal of Neurolinguistics, 50, 53-70.

4.Huang, H.W., Nascimben, M., Wang, Y.Y., Fong, D.Y., Tzeng, O.J.L., Huang, C.M. (2021). Which digit is larger? Brain responses to number and size interactions in a numerical Stroop task. Psychophysiology, 58(3), e13744.

5.Wang, S., Zhan, X., Hong, T,.Tzeng O. J. L., Richard, A. (in press). To p -down sensor y prediction in the infant brain at 6 months is correlated with language development at 12 and 18 months, Brain and Language.

A virtual reality system to study social interaction in adult zebrafish

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Abstract

The essence of social interaction is the exchange of information between individuals. During this reciprocal process, the response timing and the response predictability play an important role. However, as social stimulus is the behavior of another animal, these parameters of the stimulus are difficult to manipulate. To enable a systematic control of the social stimulus, we are developing 3D models of adult zebrafish with controllable behaviors. The virtual fish, which is displayed on a computer monitor, performs naturalistic swimming patterns and adjusts its locomotion according to the behavior of a real animal swimming in an adjacent tank. The virtual and real animals thus establish a close-loop interaction in which experimenters have a full access to manipulate the response of the virtual animal through computer programing. To enable measurements of brain activity during behavior, we are also developing a VR system using a 6-axis force/torque sensor that in principal enables a head-restrained zebrafish to navigate in a 3D virtual space. This VR system is integrated into a two-photon microscope for non-invasive measurements of activity throughout the dorsal telencephalon. In addition, the respiration and the eye angle of the adult animal are simultaneously monitored, which enables us to correlate neural activities to behaviors driven by emotions and visual attention. Overall, this ongoing project demonstrates the potential of using virtual reality techniques to investigate the role of reciprocal interaction during social behavior.

Investigating the circatidal rhythm in vertebrates using Periophthalmus modestus (Shuttles Hoppfish)

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Abstract

The behavior of intertidal organisms may be affected by the sun or the moon. For example, circadian rhythm, annual rhythm, and seasonal rhythm are modulated by the sun. In contrast, circalunar rhythm, circasemilunar rhythm, and circatidal rhythm may be regulated by the moon. Current research primarily focuses on the circatidal rhythm of invertebrates such as crustaceans, mollusks, and insects. However, whether circatidal rhythm exists in other intertidal vertebrates is unclear. Thus, we investigate the circatidal rhythm of an intertidal vertebrate Periophthalmus modestus in a stimulated tidal environment. Using video cameras to monitor and analyze the activity individually, we found that P. modestus has tidal rhythmic behaviors such as movement time, dry, and wet zone location preference under both 6.5:6.5 high-low tide cycle and constant conditions. Furthermore, the circadian rhythm is relatively weak compared to the circatidal rhythm. Together, our results suggest that the circatidal clock may be a conserved biological clock in animals, including osteichthyes.

Optogenetic inhibition of vCA1 suppresses LH-related sleep disturbance induced by footshock in mice

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Li Jou Lai, Kai Hang Deng, Yi-Tse Hsiao
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Abstract

Sleep disturbance troubles hundreds of people every night over the world. These sleepless experiences sometimes are related to unpleasant daytime experience. Recent studies have showed that ventral hippocampus CA1 (vCA1), known as a critical brain area that process memory, is enriched in anxiogenic experience-sensitive cells. Meanwhile, lateral hypothalamus (LH) has been implicated in wakefulness promotion and also mediated stress response. In previous studies done by our lab team, we found a significant increase of wakefulness ratio in TRAP(Fos2A-iCreER) mice during their resting phase, following chemogenetic activation of LH neurons that had been“Trapped”after giving inescapable footshock stimuli (IFS). We proposed that there is a direct neuron activation route from vCA1 to LH activated during IFS conditioning. In following researches, we extended the previous experiments by application of optogenetic techniques, using virus-carried light-activated membrane chloride pump Halorhodopsin (NpHR) to locally inhibit the activation of vCA1 neurons during IFS conditioning. At the LH we injected Cre-DIO (double floxed inverse open reading frame) hM3Dq virus with mCherry reporter gene to stimulate IFS-activated cells. The effects to sleep disturbance was observed by electroencephalography (EEG) 12 hours sleep recording after different doses of clozapine (CLO) intraperitoneal injection. The preliminary results show that although wakefulness ratio is notably higher in the first 2 hours of the resting phase, there are no significant difference of wakefulness, NREM sleep and REM sleep ratios in following hours between different groups of CLO doses. Fluorescent microscope image results show that the expression of hM3Dq is remarkably reduced compared to previous experiments.

CPEB2-Activated Axonal Translation of VGLUT2 mRNA Promotes Glutamatergic Transmission and Presynaptic Plasticity

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Wen-Hsin Lu, Tzu-Tung Chang, Yao-Ming Chang, Chia-Hsuan Lin, Ching-Shu Suen, Ming-Jing Hwang and Yi-Shuian Huang

Abstract

Remodeling the synaptic proteome to sustain long-term plasticity and memory can depend on locally translated mRNAs. However, the regulatory mechanisms have been biasedly discovered in postsynaptic (dendritic) rather than presynaptic (axonal) compartments due to the lack of distinct polyribosomes in the tiny domain of adult mammalian forebrain axons. Cytoplasmic polyadenylation element binding protein 2 (CPEB2)-controlled translation is important for postsynaptic function and spatial memory. We therefore investigated the presynaptic role of CPEB2 in Schaffer collateral-CA1 and temporoammonic-CA1 circuits and found defective fiber volley amplitude and paired-pulse facilitation in CPEB2-deficient presynaptic afferents. By cross-comparing CPEB2-immunoprecipitated transcriptome with a learning-associated axonal translatome in the adult cortex, we identified and validated that Slc17a6, encoding vesicular glutamate transporter 2 (VGLUT2), is translationally upregulated by CPEB2. Blocking activity-induced axonal Slc17a6 translation by CPEB2 deficiency or cycloheximide diminished the releasable pool of VGLUT2-containing vesicles. Collectively, CPEB2-regulated presynaptic translation supports glutamatergic transmission, long-term potentiation and memory.

Involvement of ASIC1a in ASIC4-positive BNST/amygdala neurons in modulating anxiety and fear

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Abstract

ASIC4 is a member of acid-sensing ion channels and widely expressed in the CNS. However, the physiological function of ASIC4 remains unclear. Previous studies have shown that ASIC4 can interact with ASIC1a and counteract the ASIC1a-mediated anxiety-like responses. Here we used genetic approaches to probe the role of ASIC4 in anxiety-associated nuclei in mouse models. We discovered that chemo-optogenetically activating ASIC4-positive cells induced anxiety-like responses in mice. Studies of mice with a disrupted ASIC4 gene in specific brain regions suggested that ASIC4 in the amygdala and the bed nucleus of the stria terminalis (BNST) are implicated in fear and anxiety. Interestingly, conditional knockout of ASIC1a in ASIC4 positive cells resulted in reduced anxiety behavioral phenotypes in both fear and anxiety. In situ hybridization data suggested a possible surface membrane protein modulation role for ASIC4 in regulating ASIC1a, so we performed point-mutations on two glycosylation sites, Asn191 and Asn341, which resulted in differential effects on ASIC4 biogenesis. Furthermore, these Asn191 and Asn341 mutations increased ASIC1a surface protein expression and current density. More importantly, expression of ASIC4 in the amygdala and bed nucleus of the stria terminalis of ASIC4 knockout mice using viral vector-mediated gene transfer resulted in rescue of the anxious phenotypes. Together, these data suggest ASIC4 plays an important role in fear and anxiety-related behaviors, with the glycosylation of ASIC4 as one of the possible mechanisms.

Exploring Sng Behavior in Mouse Gait

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Gary Chieh-Wei Lee, Cheng-Han Lee, Chih-Cheng Chen
李杰威、李政翰、陳志成

Abstract

Sngception (痠覺) describes the response of the somatosensory nervous system to tissue acidosis and is closely related to nociception. This ambiguity has condemned it to remain neglected in neuroscience studies causing its underlining mechanism largely undiscovered. Sngception has been shown to be a central concern in fibromyalgia, radiculopathy and other related somatosensorial conditions. To pave the way for the understanding of sngception's molecular mechanism, it's urgent to develop and establish a monitoring system for sngception-related behaviors in animal models. Sngception is thought to be caused by tissue acidosis, which is, in term, induced by inflammation, ischemia, fatiguing exercise, and the like. When people suffer from unpleasant sensations, gait is usually modified in order to guard the uncomfortable tissue. Gait analysis is widely used in monitoring nociception in clinical and animal models of pain. We hypothesize that this system may also be valuable in monitoring sngception-related behaviors. Our preliminary results, analyzed from mice paw imaging show that spatial, structural, and temporal gait parameters have a tendency to change after temporary muscle acidosis induced through intramuscular acidic saline injection. This suggests that the technique has potential in monitoring sng behavior, which could lead to the discovery of its molecular mechanism. In this study, we will analyze sng- and pain-induced gait change and further investigate the involvement of acid sensing ion channels through both pharmacological and genetic approaches.

An unexpected role of proprioceptors in the development of chronic muscle pain

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李政翰，陳志成

Abstract

Fibromyalgia affects 2% to 8% of the adult population with high prevalence in women. Patients always suffer from chronic widespread musculoskeletal pain. However, how FM pain developed is still a mystery. Clinical studies demonstrated that intramuscularly injection of acidic solution would cause pain. In fibromyalgia mouse model, repeated acid injection in muscle, further developed long-lasting mechanical hyperalgesia. This highlights the importance of peripheral acid signaling in chronic muscle pain development. Previous findings point out the critical role of Acid-Sensing Ion Channel 3 (ASIC3) in development of acid-induced mechanical hyperalgesia. ASIC3 predominately expresses in peripheral sensory neurons including nociceptors and proprioceptors. It's worth to discover the contribution of each population of ASIC3-expressing sensory neurons in development of acid-induced chronic pain. We first test the mechanical hyperalgesia level in nociceptors or proprioceptors ASIC3 conditional knockout mouse (Asic3Pv, proprioceptors or Asic3Nav1.8, nociceptors) after acid induction. Surprisingly, Asic3Pv but not Asic3Nav1.8 mice showed no prime responses after acid induction. This indicated that proprioceptors may play an additional role in sensing muscle acidosis, which mediated by ASIC3. Further, we use optochemogenetic tool (CTZ-LMO3 system) to specific activate Nav1.8+ and Pv+ muscle afferents to address the population of muscle afferents in acid-induced chronic hyperalgesia. Excitingly, specific activate Pv+ muscle afferents, mice were primed to induce mechanical hyperalgesia, but not Nav1.8+. Further, we explored a subtype of metabotropic glutamate receptor, mGluR5-PLD, mediates the Pv+ neuron-dependent prime effect and cellular neuronal activation (monitored by phosphorylated ERK level) by the mGluR5-PLD inhibitor, PCCG13. To further understand proprioceptor ASIC3-mediated, acid-induced chronic hyperalgesia is developed through glutamate-mGluR5 signaling. We modified the recipe of acid-induced hyperalgesia in following up first inject pH6.4 and ASIC3 potenciator, RPRFamide, with an acid injection one day apart in wild type mice. Exhilaratingly, PCCG13 blocks ASIC3-mediated, acid-induced chronic hyperalgesia. Further, in acid-induced chronic hyperalgesia in Asic3Nav1.8 mice, supposed ASIC3 expression is normal in proprioceptors, PCCG13 also blocks the development of chronic hyperalgesia. Taken all together, proprioceptors may contribute to acid induced-priming during development of chronic muscle hyperalgesia through ASIC3 and peripheral mGluR5-dependent glutamate signaling.

Basal forebrain glutamatergic neurons inhibit reward-seeking behavior and the activity of bursting neurons

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Abstract

Basal forebrain (BF) is one of the most prominent neuromodulatory systems and plays key roles in attention, arousal and decision making. While most BF studies have focused on its cholinergic and GABAergic neurons, the functions of BF glutamatergic (Vglut2) neurons remain largely unknown. Recent studies have found that subcortical glutamatergic neurons in several brain regions, including the BF, send prominent projections to the lateral habenula (LHb), a critical hub of the brain's aversion circuitry. Moreover, many such glutamatergic neurons inhibit reward-seeking behavior and encode negative valence. These observations raise the question of whether BF glutamatergic neurons may serve a similar role in the processing of aversive information and oppose the processing of reward information by another group of BF neurons, the BF bursting neurons. Using cell-type specific optogenetic manipulations and neuronal recording in head-fixed Vglut2-cre mice, here we show that BF Vglut2 neurons transiently inhibit reward-seeking behavior and inhibit the activity of BF bursting neurons. Mice were trained to perform a reward-seeking task, in which an auditory cue is paired with water reward in two-thirds of trials. We found that photostimulation of BF-LHb Vglut2 neurons led to a biphasic effect of the reward-seeking licking response, which was composed of an initial transient inhibition followed by a rebound facilitation. At the neuronal activity level, photostimulation of BF Vglut2 neurons biphasically modulated the activity of BF bursting neurons, starting with a transient inhibition phase followed by a rebound excitation. Moreover, photostimulation of BF-LHb Vglut2 neurons led to consistent effects on bursting neurons with those described above. These results indicated that the modulation of BF Vglut2 neurons on reward-seeking processing was mainly via the LHb. Together, our results reveal a novel biphasic modulation of BF-LHb Vglut2 neurons at both behavioral and neural activity levels, and suggest that BF-LHb Vglut2 neurons play an opposing role to the BF bursting neurons. The opponent interactions between BF bursting neurons and Vglut2 BF neurons suggest that positive and negative valence information converge and interact within the BF.

Functional coupling between midbrain dopamine neurons and basal forebrain bursting neurons in the encoding of reward prediction error

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Abstract

Reward prediction error (RPE), the difference between received and predicted reward, has been traditionally associated with neuronal activity in midbrain dopaminergic (DA) neurons. However, recent studies from our group have demonstrated that a special subset of noncholinergic neurons in the basal forebrain (BF), which we refer to as BF bursting neurons, are similarly modulated by RPE. Both neuronal populations show synchronous phasic activities relative to reward delivery and reward-predicting cues, with responses modulated by subjective value and reward expectations. These observations raise the important question of whether the highly similar neural profiles in midbrain DA neurons and BF bursting neurons represent the same RPE information and result from functional coupling. To answer this question, we simultaneously recorded DA and BF activities while rats perform a licking-based delayed reward task. Here we show that the activities of DA and BF bursting neurons were tightly coupled, with DA neurons temporally leading BF bursting neurons by 10ms. We found that the responses of BF bursting neurons and DA neurons toward various behavioral events were highly similar. Moreover, the trial-by-trial fluctuation of neuronal activities in both regions were strongly coupled with each other even after the influence of common behavioral events were taken into account. Spike timing cross-correlation analysis further revealed a consistent temporal delay, with midbrain DA neurons temporally leading BF bursting neurons by ~10ms. Together, these results suggest that BF bursting neurons similarly encodes RPE information and challenges the canonical view that RPE is solely encoded by DA neurons. These results also serve as a starting point to further investigate why and how the brain uses two major neuromodulatory systems to jointly encode RPE. In the accompanying poster, we investigate the causal interactions between the two neuronal populations by optogenetically activating DA neurons.

Distinct subsets of hypothalamic SF-1 expressing neurons encode an exploratory internal state that drives animals' investigative behaviors

Shih-Che Lin (林士哲)

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Abstract

The Steroidogenic factor 1 expressing neurons in the dorsomedial/central parts of the ventromedial hypothalamus (VMH-SF1 neuron) are regarded as an essential pivot for maintaining energy homeostasis and driving several innate behaviors. Previous studies have suggested that VMH-SF1 neurons encode a predator-orientated defensive state: optogenetic and pharmacogenetic stimulation of the VMH-SF1 neurons evoked an anxious-like state that further elicited various defensive behaviors. On the other hand, silencing these neurons rendered the animal less anxious while encountering predatory cues. Nevertheless, whether the VMH-SF1 neurons would respond to hostile conditions and their behavioral relevance remain mostly elusive. We performed in vivo calcium imaging with fiber photometry and a head-mounted miniature microscope (miniscope) to monitor the real-time activities of the VMH-SF1 neurons in response to predatory- or conspecific-cues in freely-roaming mice. We found that the VMH-SF1 neurons were robustly activated by conspecific exposure, yet encountering predatory cues induced relatively moderate neural responses. Moreover, VMH-SF1 neuronal activities showed a strong temporal correlation with exploratory but not defensive behaviors. The miniscope recording further revealed that conspecific- and predatory cues recruited distinct subsets of VMH-SF1 neurons, and the stimulus-induced calcium dynamics of these distinct subpopulations reliably encode the identity of the stimulus. However, artificially manipulating all VMH-SF1 neurons robustly altered animals' defensive states. This discrepancy implied that functional interpretations derived from conventional manipulations without selectivity to stimulus-selective subsets might not truly reflect the behaviors controlled by these neurons in vivo. Altogether, we suggest that the VMH-SF1 neurons are heterogeneous and can be further classified into several functionally distinct groups based on their stimulus selectivity. A distinct subset of VMH-SF1 neurons could prompt animals' investigative behaviors upon detecting the presence of their preferred external stimulus, yet another subset facilitates defensive state-related behaviors.

Generational synaptic functions of GABAA receptor β3 subunit deteriorations in an animal model of social defcit

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Abstract

Disruption of normal brain development is implicated in numerous psychiatric disorders with neurodevelopmental origins, including autism spectrum disorder (ASD). Widespread abnormalities in brain structure and functions caused by dysregulations of neurodevelopmental processes has been recently shown to exert adverse effects across generations. An imbalance between excitatory/inhibitory (E/I) transmission is the putative hypothesis of ASD pathogenesis, supporting by the specific implications of inhibitory γ-aminobutyric acid (GABA)ergic system in autistic individuals and animal models of ASD. However, the contribution of GABAergic system in the neuropathophysiology across generations of ASD is still unknown. Here, we uncover profound alterations in the expression and function of GABAA receptors (GABAARs) in the amygdala across generations of the VPA-induced animal model of ASD. The F2 generation was produced by mating an F1 VPA-induced male offspring with naïve females after a single injection of VPA on embryonic day (E12.5) in F0. Autism-like behaviors were assessed by animal behavior tests. Expression and functional properties of GABAARs and related proteins were examined by using western blotting and electrophysiological techniques. Social deficit, repetitive behavior, and emotional comorbidities were demonstrated across two generations of the VPA-induced offspring. Decreased synaptic GABAAR and gephyrin levels, and inhibitory transmission were found in the amygdala from two generations of the VPA-induced offspring with greater reductions in the F2 generation. Weaker association of gephyrin with GABAAR was shown in the F2 generation than the F1 generation. Moreover, dysregulated NMDA-induced enhancements of gephyrin and GABAAR at the synapse in the VPA-induced offspring was worsened in the F2 generation than the F1 generation. Taken together, these findings revealed the E/I synaptic abnormalities in the amygdala from two generations of the VPA-induced offspring with GABAergic deteriorations in the F2 generation, suggesting a potential therapeutic role of the GABAergic system to generational pathophysiology of ASD.

Dopamine signaling in the regulation of neuroinflammation and glymphatic dysfunction during chronic feeding with high fat diet

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Abstract

Depression is associated with the change of functional connection between the frontal cortex and the striatum, which is called fronto-striatal (FS) circuit in the central nervous system (CNS). The disruption of dopamine (DA) transmission in. Neuroinflammation in the CNS is triggered by different types of stimuli, such as peripheral inflammation, traumatic brain injury, viral infection, chronic stress, etc. Glia, astrocytes, and microglia, play the major inducers in the initiation and progress of neuroinflammation. Obesity is due to metabolic abnormalities and becomes one of the risks of depression and metabolic disorders. It is an increasing interest in examining the role of the glymphatic system in the development of neurodegenerative diseases. We have previously demonstrated that the reactivity of glia in the CNS was induced in the hypothalamus and striatum by chronic feeding with high fat diet (HFD). Based on the role of the DA signaling in adaptive immunity, we attempted to define the involvement of DA and its receptors (D1R and D2R) in HFD-induced glial reactivity in the FS circuit and the glymphatic deregulation. At first, the regional change in DR gene expression was examined at the different time points of HFD feeding. D1R expression was insignificantly altered in the analyzed brain regions. Yet, the temporal and spatial changes of D2R expression by HFD feeding were observed. Moreover, HFD feeding reduced the gene expression of aquaporin 4 (AQP4), a water channel protein that is intensively present at the vascular astrocytic endfeet and promotes lymphatic transport. Furthermore, the in vitro experiments showed that AQP4 expression was downregulated by the addition of DA or D2R antagonist trifluoperazine (TFP) in inflammagen-stimulated striatal astrocytes. These results indicate that chronic feeding by HFD could cause glymphatic dysfunction. Thus, DA/D2R signaling in the regulation of glial function in the FS is to be determined in chronically HFD-fed mice. We are also to determining the mechanisms underlying the regulation of AQP4 expression by chronic HFD feeding and the imbalance of the glymphatic system in obese mice.

Effects of sleep restriction on brain function and cognition-enhancing protein klotho

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Abstract

Sleep is a physiologic state that performs an essential restorative function and facilitates memory consolidation. Sleep restriction may impair hippocampal neuronal plasticity and memory process. Klotho is initially identified as an anti-aging protein. Recent studies have found that klotho improves cognition through enhancing long-term potentiation and enriching the synaptic NR2B and NMDA receptors. Although klotho is viewed as a potential treatment for cognitive and neurodegenerative disorders, whether it is able to alleviates the detrimental effects induced by sleep restriction remains elusive. Therefore, the objective of this study is to explore whether sleep restriction causes cognitive impairment by regulating klotho protein. Male C57BL/6 mice were randomly assigned to control and sleep restriction (SR) groups after evaluating behavior by using open field and Morris water maze. Mice of SR group were placed into the SR box for 20 hrs per day. After 7-day sleep restriction, both groups were conducted in the behavioral tests again to investigate the effects of sleep restriction on locomotion and cognition. The levels of klotho and its downstream NR2B protein expression in the cognition-related brain regions were analyzed by western blotting. The results demonstrated that mice of SR group spent more time to find the platform in the test trial in Morris water maze, indicating that sleep restriction impairs spatial memory. However, SR treatment didn’t affect locomotor activity in the open field. SR treatment induced down-regulation in klotho and NR2B protein levels in the prefrontal cortex. Taken together, sleep restriction impairs spatial memory, but has no effects on locomotion. The impaired spatial memory induced by sleep restriction might due to the regulation of klotho levels and related pathway.

Impact of information transfer in Periplaneta group dynamics and aggregation behaviour

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Abstract

Optimal foraging theory, Selfish Herd, and several top-down models fall short of explaining the factors that determine group movement and decision-making for animals that do not follow rigid hierarchies or centralised control. These models define intergroup relations as immutable rules based on proximity, without considering an animal's sensory system or information gained from conspecifics. Thus, animal groups are modelled as an aggregation of particles, disregarding new properties that emerge as members cooperate or compete. The American cockroach (\textit{Periplaneta Americana}) does not exhibit rigid patterns of social hierarchy or task allocation. They seem to rely on `collective wisdom' and show a preference for aggregating with peers rather than venturing alone into unbeknownst territories in search of food. The simplicity and horizontality of their social interactions make them an ideal organism for studying information dissemination and its impact on system-wide behavioural patterns. This study draws on models and techniques used in network and information theory and trajectory forecasting to understand the factors that modulate information exchange and group decision-making in moving insects. It contrasts cockroach group movement in an open space, where they can interact freely, with their dynamics in a maze that restricts their interactions. We described and explained collective movement using mathematical and computational tools by using prediction models and mutual information to identify the most useful features to forecast individual and group behaviour. Then, we determined the impact of information transfer in insect groups by contrasting group behaviour against the non-interacting aggregation of individual behaviours. Finally, we concluded that communication between Periplaneta acts as a weak attractive force, that influences their decisions only when in close proximity of their peers. Thus, communication ensures that groups of animals maintain cohesiveness that protects individuals from predators or environmental hazards.

Investigating the role of Cap-methyltransferase 2 in cerebellar development and neurodegeneration

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Abstract

Methylation of messenger RNA (mRNA) is an abundant event in the central nervous system, but its effects on regulating gene expression and biological processes are poorly understood. A pre-mRNA undergoes post-transcriptional processing and modification (i.e., splicing, polyadenylation and 7-methylguanosine capping) before becoming a mature mRNA to be translated in the cytoplasm. In higher eukaryotic organisms, the first and second nucleotide are methylated at the 2' O-ribose position by cap methyltransferase (CMTR) 1 and 2, respectively. CMTR1 regulates brain development and neuromorphogenesis, but the role of CMTR2 in the brain remains completely unexplored. To understand the physiological function of CMTR2, we generated Cmtr2 global knockout mice and found them unable to develop beyond the gastrulation stage. Thus, we used Nestin-Cre mice to generate conditional knockout of Cmtr2 (Cmtr2-cKO) in neural and glial progenitor cells and investigated Cmtr2 function in the nervous system. Cmtr2-cKO mice with mild cerebellar atrophy showed severe motor incoordination in beam walking and rotarod assays. Histological analyses showed reduced thickness of the cerebellar molecular layer, which is the dendritic layer of Purkinje cells (PCs). Inositol 1,2,3-triphosphate receptor type (ITPR1) immunohistochemistry, which labels PCs, revealed increased axonal swellings (torpedoes) and dendritic swellings in Cmtr2-Cko PCs. Notably, evident neurodegeneration and death of PCs especially in Lobules IV-V were observed in aging Cmtr2-cKO mice (18-25 months). Using Visium spatial transcriptomics analysis, we identified differential expression of mitochondrion-related, genes in Cmtr2-cKO PCs. Together, we hypothesize that CMTR2 deficiency-induced mitochondrial stress and dysfunction result in abnormal axonal and dendritic swellings of PCs, thereby leading to age-dependent neurodegeneration. The mitochondria functional assay will be performed to validate our hypothesis. Moreover, we will also identify the target mRNAs regulated by CMTR2 in PCs to better understand the molecular action of CMTR2 in the cerebellum.

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投稿學會：台灣基礎神經科學學會	編號: P1-16

Wdr4 Promotes Cerebellar Development and Locomotion through Arhgap17-Mediated Rac1 Activation

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Abstract

Patients with mutations of WDR4, a substrate adaptor of the CUL4 E3 ligase complex, develop cerebellar atrophy and gait phenotypes. However, the underlying mechanisms remain unexplored. Here, we identify a crucial role of Wdr4 in cerebellar development. Wdr4 deficiency in granule neuron progenitors (GNPs) not only reduces foliation and the sizes of external and internal granular layers but also compromises Purkinje neuron organization and the size of the molecular layer, leading to locomotion defects. Mechanistically, Wdr4 supports the proliferation of GNPs by preventing their cell cycle exit. This effect is mediated by Wdr4-induced ubiquitination and degradation of Arhgap17, thereby activating Rac1 to facilitate cell cycle progression. Disease-associated Wdr4 variants, however, cannot provide GNP cell cycle maintenance. Our study identifies Wdr4 as a previously unappreciated participant in cerebellar development and locomotion, providing potential insights into treatment strategies for diseases with WDR4 mutations, such as primordial dwarfism and Galloway-Mowat syndrome.

投稿學會：台灣基礎神經科學學會	編號: P1-17

The function of Wuho in cortical development

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Abstract

Wuho (also known as WDR4) is an essential gene for embryonic development. It regulates many critical physiological processes, including tRNA modification, genome stability, and germ cell homeostasis. As Wuho mutations in humans were linked to microcephaly primordial dwarfism, we study the function of the Wuho gene in cortical development. We first generated Wuho conditional knockout (cKO), in which Wuho is deleted by Emx1-Cre in the cortical progenitors and their progeny, the cortical excitatory neurons. We found the cKO mice weigh less and have a shorter lifespan than their wild-type littermates. Further, agreeing with the microcephalic phenotype found in the patients, cKO mice also have a smaller and thinner cortex. To investigate the causes of microcephaly in the cKO mice, we compared progenitor proliferation/differentiation and cell death in WT and cKO mice. We found a significantly increased number of apoptotic cells in the cKO cortices. Interestingly, the distribution of these apoptotic cells is not uniform in the cKO cortices: more of them are found in the rostro-medial cortex. We are currently investigating the molecular mechanisms for Wuho to regulate cell survival during cortical development.

投稿學會：台灣基礎神經科學學會 | 編號: P1-18

To investigate the mechanisms regulating border formation of entorhinal cortex

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Abstract

The cerebral cortex consists of multiple functional domains, and each has specific functions, location, and neuronal properties. We study how, during development, a specific cortical region arises at a specific location, acquires its specific properties, forms appropriate neuronal connections, and generates boundaries with adjacent cortical regions. We previously identified COUP-TFI plays a critical role in the development of the medial entorhinal cortex (MEC), and also controls the location and integrity of neocortex (NC)/MEC border through differential cell affinities. We also demonstrated that protocadherin 19 (Pcdh19) is required for COUP-TFI-induced cell clustering. To further investigate the role of Pcdh19 in NC/MEC border formation, we analyzed the NC/MEC border in the Pcdh19 null mutants. Surprisingly, we detected a sharp border between NC and MEC in the Pcdh19 null mutants at P7, similar to wild type mice. This suggests that, in addition to Pcdh19, other adhesion factors might be involved in NC/MEC border formation. Moreover, we are interested in the mechanisms, which segregate EC into two functionally distinct domains, MEC and lateral entorhinal cortex (LEC). Thus, we analyzed published scRNA-seq data from mouse brains to identify genes that are differentially expressed among these regions. We will focus on the genes encoding cell adhesion molecules as they are likely to regulate border formation. This study will contribute to the establishment of cortical functional domains during cortical development.

投稿學會：台灣基礎神經科學學會	編號: P1-19

Linking hippocampal patterning with hippocampus-related behaviors

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Abstract

COUP-TFI (chick ovalbumin upstream transcription factor I, or NR2F1), an orphan member of the nuclear receptor superfamily, is an important regulator of neurogenesis, cellular differentiation, and cell migration. It is also involved in the development of hippocampus, as the loss of COUP-TFI leads to hippocampal hypoplasia. We recently identified a novel function of COUP-TFI as the hippocampal patterning factor: First, we discovered a dose-dependent relationship between COUP-TFI expression level and the hippocampal volume, as the hippocampal volume is reduced in COUP-TFI conditional knockout (cKO) mice and expanded in conditional transgenic (cTG) mice. Second, we found hippocampus was dorsalized in the cKO and ventralized in the cTG. Thus, we investigate the effect of the patterning changes of hippocampus on mouse behaviors. The hippocampus has dual functions, with the dorsal part involved in spatial learning and memory and the ventral part involved in emotions and anxiety. We have performed a battery of behavior experiments exploring the possible disruption in hippocampus-related behaviors. We observe that the loss of COUP-TFI (in cKO) results in alleviated anxiety-like behaviors and excess COUP-TFI (in cTG) leads to impaired spatial memory. Our findings suggest that COUP-TFI regulates hippocampal patterning which in turn affects mouse behaviors. We also find out how these behavioral tasks activate neurons in different subfields of the hippocampus. Due to the observed difference in anxiety-like behaviors in the mutant mice, we are currently investigating the effect of external stress on the mutant mice.

投稿學會：台灣基礎神經科學學會	編號: P1-20

Neuronal splicing regulator RBFOX3 mediates seizures via regulating Vamp1 expression preferentially in NPY-expressing GABAergic neurons

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Abstract

Epilepsy, which is also called a seizure disorder, is one of the most common neurological diseases that affects around 50 million people worldwide. Approximately 50 % of people with epilepsy have a genetic basis. With the genome-wide association studies (GWAS) and family studies, a number of genetic changes have been associated with epilepsy, including a neuronal splicing regulator gene, RNA binding fox-1 homolog 3 (RBFOX3). RBFOX3, also known as NeuN, is a well-recognized marker of postmitotic neurons that has widely been used in neuroscience research. It has been identified as an RNA alternative splicing regulator that mediates the hippocampal circuit balance and function, neurogenesis, synaptogenesis, and promotes neuronal differentiation during development. A causal relationship between genetic defect and epilepsy has been supported by observations that Rbfox3 knockout mice exhibit enhanced seizure susceptibility induced by kainic acid (KA) treatment, a well-established model of temporal lobe seizures. However, the mechanism of seizure mediation by RBFOX3 is still unclear. Here, we used different kinds of cell type-specific Rbfox3 conditional knockout mice (Gad2-Cre for GABAergic neurons; Camk2α-Cre glutamatergic neurons; Pomc-Cre for hippocampal dentate gyrus granule cells (DGGCs); and PV-Cre, SOM-Cre, VIP-Cre, Npy-Cre, CR-Cre, Cck-Cre, and Nos1-Cre for seven subtypes of GABAergic neurons) as models to enable genetic dissection of Rbfox3 and identify the pathophysiological mechanisms underpinning epilepsy. Mice with selective loss of Rbfox3 in GABAergic neurons but not glutamatergic neurons exhibit spontaneous seizures and high premature mortality due to increased presynaptic release, postsynaptic potential, neuronal excitability, and synaptic transmission in hippocampal DGGCs. Attenuating early excitatory GABA action by administering bumetanide rescued seizure phenotypes. Rbfox3 deletion reduced the expression level of VAMP1, a GABAergic neuron-specific presynaptic protein, in the hippocampus. Postnatal restoration of VAMP1 rescued premature mortality and neuronal excitability in DGGCs. Furthermore, loss of Rbfox3 in GABAergic neurons showed fewer neuropeptide Y (NPY)– expressing GABAergic neurons. In addition, deletion of Rbfox3 in NPY-expressing GABAergic neurons decreased intrinsic excitability and increased seizure susceptibility. Our results provide evidence for the crucial role of RBFOX3 in the pathogenesis of epilepsy and suggest the importance of an alternative splicing regulator in mediating brain function.

投稿學會：台灣基礎神經科學學會	編號: P1-21

Characterization of the molecular and cellular defects underlying memory consolidation defect in CMTR1-cKO mice

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Abstract

Eukaryotic mRNA is 5 -end-capped with m7 guanosine, known as cap0 (m7GpppNpNp, N: any nucleotide). Cap methyltransferase (CMTR1) further catalyzes 2 -O-ribose methylation of the first transcribed nucleotide (N1 2 -O-Me) to produce the cap1 (m7GpppNmNp) structure in all eukaryotes except yeasts. Although the cap0 structure is essential for mRNA stability and cap-dependent translation, it is not known whether cap1 modification also plays a role in regulating posttranscriptional gene expression. We found that CMTR1 deficiency affects dendritic arborization and cortical development. Because CMTR1 is highly expressed in the hippocampus, we investigate whether CMTR1 modulates synaptic plasticity and spatial memory by using conditional knockout (cKOCamk2, Cmtr1f/f, Camk2-Cre/+) mice whose Cmtr1 gene is ablated in the hippocampal CA1 region after postnatal 2-3 weeks. We found that CMTR1-cKO mice have impaired memory consolidation in the Morris water maze. Dendritic spine number was reduced in CMTR1-knockdown cortical neurons. Although one train of high-frequency stimulation (HFS) and Theta-burst stimulation (TBS) – evoked long-term potentiation (LTP) was comparable between cWT and cKO mice, long-lasting LTP elicited by 4 trains of HFS and TBS was found to be diminished in the cKO group. My recent transcriptome study projects the possibility of the involvement of NMDAR-related pathways. Further study is required to understand the molecular mechanism underlying impaired memory consolidation in CMTR1-cKO mice.

投稿學會：台灣基礎神經科學學會	編號: P1-22

Effects of chronic antibiotics exposure on anxiety-related behavior

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Abstract

Microbiota in the gut is essential to various aspects of physiology. Imbalance of gut microbiota influences gut-brain communication that induces alterations in brain function, including emotional processing. Studies have revealed significant changes in gut microbiota in patients with affective disorder and stress-related rodent models. Therefore, we hypothesize that gut microbiota imbalance leads to emotional changes through stress response systems. However, the effects of gut microbiome on anxiety-related behavior are inconsistent in recent studies. Thus, this study aims to elucidate the effects of gut microbiota imbalance on anxiety-related behavior and its underlying mechanisms. We used antibiotics cocktail (ABX) treatment to induce microbiota imbalance in mice. After four-week of antibiotics exposure, anxiety-related behavior and stress response were assessed. Our results demonstrated that ABX treatment induced different levels of microbiota depletion. ABX-treated mice with complete microbiota depletion displayed hypolocomotion and increased anxiety-related behavior, but no changes in stress hormone (i.e., corticosterone) levels. In conclusion, antibiotics exposure leads to elevated levels of anxiety-related behavior, but the effect may not be related to stress response. We are working on delineating the molecular and cellular hallmarks of how the gut microbiota imbalance influences anxiety-related behavior. Further results will provide potential means to rescue the aberrant anxiety phenotype induced by antibiotics exposure.

投稿學會：台灣基礎神經科學學會	編號: P1-23

The beneficial effects of dietary restriction on social defeat-induced cognitive decline

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Abstract

Chronic social stress is a complex psychiatric condition that can lead to major depressive disorder (MDD). More than 300 million people worldwide suffer from MDD, which has core symptoms such as negative emotion and cognitive deficits. Current treatment for MDD, including selective serotonin reuptake inhibitors and ketamine-based antidepressants can only improve the emotional response but are less effective on the other associated cognitive impairment. Thus, there is an urgent need to develop a promising intervention that can treat various disease-related symptoms. Our previous research demonstrated that dietary restriction (DR, defined as 60% of daily food intake of ad libitum, AL) can considerably improve behavioral outcomes and enhance the memory performance in both young and aged mice through the microbiota-gut-brain axis. Nevertheless, the effect of DR on depression and associated cognitive impairments is largely unknown. Therefore, we used the repeated social defeat stress model (RSDS) to induce depressive-like behavior and memory dysfunction in mice, and found that one month of DR can significantly reverse these behavioral deficiencies. More importantly, DR can also affect structural alterations of hippocampal neurons, and up-regulate the hippocampal neurogenesis. However, these beneficial effects of DR were largely abolished when antibiotics were added to the drinking water of RSDS mice. In addition, DR-derived fecal microbiota to RSDS mice was adequate to imitate DR-induced advantages and highlight the significance of gut microbiota. Overall, our findings demonstrated that the DR-induced beneficial effects under RSDS require gut microbiota. Microbiome analysis, metabolomics analysis, and metagenomic sequencing will be performed to understand the mechanism underlying DR-induced pro-cognitive effects. We believe that this study will make a significant impact on the treatment of emotional response and cognitive impairment associated with MDD in the future.

投稿學會：台灣基礎神經科學學會	編號: P1-24

Investigate the underlying mechanism of gut microbiota in dietary restriction-associated benefits

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Abstract

Dietary restriction (DR), carried out as consuming 20% to 40% less of daily intake with sufficient micronutrient, is one of the most renowned diet regimens to improve physiological status, counter disease-related dysfunction, and mitigate age-related dysfunction. Mechanistically, DR improves proteostasis, regulates inflammation, modulate intracellular signaling, and maintain glycemic profile to achieve beneficial effects. Given the extreme challenge to sustain such rigid regimen in our daily life, it is crucial to pinpoint suitable downstream effectors and the physiological phenomenon to recapitulate the effect of DR. Recently, the gut microbiota, a group of commensal bacteria resided in our gut, has raised as an important factor that shape a wide range of biological functions. Various beneficial effects of DR have been proven to be correlated with the alteration of gut microbiota. Our current research aims to establish the causal relationship between DR-associated benefits and DR-derived gut microbiota, and to systematically decipher the mechanism underlying DR-associated benefits relevant to the gut microbiota, focusing on the effect of DR on pro-cognition, metabolic health, and longevity. Antibiotics-treated mice and germ-free mice would be used as loss-of-function models to examine the role of the gut microbiota. According to our hypothesis, DR-associated benefits mediated by the gut microbiota would be diminished in the absence of the gut microbiota. Furthermore, mice with normal food intake (ad libitum, AL) but receive fecal microbiota transplantation from DR would recapitulate DR-associated benefits. Next, to uncover underlying bacteria-host interaction and identify potential probiotics and postbiotics, we would implement transcriptomic, metagenomics, and metabolomics approach. These identified probiotics and postbiotics would be subjected to further in vivo validation in normal mice as well as diseased models. We believed this study would provide a comprehensive understanding of how DR-derived gut microbiota elicit beneficial effects, providing a solid backbone to identify a druggable target to recapitulate DR-associated benefits and ameliorate diseases.

投稿學會：台灣基礎神經科學學會	編號: P1-25

Light dark cycle influences Gut microbe daily oscillation independent of peripheral clock

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Abstract

Gut microbiota could interact with the body and further modulate physiological function. Recent research has discovered that gut microbiota displays diurnal oscillatory rhythm, which could be dampened by constant darkness or an abnormal light environment. Thus, it brings our interest in how gut microbiota is affected by the environment without directly receiving light signals. Recent evidence suggests that the crosstalk between the intestinal immune system and gut microbiota may contribute to the circadian rhythm of gut microbiota. Here, we focus on NOD2, a subtype of NOD-like receptors (NLRs), and its downstream pathway. We discovered that NOD2 and its downstream protein possess circadian rhythm under a normal light-dark (LD) cycle. Moreover, the oscillation has deteriorated under the dim-light-at-night (dLAN) cycle. To investigate how light signals regulate the NOD2 oscillation, we performed two set of experiments. First we conditionally knock out the peripheral clock gene, Bmal, in intestine epithelial cells and. Suprisingly, without the peripheral clock, diurnal rhythms of NOD2 and its downstream are sustained in the intestine epithelium. Due to the peripheral clock could not regulate the oscillation of the NOD2 pathway, we next examine the central clock, the suprachiasmatic nucleus (SCN). By lesioning SCN, we discovered that the diurnal oscillation of the is dampened. Together, our results suggest that the daily oscillation of gut microbe is control by central clock and external light dark cycle and NOD2 pathway, but not intestine clock.

Nesting behavior induced alterations in the gut microbiota of two passerine bird species

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Abstract

The bidirectional neurohumoral communication of gut-brain axis is believed to integrate the gut and central nervous activities mediated by gut microbiota, and thus the concept of the microbiota-gut-brain axis is emerging. Recent studies have shed light on how gut microbiota affect animal behavior via the alterations of several neurological processes such as neurotransmitter turnover, neurogenesis, and neuronal morphology. Specifically, the oxytocin system and parenting behavior has been well-studied in rodent. However, little is known about how microbiota-gut-brain axis influence the parenting behavior prior to, and in the absence of, the stimuli associated with parturition, egg laying or offspring. Nesting behavior in birds is one of the robust early parenting behaviors to study the modulation effect of gut microbiota before the birth of offspring. In this study, to investigate the association among the gut microbiota, neuron activity and nesting behaviors, a series of nesting behavior experiment was conducted using the avian model, zebra finch (Taeniopygia guttata) and society finch (Lonchura striata domestica). Using 16S rRNA amplicon sequencing, we found that the composition of finch gut microbiota variated between a nesting and two non-nesting control groups in both finch species. In addition, certain nesting behaviors, such as duration of nest material fetching in males and time spent in the nesting box in females, appeared to correlate with the variation of gut microbes. Among the gut microbial communities, a bacterial family Campylobacterota, previously known as Epsilonproteobacteria, became the predominant in nesting finches. While the usage of nest material increased after four-days Gram-negative-specific antibiotic treatment compared to the finches drinking water. Collectively, these results suggest that gut microbial signals are closed related for programming of nesting behaviors in the passerines.

投稿學會：台灣基礎神經科學學會	編號: P1-27

Intrinsically photosensitive retinal ganglion cells inhibit socio-sexual recognition memory through supraoptic oxytocin neurons

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Abstract

Social memory between the same gender or even different gender is a complex and heavily modulated process in the nervous system. The regulation of memory formation could be influenced by both the internal status of the animal and the external environmental condition. Among many external stimulations, light profoundly affects physiology, behavior, and cognitive functions in humans and rodents. It has been shown that various forms of recognition memory, such as odor and object memory, are downregulated by acute light exposure in rodents. However, the neuronal circuitry involved in light-dependent social recognition memory modulation remains unclear. Here, we show that acute light exposure could impair the socio-sexual recognition memory (SSRM) in male mice. Activating oxytocin neurons in the SON (SONOT neurons) using channelrhodopsin is sufficient to enhance the SSRM performance in male mice. On the contrary, light exposure could inhibit SONOT neurons through M1 SON-projecting ipRGCs and GABAergic neurons (pSONGABA) in the pSON. Together, these results show that sensory input such as light could modulate SSRM through a minimal ipRGCs-pSONGABA-SONOT neuronal circuitry. Our findings demonstrate the neural basis of how luminance affects cognitive functions through the oxytocin system, which is a powerful modulatory neurohormone in the central nervous system.

投稿學會：台灣基礎神經科學學會	編號: P1-28

Positive correlations between social hierarchy and memory in weaning mice and young children

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Abstract

Social hierarchy is prevalent in various animal groups and plays an essential role in maintaining the social structure. Most of the current research on mice focuses on the social hierarchy of adult but not young mice. Since young mice do not perform aggressive behavior, we used the tube test to establish the first social hierarchy for weanling mice and examined a variety of behaviors across social ranks. Surprisingly, there is no correlation between the social ranks and mobility, depression, and anxiety phenotypes of young mice. In contrast, the Novel Object Recognition Test and Y maze showed that the weanling mice with a higher social hierarchy have better memory ability. From the qPCR results, we also found higher expression of memory-related genes in mice with higher rank. Next, we injected memory-improving drugs into mice and found that mice treated with drugs showed not only better memory but also social dominance, further support the relationship between social hierarchy and memory. Lastly, our findings in mice led us to examine this phenomenon in preschool children. Consistent with our findings in weanling mice, children with higher dominance level also showed better memory ability than subordinate children. Our study shows remarkable similarities between humans and mice in the positive correlation between memory and social hierarchy. These findings may provide new perspectives on social interaction research in the fields of basic biology, psychology, and education.

A research proposal for investigating the role of microtubule dynamics during long-term memory formation in Drosophila

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Abstract

Microtubules maintain neuronal survival and functions by physically supporting neuronal morphology, constituting tracks for cargo transportation, and mediating local signaling events. Previous studies implicate that dynamic microtubules are important for learning and memory by participating in the molecular mechanisms of synaptic plasticity. However, it is unclear how microtubules in engram cells contributes to memory formation. Here, we propose to investigate the role of dynamic microtubules in the well-established olfactory memory circuit of fruit flies. We will apply expansion microscopy to detect and examine whether microtubules in engram cells are remodeled or distinctively modified during LTM formation. In addition, we endeavor to adapt optogenetic tools to acutely control microtubule remodeling in adult fly's brain, which may allow us to directly study their role in LTM formation.

投稿學會：台灣計算神經科學學會	編號: P1-30

The hybrid wiring pattern in a fly brain diversifies olfactory information processing

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Abstract

Olfactory information is processed in the lateral horn, LH, and the mushroom body, MB, for innate and learned behaviors, respectively. The wiring pattern in LH is conserved and can be characterized into different groups for specific odor groups. However, the debates over how olfactory projection neurons connect to the intrinsic mushroom body neurons, Kenyon cells, last for decades. Previous studies claim that the wiring pattern is random for better memory capacity by random sampling. However, from a development angle, these two neuron types have spatial innervation preferences. The anatomic structure offers the possibility that the connection pattern is not fully random. Thus, disputes do not come to an end. To answer the question, we analyze the most resolved neuronal connection data – the FlyEM dataset which offers hemibrain data of one individual brain with synaptic data. Our results suggest that the circuitry has preference instead of full randomness and it is supported by spatial innervation preference. Furthermore, there is a hybrid connection pattern that confers the sensitive detection and experience generalization to food odors. On the other hand, for other odors, the pattern maintains a higher memory capacity. To sum up, the mushroom body performs different strategies for different odors.

投稿學會：台灣基礎神經科學學會	編號: P1-31

Exploring the osmosensing mechanism in a pair of thirst-broadcasting neurons

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Abstract

Thirst is an internal state driven by increased blood osmolality resulting from dehydration. It motivates the animal to seek and drink water to restore body fluid homeostasis. Loss of fluid balance affects essential functions of animals which could threaten survival. Therefore, a robust osmosensing system is required to detect the fluid imbalance and elicit thirst responses. Here, we use the fruit fly Drosophila to study the osmosensing mechanism. Like mammals, the fly also exhibits thirst-driven behaviors. Our previous works discovered a pair of Leucokinin-expressing neurons (LHLK neurons) in the fly brain that responds to increased extracellular osmolality and regulates thirst-driven behavior. However, the underlying molecular mechanism that confers osmosensitivity to these neurons remains unclear. To study this question, we have first established a real-time imaging system to monitor Ca2+ signals in LHLK neurons under hypertonic stimulations ex vivo. We found that hypertonic stimulations increased the Ca2+ level in LHLK neurons, and the dynamics of the Ca2+ signals were highly correlated with the shrinkage of the cell body. This observation agreed with the long-standing hypothesis that osmosensation is mediated by mechanical sensors that detect membrane tension. Through an RNAi screening, we identified Pickpocket 26 (PPK26), a fly homolog of mammalian Acid Sensing Ion Channel (ASIC), as an osmosensor in LHLK neurons. Knockdown of ppk26 in LHLK neurons lowered the maximum value of the hypertonicity-induced Ca2+ activity without affecting its initial response rate and the cell shrinkage. Therefore, we proposed a two-phase osmosensing model where the less sensitive PPK26 cooperates with a more sensitive sensor to confer the full range of osmosensitivity in LHLK neurons. To further verify our hypothesis, we are now identifying the additional osmosensor in LHLK neurons. Results from this study will advance our understanding of the thirst sensation, a desire we experience every day.

投稿學會：台灣基礎神經科學學會	編號: P1-32

Endolysosomal 2Cl-/H+ exchanger coordinates neuron-glia crosstalk to control synaptic bouton development

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Abstract

Neurons and glia are highly polarized to adapt the demand for complex cellular connectivity and communication in the nervous system. Therefore, proper endolysosomal system that dictates the membrane and protein trafficking and turnover is crucial for maintaining such polarity. In mammals, Clcn3 and Clcn4, a subset of the CLC family, are two major 2Cl-/H+ exchangers expressed in the neural endolysosomes. Most importantly, recent clinical studies have identified various types of the mutations in both human CLCN3 and CLCN4, and the probands show severe neurodevelopmental defects leading to developmental delay, intellectual disability, and epilepsy. Similarly, double knockouts of mouse Clcn3 and Clcn4 result in prenatal lethality. Nonetheless, what roles CLCN exchangers play in neurodevelopment and how disease-associated variants dampen such roles are largely unexplored. In this study, through a forward genetic screen, we identify a mutation in clc-c which encodes the sole fly homolog of human CLCN3 and CLCN4. clc-c mutants are deficient in larval and pupal development. Furthermore, the mutants show outgrowth of the larval neuromuscular junction synaptic bouton, characterized as numerous main and satellite boutons. Clc-c is universally expressed, and the bouton defect results from loss of Clc-c in either of neurons, glia, and muscles. Although Clc-c is localized in distinct compartments of the endolysosomal system, its loss predominantly causes the defects in early and recycling endosomes. Mechanistically, we find that the elevated Mad signaling underlies the synaptic bouton outgrowth. Most intriguingly, disease-associated human CLCN4 variants exhibit partial/full activity, loss of function, or dominant-negative effect in a cell-type specific manner. Lastly, when expressed in the fly visual system, we can provide much precise diagnosis for defining the severity of human CLCN4 variants. Overall, our work reveals that the endosomal 2Cl-/H+ exchanger regulates neuron-glia communication during synaptic bouton development, and its pathogenic human variants hold differential activities in different cells.

投稿學會：台灣基礎神經科學學會	編號: P1-33

Modeling frequent human variants of Flower reveals its regulation on synaptic vesicle recycling and synaptic bouton architecture through distinct mechanisms

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Abstract

The activity-dependent change in synaptic structure and activity is essential for the plasticity of neural network. Endocytosis of the synaptic vesicle (SV) is tightly coupled to exocytosis which releases neurotransmitters to keep neurotransmission continuity. Mild activity stimulations elicit clathrin-mediated endocytosis (CME), while intense stimuli triggers activity-dependent bulk endocytosis (ADBE). Therefore, such stimuli-dependent mode switch is able to boost synaptic strength upon demand, yet the underpinning mechanism remains elusive. Here we investigate structure-function relationship of the Flower Ca2+ channel which promotes CME and ADBE respectively through channel-dependent and -independent functions. By characterizing the functional equilibrium between alternative splicing isoforms of Flower and its human homolog, CACFD1, in the fly system, we found that CACFD1 isoform 4 can function as Flower. Moreover, both their transmembrane domain region and cytosolic region are necessary for their sorting and localization to the SV. Furthermore, through the sequencing databases for healthy human population and the patients suffering from various disorders, numbers of frequently carried CACFD1 variants which result from missense mutations in evolutionarily conserved residues mainly spanning transmembrane domain region, as well as copy number gain are identified and subsequently studied in their functional impact. Interestingly, we found that these variants display the differential loss of the abilities to control SV endocytosis but also synaptic bouton formation. Hence, our work provides new mechanistic insights into the coordination between synaptic activity and structure. In addition, our data reveal that these CACFD1 variants may have potential pathogenic impacts on human health.

投稿學會：台灣基礎神經科學學會	編號: P1-34

Studying the atypical localization of the centrosomal protein Cep170 during neuronal morphogenesis

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Abstract

Microtubules are essential cellular structures in neurons and participate in essentially every step of neuronal development. Proteins that interact with microtubules are called microtubule-associated proteins (MAPs) and affect neuronal development. Using quantitative proteomics to compare MAPs from undifferentiated stem cells and stem cell-derived neurons, we found that Cep170 is more enriched on neuronal microtubules. Cep170 is a forkhead-associated (FHA) domain-containing centrosomal protein and localizes to the subdistal appendage of the centriole in mitotic cells. Its mutations have also been found to be associated with human brain abnormalities, such as microcephaly and lissencephaly. These indicate that Cep170 plays an important role in the development of the central nervous system. To understand the role of Cep170 in neurons, loss- and gain-of-function experiments were conducted. The result shows that Cep170 promotes neurite elongation in both stem cell-derived neurons and primary neurons, and both axons and dendrites are promoted. However, no morphological phenotypes can be observed when Cep170 is depleted. We observed that Cep170 exhibits distinct localizations in neurons: 1) a single spot in the soma, 2) as discrete puncta along the neurite, 3) enriched at the tip of the axon. To find out how these distinct localizations affect neuron development, different truncations of Cep170 which compromise specific aforementioned localizations were overexpressed in neurons. The result shows that the punctate distribution along the neurite requires both the microtubule-binding domain and the FHA domain, while the tip enrichment is depended on the FHA domain. Also, we discovered that microtubule stability affects the distribution of Cep170 puncta along the neurites. On the other hand, the Cep170 localization at the axon tips is independent from microtubules.

投稿學會：台灣計算神經科學學會	編號: P1-35

Degree of dispersion in the cerebral cortex and the correlation with mental illness

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Abstract

Schizophrenia is a mental disorder which have high prevalence rate in global, approximately 1%. Symptoms of schizophrenia are complex include hallucination, delusion, lack of ability to normal social expression and some cognitive issue. Despite the known symptoms to identify and characterize schizophrenia, the pathological causes remain largely unclear. Magnetic resonance imaging (MRI) analyses provided structural related measurements of brain, these measurements could be catalogued by the surface-based and volume-based analyses. While grey matter volume or subcortical volume can be examined by volume-based analysis, surface-based analysis allowed us to evaluate the cortical thickness or local gyrification index of the distinct coordinate on the surface of cerebral cortex. To date, studies and clinical cases have identified several structural abnormalities in the brain of schizophrenia patients. Grey matter volume and cortical thickness showed a regional-specific different in schizophrenic cases, especially in frontal and temporal lobe. Nonetheless, our complex cerebral structures, such as gyrification pattern, are highly associated with the map of functional areas regions and multiple functional areas compose a single lobe. Here, to decipher the relationship between structural changes and functions, we performed variation analysis of neighbouring voxels or vertices using T1-weighted MRI analysis of subjects included 331 normal controls and 194 cases with Brodmann area and Destrieux Atlas. Based on our results, we identified several functional areas affected in schizophrenia and further genetic association test illustrate the possible genetic cause of schizophrenia.

投稿學會：台灣基礎神經科學學會	編號: P1-36

Genetics association between schizophrenia and cerebral functional areas

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Abstract

Schizophrenia is a mental disease that impacts people's ability to express symptoms like delusion, hallucination, and no interest in social activities; the cause of the disease still remains unclear. In the past, magnetic resonance imaging (MRI) studies of schizophrenia, have shown some abnormalities in cortical structures compared to normal control, especially such as decreased grey matter volume in the prefrontal cortex and temporal lobe and temporal lobe. However, each lobe contains multiple functional areas and the phenotype of schizophrenia may not be resulted from a single area, which lets us hypothesize that the different combination of brain functional areas might be involved in the causes the symptoms of schizophrenia. Here, we performed in silico analysis of T1-weight MRI of 331 healthy control and 194 schizophrenia patients from the TAMI database. Global and regional cerebral grey matter volume differences between healthy control and schizophrenia patients were analyzed based on automated anatomical Labeling (AAL atlas) and Brodmann areas (BAs). Following group comparison and a general linear model using voxel-wise t-test analyses showed total grey matter volume was significantly decreased in schizophrenia patientspeople with schizophrenia. Our results showed multiple functional BAs were significantly affected in the cerebrum of schizophrenia patients. In addition, further investigations using a genome-wide association study (GWAS) suggested certain SNPs may affect the grey matter volume of the distinct BAs. Together with the expression pattern, these data will may provide insights in the cause of schizophrenia.

投稿學會：台灣基礎神經科學學會 | 編號: P1-37

To investigate the role of Akt1, a schizophrenia candidate gene, in reward-based decision making- neural mechanism of dorsomedial striatum from multidisciplinary approaches

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Abstract

Schizophrenia (SZ) is a neuropsychiatric disorder with severe cognitive deficits. Accumulating evidence from human genetic studies suggests that multiple susceptibility genes contribute to the pathogenesis of SZ, including AKT1, a kinase intermediate downstream of dopamine D2 receptor. Alterations of dopaminergic transmission have been implicated in the pathogenesis of SZ, and SZ patients also show worse performance than healthy controls in many decision-making tasks. Recent findings reveal Akt1 participates in the modulation of reward-based decision making, especially in the striatum. However, the importance of Akt1 in dorsomedial striatum (DMS) during decision making remain elusive. To this end, we proposed 4 specific aims in this study. (1) the impact of Akt1 in a probabilistic 2-choice-foraging-task. (2) The role of Akt1 in the regulation of DMS neural activity during different stages of decision-making. (3) The causal relationship between DMS neural activity and decision-making behavior. (4) The cell-type-specific role of DMS neurons in decision-making. Our results indicated that (1) Akt1 HET mice required fewer trials to achieve the criteria and higher ratio of win-stay behavior compared to WT. Taking advantage of a Bayesian approach to estimate the parameters in modified reinforcement learning model, we found that HET mice have a higher learning rate in the no-reward outcomes and lower choice consistency. (2) The in vivo recording showed that no-reward-evoked DMS LFP power is highly correlated with their behavioral performance and model parameters. The decoding of DMS-LFP by machine-learning reveals the choice-related information is embedded in DMS neural activity and it also shows the genotypic difference. (3) The direct inhibition of DMS by the chemogentics in HET mice make WT-like behavior, including higher accumulated trials and lower ratio of win-stay behavior. (4) The behavioral results from cell-type-specific modulation in DMS through parvalbumin-cre mice showed that the lesion of PV interneurons made the higher ratio of win-stay behavior, higher learning rate and lower choice consistency. Collectively, our results suggest Akt1 deficiency cause the alternation of neural oscillation in the DMS potentially through parvalbumin-interneurons in DMS, which is contributed to the learning rate which resulted in the differential selection of choice strategy during decision making.

投稿學會：台灣基礎神經科學學會	編號: P1-38

The morphological characteristics of vasopressin neurons in zebrafish brain

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Abstract

Arginine vasopressin (AVP) is a nonapeptide produced by the hypothalamus and secreted from the pituitary. Vasopressin is well known for its functions as a hormone to regulate water reabsorption and ion balance. Besides, vasopressin also acts as a neurotransmitter and modulate various social behavior, especially aggression. Previous study in the bluehead wrasse showed that injected vasopressin increases aggression in non-territorial males while decreasing aggression in territorial males. However, the morphology and function of vasopressin meurons on teleost fish remain unclear. In the present study, we use zebrafish (Danio rerio) as model animal to study the morphology of vasopressin neurons and their effects on aggressive behavior. We first investigate the distribution of vasopressin neurons and their cell type in the whole zebrafish brain. Vasopressin neurons in the zebrafish brain are located in the anterior part of parvocellular preoptic nucleus (PPa), magnocellular preoptic nucleus (PM), ventromedial thalamic nucleus (Vm) and posterior part of parvocellular preoptic nucleus (PPp). Our immunohistochemistry/in situ hybridization results found that, about 9.5% of vasopressin neurons are also oxytocinergic neurons but not glutamatergic neurons, GABAergic neurons, and dopaminergic neurons. To evaluate the neural activity of vasopressin neurons, we also perform various behavior tests under 2 different durations of environmental stress (1hr and 4hr 5mM NH4+ exposure) on the zebrafish and observe the behavior changes. We performed mirror biting test and found that the biting number of the zebrafish is significantly reduced after 1hr stress exposure but did not affect after 4hr stress exposure. These indicate that the aggressiveness of zebrafish is reduced after stress exposure. Both environmental stresses did not affect anxiety levels and social preference in zebrafish. Overall, our study provides insight into the cell type, projection, and function in central nervous system of vasopressin neurons on teleost fish.

Tracking the movement of zebrafish larrve by multispectral imaging system

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Abstract

In social behavior, a visual signal is an important factor. Zebrafish larvae exhibit shoaling behavior at 14 days post fertilization. They show preference for specific shoaling partners according to the specific characteristics in the skin such as body color and the pattern of stripes. However, the development of choosing a preferred partner is unknown. Also, the size of zebrafish larvae is small so it is difficult to obtain detailed information of the tiny structure of larvae that allows us to distinguish the different individuals. Compared to adult fish, the threshold for image analysis is high, and under normal camera shooting, the errors of computer tracking occur frequently. Multispectral imaging in the invisible light bands is known for non-invasive detection characteristics and can be used for freshness qualifying products. However, commercial hyperspectral cameras are costly. We designed a low-cost multispectral imaging system in the present study with a 3D printed outer casing, 24-wavelength LEDs, a microcontroller unit, and a no IR-cut digital camera. We collected a multispectral data cube by imaging in 24 wavelengths and 1 backlight for the contours of samples in this multispectral imaging system. Taking the wildtype zebrafish as the standard, multispectral data cubes were imaged for deep learning. The data cubes were first subjected to background removal, ROI extraction, and Hyperstack pre-processing, and then feature compression was accomplished by an encoder-decoder convolutional neural network (E-D CNN) for establishing a spectral map and morphological feature database. This multispectral imaging system and deep learning model developed in the present study would be utilized in zebrafish larvae social behavior analysis.

投稿學會：台灣基礎神經科學學會	編號: P1-40

Neural circuit remodeling in the primary motor cortex during continual motor learning

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Abstract

Motor learning incorporates rapid formation and selective stabilization of synapses in the primary motor cortex (M1). Therefore, learning multiple tasks requires continual synaptic re-organization. However, it is unknown how re-organization of a part of the network does not lead to a severe loss of previously learned information, a phenomenon called catastrophic forgetting, which is a challenging issue in training artificial neural networks. Here we have established a mouse model of continual learning paradigm that is quantifiable, comparable, and has a different spectrum of difficulty. We adopted a programmable joystick that enables pre-determined movement trajectories of various lengths, turning angles, and artificial friction. The mice were trained to operate the joystick with their forearm to complete designed movement trajectories to obtain a sucrose reward. We established a relationship between task difficulty and behavioral performances by monitoring the trial attempts, success rates, and movement accuracy. We trained continually with three different tasks and simultaneously monitored the dendritic morphology of the pyramidal neurons in the M1 of the contralateral side of the movement arm with in vivo two-photon microscopy through a chronically implanted cranial window. We found that mice that learned the tasks have higher synaptic dynamics than non-learner control. Moreover, synapses have a high turnover during the first task, but learning multiple tasks reduces the turnover. Overall, we demonstrate that the synapses become more persistent with each subsequent task, even though the later tasks are more complicated than the first task. The new insights from this study will enable us to understand the underlying mechanism of circuit remodeling and retention of pre-existing information in the neural network.

投稿學會：台灣基礎神經科學學會 | 編號: P1-41

The functional role of striatal projection neurons in the striosome in encoding motor and reward information during motor learning

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Abstract

Optimizely acquiring motor skills by reward-based feedback is a fundamental instinct to enable the animal to achieve its goal effectively. As the input station of the basal ganglia, the striatum incorporates and pre-processes the information related to both reward and motor skills and transmit to the downstream circuit to enforce the learning performance. The early studies show that the striatal projection neurons (SPNs) in the different striatal compartments, the striosome and the matrix, play a crucial role associated with reward. Different cell-types of SPNs in the dorsolateral striatum (DLS) could develop a unique firing pattern in responsible to different motor skills. However, how does the SPNs in the striosome represent the information of reward driven motor skills is not clear. Here we have established a uniform paradigm and different degrees of complexity lever-pushing task machine to train the mice with fluorescent calcium indicator and using in vivo two-photon imaging via a gradient refractive index (GRIN) lens to observe the calcium signals in the SPNs of striosome in DLS on well-trained mice. We show that, in the striosome, different cell populations of SPNs are represented to different factors of the motor tasks i.e. pushing velocity, licking rate, received reward, and amount of reward. These representatives also demonstrate that, in the different cell populations with the diverse task complexity, the striosome circuit is involved in processing the information of motor skills and reward. The discovery of motor skills and reward information encoded in the SPNs of striosome is a robust niche to further explore the shaping mechanism of reward-feedback to enhance the motor skills development.

投稿學會：台灣基礎神經科學學會	編號: P1-42

Causal interactions between neuronal activities in midbrain dopaminergic neurons and basal forebrain neurons

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Abstract

Reward prediction error (RPE), the difference between received and predicted reward, has been traditionally associated with neuronal activity in midbrain dopaminergic (DA) neurons in the ventral tegmental area (VTA). However, recent studies from our group have demonstrated that a special subset of noncholinergic neurons in the basal forebrain (BF), which we refer to as BF bursting neurons, are similarly modulated by RPE. In the accompanying poster, we show that the activities of BF and VTA neurons are functionally coupled in terms of both response amplitude and spike timing, with DA neuron spiking temporally leading BF spiking by roughly 10 msec. These observations raised the question of whether DA activity directly can cause the spiking of BF neurons. To test this idea, we selectively excited VTA DA neurons using optogenetic tools in DAT-cre mice while recording neuronal responses in the BF. Here we show that optogenetic activation of VTA DA neurons induced robust and transient activation of many BF bursting neurons within 5-15 msec. Increasing the frequency of DA neuron activation led to slower and less reliable BF responses, including decreased spiking fidelity, increased spiking latencies and variabilities. These effects were further exacerbated by isoflurane anesthesia. Together, these results revealed a novel and strong causal coupling between VTA DA neurons and BF bursting neurons, acting perhaps through a poly-synaptic pathway. This surprising finding suggests that the brain uses two major neuromodulatory systems to jointly encode reward prediction error.

投稿學會：台灣基礎神經科學學會	編號: P1-43

14-3-3 proteins regulate Eag1 K+ channel degradation mediated by Cullin 7

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Abstract

The ether-à-go-go (Eag) potassium (K+) channel belongs to the superfamily of voltage-gated K+ channel. The neuron-specific voltage-dependent Eag1 potassium channel are linked to congenital neurodevelopmental diseases. Disease-causing mutant Eag1 channels manifest aberrant gating function and defective protein homeostasis. Both the E3 ubiquitin ligase cullin 7 and the small acid protein 14-3-3 serve as Eag1 binding partners. Cullin 7 mediates proteasomal and lysosomal degradation of Eag1 proteins. 14-3-3 proteins modulate the functional expression of the K+ channel in neurons. Co-expression with difopein, a peptide inhibitor of 14-3-3 proteins, increased mature and immature Eag1 by repressing protein degradation. Endogenous 14-3-3 proteins also contribute to excitotoxicity-induced proteasomal degradation of Eag1 protein in neurons. Inhibition of endogenous 14-3-3 function effectively perturbs the interaction of Eag1 with cullin 7. Further studies suggest that 14-3-3 proteins play a critical role in facilitating the binding of cullin 7 to two cytoplamsic domains of Eag1, both of which are essential for Eag1 degradation by cullin 7. These findings demonstrate a regulatory role of 14-3-3 in cullin 7–mediated Eag1 degradation in neurons.

投稿學會：	編號: P1-44

Abnormal ankle proprioceptive acuity in young adults with a probable developmental coordination disorder

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Abstract

Background: Published literature has suggested that adults with a probable developmental coordination disorder (pDCD) showed abnormal upper limb position sense of the wrist. However, it is still unclear if the lower limb (i.e., ankle) proprioceptive function is impaired in adults with pDCD. Objective: This study aims to determine ankle position sense and its relation to different domains of motor functions in young adults with or without pDCD. Methods: Participants were young adults (N=28) aged from 19-22 years old, including 10 pDCD participants and 18 heathy controls. Young adults with pDCD were screened by the Bruininks − Oseretsky Test of Motor Profciency 2nd Edition (BOT-2) that total standard score of < 40 (<17th) which equals one standard deviation below the mean. Ankle position sense acuity was assessed using joint position sense matching paradigm under contralateral and ipsilateral conditions. Position sense error (PE) and position sense error variability (SDPE) were obtained to measure ankle position sense acuity. Result: The results showed that young adults with pDCD exhibited a significantly increased SDPE on both contralateral and ipsilateral conditions ($p < .05$) when compared to controls. In addition, the ankle position sense SDPE was significantly correlated with levels of fine manual control ($r = -.46$, $p = .014$), manual coordination($r = -.54$, $p = .003$), agility & strength ($r = -.52$, $p = .005$) and total score ($r = -.55$, $p = .002$) measured by BOT-2. That is, young adults with a more decreased position sense precision tended to show lower levels of motor proficiency. In summary, these results confirmed that impaired ankle position sense acuity in young adults with pDCD, which could contribute to motor abnormalities in young adults with pDCD.

投稿學會：	編號: P1-45

The relationship between motor proficiency and lower limb proprioception in healthy young adults

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Abstract

Proprioception allows humans to perform precise and coordinated movements by repeatedly updating information about limb and body movements. Empirical evidence has shown that proprioceptive sensitivity is closely related to motor proficiency. Still, it remains unclear how neural correlates underlie proprioceptive-motor processes and to what extent these measures correlate with a person's motor abilities. The aim of this study was to examine the behavioral and neurophysiological performances during the ankle proprioceptive-motor tasks, and how they are related to individuals' levels of motor proficiency. A total of 29 healthy young adults aged 20.45±1.06 years were recruited. All participants were asked to place their dominant foot on the paddle of the ankle apparatus, which passively moved the ankle joint at constant velocities of 22°-1. Participants were required to press the button held by the dominant hand as quickly as possible once they sensed the motion produced by the apparatus. We evaluated behavioral measures (i.e., motion detection time, MDT; its standard deviation, MDT-SD) and P3 components related to the proprioceptive-motor task. The motor function was examined by the Bruininks-Oseretsky Test of Motor Proficiency 2nd edition long-form (BOT-2, LF). Spearman's rank correlation coefficient analysis revealed that standard scores of BOT-2 total motor composites significantly correlated with the MDT ($r = -.615$, $p < .001$) and MDT-SD ($r = -.518$, $p = .004$). Furthermore, ERP findings revealed a significant negative correlation between P3 amplitude and MDT during the ankle motion detection task ($r = -.610$, $p < .001$) and MDT-SD ($r = -.665$, $p < .001$). The total scores of BOT-2 also significantly correlated with P3b amplitude ($r = .457$, $p = .025$) and P3b latency ($r = -.569$, $p = .004$). The results suggested that levels of motor proficiency are correlated with motion detection time and P3b component related to ankle proprioceptive tasks in young adults. Individuals with higher levels of motor coordination tended to show higher levels of ankle proprioceptive sensitivity that is associated with a greater ability to allocate proprioceptive signals.

投稿學會：台灣基礎神經科學學會	編號: P1-46

Immunoproteasome inhibition modulates microglial polarization in erythrophagocytosis

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Abstract

Objective: Intracerebral hemorrhage-induced proteostasis disturbance/proteasome over-activation exacerbated ER stress and neuroinflammation, leading to neurological deficits. Immunoproteasome plays an important role in various neurological diseases under inflammatory and pathological conditions. The microglia M1/M2 functional phenotypes polarization may either exacerbate damage or induce repair and regeneration depending on different signals received by microglial receptors during pathological conditions. We intend to study the effect of immunoproteasome inhibition in facilitating erythrophagocytosis and microglia polarization in vitro ICH model. Materials & Methods: Rat primary microglia and BV2 cells and fluorescently labeled erythrocytes were used to study erythrophagocytosis in vitro with microglia phenotypic changes quantified by M1 (iNOS, CD86, CD16) and M2 (Arginase-1, CD163, CD206) gene expression, immunofluorescence staining, flow cytometry, and Western blot analysis. Results: Both flow cytometry and western blot showed that immunoproteasome inhibition by ONX-0914 (100 nM) increased microglia phagocytosis activation and promoted microglia activation toward M2 polarization accompanied by ROS and inflammatory cytokines reduction. Conclusion: Immunoproteasome inhibition may achieve neuroprotective effects through erythrophagocytosis by M2 microglia polarization and may lead to a novel treatment strategy for intracerebral hemorrhage recovery.

投稿學會：台灣基礎神經科學學會	編號: P1-47

Ischemia-induced M2-to-M1 transition in microglia was blocked by leptin that was independent from autophagy inhibition

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Abstract

We previously demonstrated that leptin can protect brain from ischemia-induced inflammation. To further understand how leptin protected brain from ischemic insult, leptin's impact upon the ischemia-induced autophagy and M2-to-M1 phenotype transition were investigated in microglia. It is known that brain microglia can sense environmental changes to have either a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. Activation of M1 microglia often further exacerbate brain injury whereas of M2 microglia may protect the injured brain. Ischemia-stimulated autophagy has been reported to promote M1 polarization of microglia. We, therefore, were interested to know if leptin blocked the M2-to-M1 phenotype transition in ischemic microglia, by inhibiting of the autophagy. In the study, an in vitro ischemic model (GOSD: glucose-oxygen-serum deprivation) was used to evaluate the impacts of leptin upon ischemic microglia. M1 and M2 microglia were distinguished from each other based on their secretory markers, surface markers and function. The current results showed that M1 markers (CD16, TNF-α, IFN-) were significantly stimulated by GOSD (2h) whereas M2 markers (CD206, IL-10, TGF-β1) were not, except IL-4. Phagocytic activity of microglia (M2 function) was inhibited by GOSD. Leptin, however, blocked the GOSD-increased expression of CD16, TNF-α, IFN- , and IL-4 but further elevated the protein expression of CD206 and TGF-β1 as well as the phagocytic activity of M2 microglia under GOSD condition. The above results suggested that ischemic stress promoted the M2-to-M1 phenotype transition in microglia whereas leptin blocked that and provided a less inflammatory environment in ischemic brain. GOSD-stimulated autophagy of microglia was not blocked instead increased by leptin co-treatment, indicating leptin-inhibited M2-to-M1 transition was likely not due to autophagy inhibition. The role of leptin-increased autophagy in GOSD-treated microglia is worth further investigation. In overall, the study has further expanded our knowledge about the mechanism(s) underlying the leptin-mediated protection of ischemic brain. The therapeutic value of leptin in the control of cerebral ischemia is also revealed.

投稿學會：台灣認知神經科學學會	編號: P1-48

The Excitatory–Inhibitory metabolite activity in the prefrontal cortex mediates the relationship between sensory responsivity and autistic traits

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Abstract

An imbalance between excitation and inhibition (E–I) within specific brain areas has been hypothesized to be a major cause of autism spectrum disorders (ASD). Although this theoretical model is promising, the existing empirical evidence is now only partial and investigating the causal roles of balance between brain E–I levels in major characteristics of ASD remains unresolved. In this study, therefore, we recruited 120 adolescents and young adults (28 individuals with ASD and 92 neurotypical controls) through evaluations of sensory features and autistic traits as well as brain magnetic resonance spectroscopy (MRS) measurements. We then stratified all participants based on their levels of sensory responsivity into two subgroups (those with and without sensory over-responsivity, or SOR and NSOR, respectively). Behaviorally, compared to those with the NSOR group, participants with the SOR group were more likely to be diagnosed with ASD. In addition, the SOR group had greater levels of sensory responsivity and more severe autistic traits than the NSOR group. Neuropsychologically, elevated Glx/GABA ratios within the auditory cortex, the somatosensory cortex, and the prefrontal cortex (PFC) were observed in the SOR group, and an increased cortical excitatory in the PFC correlated with both degrees of sensory responsivity and autistic traits. Results of mediation analysis further indicated that levels of brain E–I balance served as a mediator for the severity of sensory features–autistic symptoms relation in the SOR participants. Specifically, an elevated Glx/GABA ratio in the PFC was associated with higher levels of sensory responsivity and more severe of autistic traits. These findings not only provide supportive evidence that alterations in the prefrontal E–I levels have causal influences on ASD-associated symptoms, but also have implications for prognostic predictions of ASD, and, ultimately, to targeted ASD interventions.

Context effects on visual perception and probability estimation

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Abstract

Many cognitive functions—from perception, learning and memory, to judgment and decision making—are strongly affected by the context of our experience. But do context effects seen in one domain of cognition (e.g. perception) relate to those seen in another domain (e.g. judgment)? While context effects have been extensively studied, few studies compared context effects between different domains of cognition. Characterizing the similarities and differences in how context impacts different cognitive functions can provide insights into the nature of cognition, for example, whether there are common principles that guide context-dependent computations in perception and judgment. To address this issue, in this study human subjects (N=62) performed two tasks, a color perception task and a reward probability estimation task. In the perceptual task, the subjects had to judge the degree of blueness of a colored disc in each trial. The color ranged from completely blue, ambiguous (in between blue and purple), to completely purple. In the probability estimation task, the subjects in each trial had to estimate the reward probability associated with a visual stimulus. Different visual stimuli represented different reward probabilities that ranged from small, medium, to large. Context was similarly manipulated between the two tasks. In both tasks, the subjects faced three different contexts in different blocks of trials. Each context consisted of stimuli that differed in the degree of blueness (perceptual task) and reward probability (probability estimation task). Context was systematically manipulated such that the experience of a single stimulus differed between contexts in the other stimuli that were present in the same blocks of trials. We found similar effects of context across the two tasks. The subjects were more susceptible to the impact of other stimuli present in the same context when they faced a stimulus that carried larger uncertainty—in the perceptual task, it was the ambiguous stimulus whose color was in between purple and blue; in the probability estimation task, it was the stimulus that had 50% chance of reward. Computational modeling of behavioral data suggested that these effects were driven by two computational principles, namely reference dependency and uncertainty dependency, and their interactions. Our results identified the common principles for context-dependent computations in perception and judgment under uncertainty.

投稿學會：	編號: P1-50

Divergent Impacts of Complexity on Spatial and Temporal Sequence Learning

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Abstract

Sequence learning refers to improvements in performance through repeating the same series of movements. The current study aims to quantify the impacts of spatial complexity of a sequence on sequence learning in spatial and temporal domains. In the spatial domain, we compared the learning effect in the Serial Reaction Time Task (SRTT) under factorial combinations of different complexity and sequence length. While the learning effect indexed by the RT difference between the Random and Regular sequence is smaller in the high than low complexity, it did not differ between short and long sequences. On the other hand, the trends of learning rates remain the same even under the two different complexities. These results suggest that complexity does modulate the overall amount, but not the speed, of sequence learning. In the temporal domain, the learning was examined by measuring RT to flashes separated by a repeated sequence different time intervals. The comparison between Random and Regular sequences found that, unlike the spatial domain, learning only occurred under the low complexity condition of temporal SRTT. Hence, we speculate that sequence learning might not rely on a general mechanism underlying both spatial and temporal domains. Finally, we applied transcranial direct current stimulation (tDCS) over the contralateral primary motor cortex to inspect the learning of sequences varying both in spatial and temporal complexities, and attempted to tease apart the impacts of tDCS on the learning of each domain. The preliminary outcomes indicate that the primary sensorimotor regions contribute to the learning of the integration of spatiotemporal variation in the motor sequence, and the spatial variation may be the predominant information that is learned.

投稿學會：台灣認知神經科學學會	編號: P1-51

The optimization of a novel statistical learning test with hidden temporal and spatial positional regularity

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Abstract

Our previous findings on statistical learning demonstrated that positional regularity in the temporal and spatial format can both be learned when the visual stimuli only presented one types of such regularity. However, information in the real world usually presents different kinds of regularity simultaneously. To determine whether people would have preferential performance in learning temporal and spatial regularity when both types of information is available, we developed novel positional statistical learning tests, which can be employed to examine the underlying neural mechanisms in the future. Specifically, each trial in the PSL test contained two consecutive frames, each of which contained two spatial positions on the left and right side of the fixation. One of 16 geometric shape that were not easily namable was assigned to occupy the left or right position in either the first or the second frame. For shapes that presented temporal regularity, it always appeared on the first or the second frame, with half of the times on the left position and the other half of the times on the right position. For shapes that presented spatial regularity, it always appeared on the left or right position, with half of the times in the first frame and the other half of the times in the second frame. After encountering independent and random presentation of temporally and spatially regular shapes across mixed trials, participants' learning performance was measured with multiple-choice questions. The results from a series of four experiments showed that 1) spatial positional regularity embedded in shapes was easier to detect than temporal positional regularity, and 2) adding non-informative monotones or unique environmental sounds to individual shape presentation did not improve the learning performance of temporal regularity, but 3) adding informative environmental sounds to indicate temporal and spatial trials (but not individual shapes) improved the learning performance of temporal regularity significantly. Overall, our findings revealed the learning preference for hidden spatial over temporal positional regularity, and the latter can become salient by combining with informative but not over-loading sounds. Future explorations with neuroimaging techniques would be pursued based on this optimized positional statistical learning paradigm..

投稿學會：台灣認知神經科學學會	編號: P1-52

Revisiting the effect of skin color on categorizing mixed-race faces spanning the Asian-White and the Asian-Black continuum: 2AFC and 3AFC tasks

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Abstract

Categorizing racially ambiguous faces has become an emerging research topic; however, most of this work has focused on biracial Black/White stimuli with Caucasian participants, and the influence of skin color is not fully understood. Here we investigated how skin color may affect the accuracy of categorizing faces spanning the Asian-White and the Asian-Black categorical continuum in Taiwanese adults. We conducted two behavioral experiments measuring participants' responses in a traditional 2AFC (2-alternative-forced-choice: own-race, other-race) and a novel 3AFC (3-alternative-forced-choice: own-race, other-race, biracial) paradigm to build the psychophysical profile of race categorization with grayscale and color face images. Forty Taiwanese adults (between 19 and 42, M = 23.27 years, 20 females) joined the study; each received a 2AFC and a 3AFC racial categorization task in two separate sessions. Each session contained four blocks (Asian-White grayscale, Asian-White color, Asian-Black grayscale, and Asian-Black color), allowing for comparison between the contribution of physiognomy and skin color within each participant. For the Asian-White morphing faces, our results show that the Taiwanese adults tend to classify the 50% morphed faces (i.e., the proportions of Asian faces and Caucasian faces are equal to half-and-half) as white, and not until 60% in the 2AFC session, and not until 70% in the 3AFC session, are morphed faces being classified as Asian, consistent with our previous findings. For the Asian-Black morphing faces, the general trend of categorization is similar to that of the Asian-White continuum; however, participants responded more accurately that the 50% morphed faces were consistently judged as biracial in the 3AFC task. Overall, the results suggest that people rely on both physiognomy and skin color to distinguish subtle differences in biracial faces. Skin color enhances perceptual richness that helps people correctly attribute morphed faces to the corresponding side of the racial continuum and correctly classify faces as biracial when faces are evenly morphed. In conclusion, this study provides cross-cultural evidence of the role of skin color may play in categorizing biracial faces in the under-represented Asian context.

投稿學會：台灣認知神經科學學會	編號: P1-53

Over- and underreactions to regime shifts and their neurocomputational substrates

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Abstract

In dynamic environments where technology, markets, competitors and even narratives change regularly, many decisions are tightly associated with our ability to detect changes in the environment in a timely fashion. Previous studies on judgment and decision making found that people show systematic biases in response to regime shift—possible changes in the environments. In particular, humans tend to overreact to imprecise signals in stable environments, but underreact to precise signals in unstable environments. Methods. The goal of this study was to investigate the neurocomputational substrates for under- and overreactions to regime shifts. In a probability estimation task, subjects had to estimate the probability of change from one regime (the red regime) to the other (the blue regime) based on the signals they received. The signals were generated from one of the regimes, which always started from the red regime but can shift to the blue regime based on some transition probability. We investigated the impact of transition probability and signal diagnosticity—the relative ratio of red to blue balls in a regime—on the ability to detect regime shifts. Results. We replicated the systematic biases shown in previous studies: compared with the ideal Bayesian model, the subjects (n=30) tended to overreact to imprecise signals (low signal diagnosticity) in stable environments (small transition probability) by giving larger probability estimates of regime-shift. By contrast, subjects tended to underreact to precise signals (large signal diagnosticity) in unstable environments (larger transition probability) compared with the ideal Bayesian. Further, we fit a quasi-Bayesian model that incorporate free parameters to separately estimate sensitivity to transition probability and signal diagnosticity under different environmental conditions. We found that sensitivity to both transition probability and signal diagnosticity are a decreasing function of their respective dimensions, consistent with a system-neglect model in which people respond primarily to the signal and secondarily to the system that generates the signal. The fMRI results showed that the ventromedial prefrontal cortex (vmPFC) represented the probability estimates of regime shift. In addition, activity in the frontoparietal control network that included the dorsomedial prefrontal cortex (dmPFC), the dorsolateral prefrontal cortex, and the posterior parietal cortex represented the diagnosticity-dependent evaluation of sensory signals critical to estimating regime shift. Finally, neural model comparison revealed that the system-neglect model better described patterns of activity in the dmPFC in response to signal diagnosticity than the Bayesian model. Together, these results indicated that under- and overreactions to regime shifts arise from the fronto-parietal control networks involved in the evaluation of sensory signals in light of system parameters, before they are being used to compute probability estimates in the vmPFC.

Monetary gains and losses are represented by high-frequency oscillatory activity in the human brain

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Abstract

Many decisions we face involve choosing between options that carry potential gains and losses. Decades of research from psychology show that people are loss averse — that “losses loom larger than gains”. Human fMRI studies showed that many brain regions, including the ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC) and ventral striatum, represent information about monetary gains and losses during decision making. It remains controversial, however, whether these regions simultaneously represent gains (positive) and losses (negative). In this study, we attempted to address this issue using human stereo electroencephalography (sEEG). In a mixed-gamble task, human subjects (n=21) on each trial faced a 50/50 lottery of a potential monetary gain or loss and had to decide whether to play the lottery. As part of treatment plan attempting to identify epileptogenic zone, multi-contact depth electrodes were implanted in different brain regions including the OFC, dorsal-to-mid cingulate cortex, amygdala and insula. These four brain regions, with a total of 330 electrode contacts across subjects, were the focus of this study. Behaviorally, we replicated loss aversion in the patient population. Lambda, the ratio of sensitivity to changes in losses to gains inferred from choice behavior was around 2.3, suggesting that subjects were loss averse. Neurally, we found evidence for gain and loss representations in high-gamma activity (80-150 Hz). However, most contacts represented either gains or losses; very few contacts represented both gain and loss information. Together, these results suggest that gains and losses are more likely to be represented by different populations of neurons in these regions rather than by the same population of neurons.

投稿學會：台灣基礎神經科學學會 | 編號: P1-55

The Role of Self Emotional Processing and Empathic Responses in Gluckschmerz and Schadenfreude

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Abstract

Empathy, the capacity to share sensory or emotional feelings of others with self-other distinction, plays a crucial role in human emotional experience, social interaction and survival. However, in certain situations, people fail to empathize with others properly. They may experience displeasure from others' good fortunes (i.e., gluckschmerz) or pleasure from others' misfortunes (i.e., schadenfreude). Gluckschmerz and schadenfreude are socially undesirable emotions and have been termed counter-empathy, antipathy, or apathy. Although many previous studies have reported the neural substrates of empathy, little attention has been paid to the neural basis underlying gluckschmerz and schadenfreude. The relationships among self emotional processing, empathic responses and gluckschmerz, and schadenfreude also remain largely unclear. In a behavioral pilot study with competitive contexts, we devised a pain-related social emotional paradigm to assess gluckschmerz and schadenfreude resulting from others' relatively rewarding and punishing pain experience, respectively. Our preliminary results show that gluckschmerz and schadenfreude respectively exhibited an inverse relationship with the change in positive and negative empathic responses, which appears to suggest that both gluckschmerz and schadenfreude are counter-empathy. In addition, compared to self emotional processing, participants' empathic responses had a larger influence on their gluckschmerz and schadenfreude. In the near future, we plan to use functional magnetic resonance imaging (fMRI) with this paradigm to examine the neural mechanisms underlying the associations among self emotional processing, empathic responses and gluckschmerz, and schadenfreude. Results obtained from this study will enhance our knowledge about the nature of socially undesirable emotions and cerebral mechanisms underlying emotional processing in social contexts.

Title:

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Abstract:

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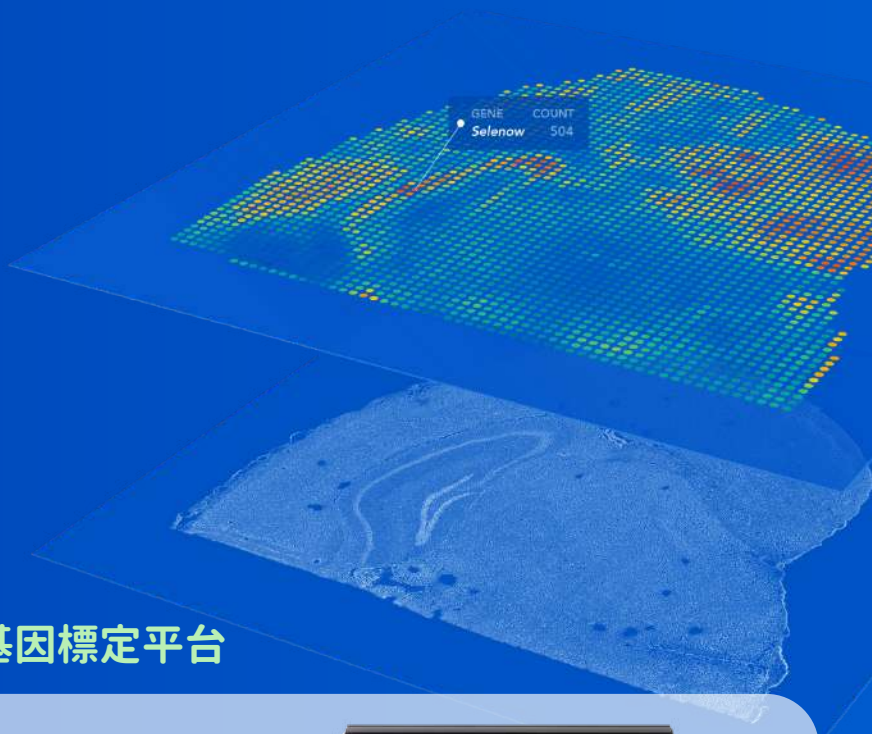

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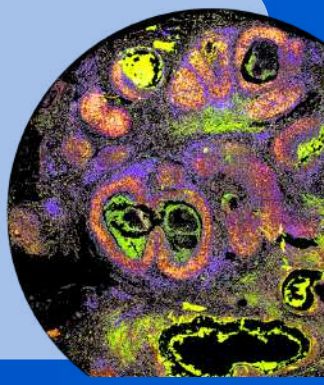

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樹突細胞被公認為最強的抗原呈現細胞，在免疫系統中扮演著指揮官角色，負責偵測病原體或突變的細胞，並且呈現其抗原訊息給 T 淋巴球，讓 T 淋巴球可以精準的辨識與殲滅。

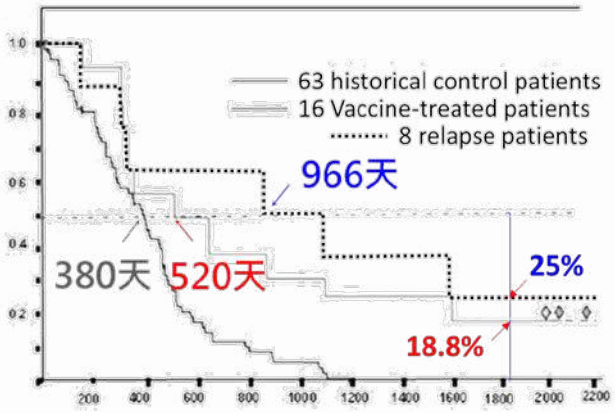
世福細胞傳承創辦人 楊文光教授研發之自體樹突細胞/腫瘤抗原輔助免疫細胞療法(ADCTA)，經臨床試驗第一/二期(與林口長庚醫院神經外科合作)和第二期(與中國醫藥大學附設醫院神經外科合作)證明其安全性且具療效，目前正在與七家醫院(基隆長庚、林口長庚、嘉義長庚、奇美醫院、台中榮總、成大醫院和高雄長庚)進行 GBM 第三期臨床試驗(計畫名稱: 自體樹突細胞/腫瘤抗原(ADCTA-SSI-G1)免疫療法輔助復發性惡性神經膠質腦瘤(GBM)現行標準治療之療效探討：一項多中心、開放式、隨機分配之第三期臨床試驗)，期望可以帶給病患安全有效的另一種選擇。

世福細胞近年來以[自體樹突細胞/腫瘤抗原輔助免疫細胞療法(ADCTA)]為基礎，已完成 DC-CIK(ADCTAK)的開發 ，並積極研發 Gamma Delta T 淋巴球，同時也具備殺手細胞(NK)、細胞因子誘導的殺手細胞(CIK)和腫瘤浸潤淋巴球(TIL)培養能力。此外，世福細胞也在 ADCTA 製程與品管上持續精進，如，腫瘤抗原的多元來源和免疫細胞活性評估。世福細胞在各方面的投入，進而擴大能收治的適應症，希望能為有需求者提供安全有效的幫助。

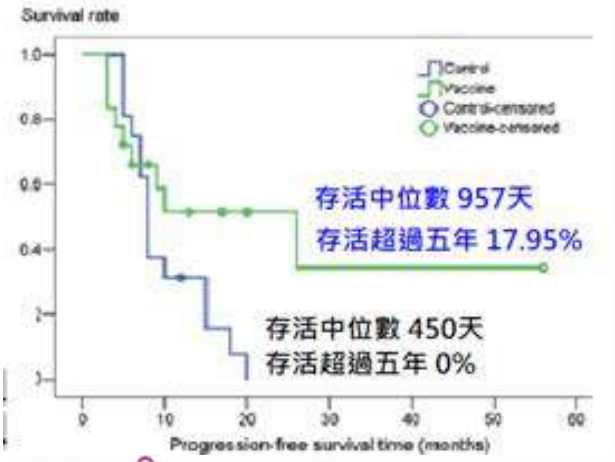
免疫細胞治療是精準化與個人化醫療，廣泛應用於癌症治療、器官修復或免疫提升等。

1. 世福細胞為台灣免疫細胞治療先驅者，具備六年的轉譯研究基礎，依法令開放與需求分析，展開產品策略規劃，以台灣目前唯一進入第三期臨床試驗之免疫細胞治療產品，這是具有先前臨床試驗實證之自體樹突細胞/腫瘤抗原製劑(ADCTA)為世福細胞產品發展之基石，持續開發多項新產品以提供尚未獲得滿足的需求：如，自體樹突-殺手細胞/腫瘤抗原製劑(DC-CIK, ADCTAK)、自然殺手細胞(NK)、細胞因子誘導的殺手細胞(CIK)、多項新興自體或異體之治療或器官功能修復產品等。
2. 製程精進新技術擴大收治病患，同時亦是世福細胞的重要能耐:如，抗原的多元來源和細胞培養與分化技術。
3. 無菌安全製程與品管全新設備自動化的投入，用於新產品開發、提高競爭力、提 高品質與效率與降低成本:如，用於細胞培養、品管檢驗與血袋凍存等。

[臨床試驗_DC(ADCTA)_GBM_PI/II]



[臨床試驗_DC(ADCTA)_GBM_PII]



計畫名稱	自體樹突細胞/腫瘤抗原(ADCTA-SSI-G1)免疫療法輔助復發性惡性神經膠質腦瘤(GBM)現行標準治療之療效探討：一項多中心、開放式、隨機分配之第三期臨床試驗
收案資訊	預計收納受試者人數：118人 預計收案期間： 2019-03-20至2024-12-31
個案分享	個案一: 至目前存活期為934天 個案二: 至目前存活期為651天 個案三: 至目前存活期為350天
聯絡資訊	聯絡部門：臨床試驗部 連絡電話：(03) 550-6696

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Neuronal discharges and network oscillations in ictogenesis

Chung-Chin Kuo (郭鐘金)
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Ph.D. Harvard University
M.D. National Taiwan University

Abstract

The nervous system is a complicated network functionally connected by electric discharges, which could lead to oscillating waves in local field potential (LFP) recordings such as electroencephalography (EEG). Epileptic seizures are brain disorders characterized by distinctive temporospatial patterns of LFP or EEG waves, and exploration of epileptogenesis may provide imperative mechanistic insight into the genesis and consequences of oscillating neural codes. With a basolateral amygdala (BLA) kindling model, we found that the dominant or "natural" frequency of oscillations is in the delta range (1–5 Hz) in BLA in both normal and seizure conditions. Interestingly, multi- and single-unit discharges are clustered into "bursts", more abundant at higher stages of seizures but remain phase-locked to delta oscillations, with the changes in synchrony preceding and outlasting that in discharging units and behaviors. In the cellular level, the rhythmic discharges are collaborating performances of a set of pyramidal and inhibitory neurons (PN and IN), and the rhythmogenic currents are provided by glutamatergic rather than intrinsic cellular pacemaking conductances (e.g. the h currents). In other words, the glutamatergic output of PNs starts a network-based "relay burst mode" of discharges especially in INs, which in turn precondition PNs into a state prone to subsequent burst discharges. PNs and INs could be grouped by synchronized discharges, respectively, and then have alternating activities as well as discernible LFP oscillations if the masses are large enough. Under such circumstances, the burst and interburst intervals will set the basic wavelength for the oscillations in the PN-IN networks, which may entrain one another to make different temporospatial patterns of resonating activities in the system. Seizures thus are erroneous continuums to normal oscillating activities in a network with a built-in synchronizing and resonating nature for information relay.

Selected recent publications:

1. Lo, Y.-T., and Kuo, C.-C. (2019) Temperature dependence of the biophysical mechanisms underlying the inhibition and enhancement effect of amiodarone on hERG channels. Molecular Pharmacology 96:330-344
2. Chou, P, Wang, G-H, Hsieh, S-W, Yang, Y-C, and Kuo, C-C (2020) Delta-frequency augmentation and synchronization in seizure discharges and telencephalic transmission. iScience 23(11):101666
3. Wang, G-H, Chou, P, Hsueh S-W, Yang, Y-C, and Kuo, C-C (2020) Glutamate transmission rather than cellular pacemaking propels excitatory-inhibitory resonance for ictogenesis in amygdala. Neurobiology of Disease 148:105188
4. Lin, Y-C, Lai, Y-C, Chou, P, Hsueh, S-W, Lin, T-H, Huang, C-S, Wang, R-W, Yang, Y-C, and Kuo, C-C (2021) How can a Na+ channel inhibitor ameliorate seizures in Lennox-Gastaut syndrome? Annals of Neurology doi:10.1002/ana.26068
5. Lee, L-N, Huang, C-S, Chuang, H-H, Lai, H-J, Yang, C-K, Yang, Y-C, and Kuo, C-C (2021) An electrophysiological perspective on Parkinson's disease: symptomatic pathogenesis and therapeutic approaches. Journal of Biomedical Science 28:85

Piecing together the SLEEP puzzle: from genes to circuitries

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University of California San Francisco

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Abstract

Sleep of sufficient duration, continuity, and intensity is necessary to promote high levels of cognitive performance during the wake period and prevent physiological changes that may predispose individuals to many adverse health outcomes. Sleep insufficiency is prevalent in our society due to the high demand for work, school, and many environmental factors, thus significantly contributing to many health conditions that we are facing. However, the full impact of sleep disruption on our health is certain to be much broader than recognized so far. Interestingly, the biological need for sleep varies dramatically among humans. We have identified a group of humans who require fewer hours of sleep each night and remain healthy for life, and we call them familial natural short sleepers. We have been using human genetics approach to identify genes/mutations that give them this unusual sleep behavior. Mouse models recapitulating human condition, coupled with in vitro molecular and neurocircuitry studies, offer new insight into the underlying mechanisms. Because of the fundamental role that sleep plays in our health, the pathways regulating sleep are intertwined with those regulating other functions. Thus, our method also offers opportunities to investigate how sleep can impact other conditions, including mood, pain, and other disease pathology. Some of these genes/mutations and the mechanistic insight learned from our studies will be presented.

Selected recent publications:

1. Hirano A, Hsu P-K, Zhang L, Xing L, McMahon T, Yamazaki M, Ptacek LJ, Fu Y-H*. DEC2 modulates orexin expression and regulates sleep. Proc Natl Acad Sci USA. 2018 Mar 12.

2. Shi G, Xing L, Wu D, Jones CR, McMahon T, Chong C, Chen J, Coppola, Geschwind D, Krystal A, Ptáček LJ, Fu Y-H*. A rare mutation of β1¬-adrenergic receptor affects sleep/wake behaviors.Neuron 2019 Sep 25;103(6):1044-1055..

3. Xing L, Shi G, Mostovoy Y, Gentry NW, Fan Z, Mcmahon TB, Kwok P-Y, Jones CR, Ptáček LJ, Fu Y-H*. Mutant Neuropeptide S receptor reduces sleep duration with preserved memory consolidation. Sci Transl Med 2019 Oct 16;11(514).

4. Shi G, Yin C, Fan Z, Xing L, Mostovoy Y, Kowk P-Y, Ashbrook LH, Krystal AD, Ptáček LJ, Fu Y-H. Mutations in metabortopic glutamate receptor 1 contribute to natural short sleep trait. Curr Biol 2021 Jan 11;31(1):13-24.

5. Dong Q, GentryNW, McMahonT, YamazakiM, Benitez-RiveraL, WangT, GanL, PtáčekLJ, FuY-H. Familial Natural Short Sleep mutations reduce Alzheimer pathology in mice. iScience 2022 March 15.

Gastric vagal afferent signaling to the basolateral amygdala mediates anxiety-like behaviors in mice with experimental colitis

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Ph.D. National Taiwan University

Abstract

Inflammatory bowel disease (IBD) is a relapsing-remitting disorder characterized by chronic inflammation of the gastrointestinal (GI) tract. Anxiety symptoms are commonly observed in IBD patients, but the mechanistic link between IBD and anxiety still remains elusive. In this study, we sought to characterize gut-to-brain signaling and brain circuitry responsible for the pathological expression of anxiety-like behaviors in male dextran sulfate sodium (DSS)-induced experimental colitis mice. We found that DSS-treated mice displayed increased anxiety-like behaviors, which were prevented by the GI vagal afferent ablation. The locus coeruleus (LC) is a relay center connecting the nucleus tractus solitarius to the basolateral amygdala (BLA) in controlling anxiety-like behaviors. Chemogenetic silencing of noradrenergic LC projections to the BLA reduced anxiety-like behaviors in DSS-treated mice. This work expands our understanding of the neural mechanisms by which IBD leads to comorbid anxiety and emphasizes a critical role of gastric vagal afferent signaling in gut-to-brain regulation of emotional states.

Selected recent publications:

1. Lin YT, Chen CC, Huang CC, Nishimori K, Hus KS (2017) Oxytocin stimulates hippocampal neurogenesis via oxytocin receptor expressed in CA3 pyramidal neurons. Nat. Commun. 8:537.

2. LinYT, Hsieh TY, Tsai TC, Chen CC, Huang CC, Hsu KS (2018) Conditional deletion of hippocampal CA2/CA3a oxytocin receptor impairs the persistence of long-term social recognition memory in mice. J. Neurosci. 38(5):1218-1231.

3. YangCY, Yu TH, Wen WL, Lin P, Hus KS (2019) Conditional deletion of CC2D1A reduces hippocampal synaptic plasticity and impairs cognitive function through Rac1 hyperactivation. J. Neurosci. 39(25):4959-4975.

4. LeeIC, Yu TS, Liu WH, Hsu KS (2021) Social transmission and buffering of stress-induced hippocampal metaplasticity in mice. J. Neurosci. 41(6):1317-1330.

5. TsaiTC, Yu TH, Hung YC, Fong LI, Hsu KS (2022) Distinct contribution of granular and agranular divisions of the retrosplenial cortex to remote contextual fear memory retrieval. J. Neurosci. 42(5):877-893.

Inflammation in depression: The new frontier of personalised psychiatry

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NIHR Senior Investigator
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PhD, University of London

Abstract

We will review the recent scientific production in immune-psychiatry from our laboratory and collaborating research groups, spanning from clinical trials to in vitro research. We will discuss what it means to be an "inflamed depressed patients" and what are the best biomarkers to use in order to make clinically relevant decisions.

Selected recent publications:

- Sforzini L, Worrell C, Kose M, Anderson IM, Aouizerate B, Arolt V, Bauer M, Baune BT, Blier P, Cleare AJ, Cowen PJ, Dinan TG, Fagiolini A, Ferrier IN, Hegerl U, Krystal AD, Leboyer M, (…), Pariante CM. A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. Mol Psychiatry. 2021 Dec 15. doi: 10.1038/s41380-021-01381-x.
-Pitharouli MC, Hagenaars SP, Glanville KP, …, Pariante CM. Elevated C-Reactive Protein in Patients With Depression, Independent of Genetic, Health, and Psychosocial Factors: Results From the UK Biobank. Am J Psychiatry. 2021 May 14:appiajp202020060947.
- Chang JP, Su KP, Mondelli V, Pariante CM. Cortisol and inflammatory biomarker levels in youths with attention deficit hyperactivity disorder (ADHD): evidence from a systematic review with meta-analysis. Transl Psychiatry. 2021 Aug 19;11(1):430. doi: 10.1038/s41398-021-01550-0.
- Borsini A, Nicolaou A, Camacho-Muñoz D, Pariante CM. Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. Mol Psychiatry. 2021 Jun 16.
-Bind RH, Biaggi A, Bairead A, Du Preez A, Hazelgrove K, Waites F, Conroy S, Dazzan P, Osborne S, Pawlby S, Sethna V, Pariante CM. Mother-infant interaction in women with depression in pregnancy and in women with a history of depression: the Psychiatry Research and Motherhood

Data-Driven and Theory-Driven Approaches in Neuroscience

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Okinawa Institute of Science and Technology Graduate University

Ph.D., The University of Tokyo

Abstract

With the progresses in molecular probe, imaging, sequencing and other technologies, unprecedented amounts of neural data are being produced. Data-driven approaches utilizing statistical machine learning are expected to deliver novel discoveries about how brains are organized and working. However, a data-driven approach alone may not be sufficient for understanding a complex system like the brain; even if we have a complete circuit diagram of a computer chip, understanding its functioning requires the knowledge of arithmetic units, instruction codes, error correction, temperature compensation, and so forth. Theory-driven approaches important in providing possible candidates of computing architectures and the approaches from both directions eventually need to converge for a coherent understanding.

This talk highlights the approaches in both directions in brain science initiatives around the world, including Japan's Brain/MINDS Project, as well as those from my own lab. Topics include utilizing connectome data for brain network modeling, analyzing animal behavior data for understanding the algorithms of decision making, and analyzing two-photon imaging data to address the circuit mechanisms of mental simulation.

Selected recent publications:

1. Doya K (2021). Canonical cortical circuits and the duality of Bayesianinference and optimal control. Current Opinion in Behavioral Sciences, 41, 160-167.
2. Miyazaki K, Miyazaki KW, Sivori G, Yamanaka A, Tanaka KF, Doya K (2020). Serotonergic projections to the orbitofrontal and medial prefrontal cortices differentially modulate waiting for future rewards. Science Advances, 6, eabc7246.
3. Fermin AS, Yoshida T, Yoshimoto J, Ito M, Tanaka SC, Doya K (2016). Model-based action planning involves cortico-cerebellar and basal ganglia networks. Scientific Reports, 6, 31378.
4. Funamizu A, Kuhn B, Doya K (2016). Neural substrate of dynamic Bayesian inference in the cerebral cortex. Nature Neuroscience, 19, 1682–1689.
5. Ito M, Doya K (2015). Distinct neural representation in the dorsolateral, dorsomedial, and ventral parts of the striatum during fixed- and free-choice tasks. Journal of Neuroscience 35:3499-3514.

Ultrasound Brain Stimulation

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Joint Appointment Investigator, Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes

Ph.D.,Bioengineering, University of Washington

Abstract

Brain is a notoriously difficult organ for therapeuticagentsto reachdue to the presence of different barriers, e.g., the blood brain barrier (BBB), in brain. Thepermeability of the CNS barrierscan be significantly enhanced using mechanical waves (e.g., focused ultrasound), through the temporal opening of the barriers, providing a promising strategy to increase delivery of therapeutic agent into the brain. Our study proposesusing aspecial form of ultrasound, thefocused extracorporeal shockwave, to open the BBB and BCSFB (blood-CSF barrier) to achieve non-invasive, controllable-focus and reversible BBB or BCSFB openingin the brains of rats. Under shockwave treatment with an intensity level of 0.1 (peak positive pressure 5.4 MPa; peak negative pressure -4.2 MPa; energy flux density 0.03 mJ/mm2)with the addition of microbubbles (2×10^6 /kg of SonoVue contrast agent or 20 % of the clinical dosage for imaging) and a single pulse, the BBB or BCSFB could be opened temporarily. The effect of enhancing doxorubicin effect on glioblastoma multiforme rat models was shown after compromising BBB by shockwaves. Moreover, the significant elevation of gastrodin concentration in CSF after BCSFB opening by shockwaves successfully suppressed the severity of epilepsy attacks in rat models.

We also explored the role of TRPV4 in mechanical force-enhanced BBB permeability, specifically its effect on tight junction. Recently, our lab demonstrated the role of mechanical waves stimulation on enhancing the glymphatic circulation in brain, suggesting the potential applications in CNS waste clearance and probably also the progression of degenerative brain disorders.

Selected recent publications:

1. Facilitating drug delivery in the central nervous system by opening the blood-cerebrospinal fluid barrier with a single low energy shockwave pulse, KungY., Chen K.Y., Liao W.H., Hsu Y.H., Wu C.H., Hsiao M.Y., Huang P.H.* and **Chen W.S**.*, *Fluids and Barriers of the CNS, 19: 3, 2022.*

2. A single low-energy shockwave pulse opens blood-cerebrospinal fluid barriers and facilitates gastrodin delivery to alleviate epilepsy, Kung, Y., Hsiao M.Y., Yang S.M., Wen T.Y., Chen M., Liao W.H., Wu C.H., Ao L., **Chen W.S.***, *Ultrasonics Sonochemistry, 78: 105730, 2021.*

3. Investigation of the therapeutic effect of doxorubicin combined with focused shockwave on glioblastoma,Liao W.H., Hsiao M.Y., Kung Y., Huang P.H.*,**Chen W.S.***, *Frontiers in Oncology, 11:711088, 2021.*

4. TRPV4 promotes acoustic wave-mediated BBB opening via Ca2+/PKC-δ pathway,Liao W. H., Hsiao M.Y., Kung Y. Liu H.L., Béra J.C., Inserra C., **Chen W.S.***, *Journal of Advanced Research, 26:15-28,2020.*

5. A single high-intensity shock wave pulse with microbubbles opens the blood-brain barrier in rats, Kung Y., Huang H.Y., Liao W.H., Huang A. P-.H., Hsiao M.Y., Wu C.H., Liu H.L., Inserra C., **Chen W.S.***, *Frontiers in Bioengineering and Biotechnology, 8:402, 2020.*

Auditory implants and molecular therapeutics for profound hearing loss

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Professor, Department of Otolaryngology, National Taiwan University College of Medicine

Director, Department of Medical Research, National Taiwan University Hospital Hsin-Chu Branch

MD, Ph.D. National Taiwan University Hospital

Abstract

Cochlear implantation is currently the treatment of choice for patients with severe to profound sensorineural hearing impairment (SNHI). Although most patients exhibit fair speech perception ability after cochlear implantation, they do not regain “natural hearing” and cannot appreciate the music satisfactorily. Cochlear implants convert external sounds into electric signals, and function as mechanical prostheses merely. Cochlear implants cannot mediate a full recovery of hearing sensitivity and/or restoration of the native inner ear sensory epithelia. Furthermore, the benefits with cochlear implants may be limited in patients withretrocochlear pathologies. As such, new biological therapeuticapproaches based on genetic and molecular tools are being developed to address these unmet clinical needs.

It can be envisaged that genetic and molecular therapies for profound SNHI will start from certain scenarios: (1) hereditary hearing impairment caused by mutations in single genes, such as *OTOF*-,*GJB2*-, *PJVK*-, *SLC26A4*-, and Usher syndrome-related SNHI; (2) SNHI caused by acute injuries to the inner ear, such as sudden deafness, ototoxicity, and noise-induced hearing loss. In this talk, I will discuss these scenarios and present our recent data in humans and experimental models.

Selected recent publications:

1. Cheng YF, Tsai YH, Huang CY, Lee YS, Lu YC, Hsu CJ, **Wu CC*** (2020) Generation and pathological characterization of a transgenic mouse modelcarrying a missense *PJVK* mutation.BiochemBiophys Res Commun., 532:675-681.(* Corresponding author)

2. Chen PY, Lin YH, Liu TC, Lin YH, Tseng LH, Yang TH, Chen PL, **Wu CC***,Hsu CJ (2020) Prediction model for audiological outcomes in patients with*GJB2* mutations. Ear Hear, 41, 143-149.(* Corresponding author)

3. Lu CY, Tsao PN, Ke YY, Lin YH, Lin YH, Hung CC, Su YN, Hsu WC, HsiehWS, Huang LM, **Wu CC***, Hsu CJ (2018) Concurrent hearing, genetic,and cytomegalovirus screening in newborns, Taiwan. J Pediatr, 199,144-150.(* Corresponding author)

4. Lin PH, Hsu CJ, Lin YH, Lin YH, Lee HY, **Wu CC***, Liu TC (2017)Etiologic and audiologic characteristics of patients with pediatric-onset unilateraland asymmetric sensorineural hearing loss. JAMA Otolaryngol Head Neck Surg,143, 912-919.(* Corresponding author)

5. **Wu CC**, Tsai CH, Hung CC, Lin YH, Lin YH, Huang FL, Tsao PN, Su YN, LeeYL, Hsieh WS, Hsu CJ (2017) Newborn genetic screening for hearingimpairment: a population-based longitudinal study. Genet Med, 19, 6-12.

Low-intensity ultrasound stimulation of mouse brain modulates neurogenesis andregulatesprotein phosphorylation

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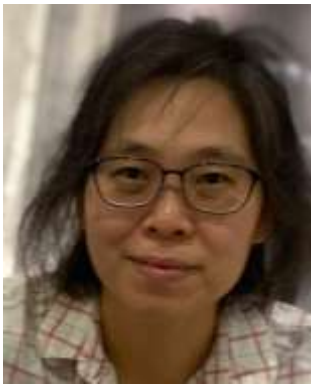
National Taiwan University



Abstract

Transcranial ultrasound stimulation is an emerging technique for the development of a non-invasive neuromodulation device for the treatment of various types of neurodegenerations and brain damages.The current studies addressing the possible therapeutic roles of ultrasound adopt the candidate approach strategy, for examples, by the intracellular calcium surge induced by the mechanosensitive ion channels, or the activation of cell signaling pathways, or the levels of brain-derived neurotrophic factor.We have previously reported the detection of ASIC1a dependent stimulation of calcium influx in mouse brain neurons and this may lead to the neurogenesis in dentate gyrus of adult mice (Elife10:e61660).The global pattern of neuronal Extracellular Regulated Kinase (p-ERK) phosphorylation of mouse brain upon ultrasound stimulation is inconsistent and restricted to certain brain regions. The variability of p-ERK pattern is reasonable since ERK servesas a convergent center of several cell signaling pathways. Thus, there is a need for some alternative markers, which together with p-ERK will provide a more robust readout. In this study, the proteomics of mouse hippocampus is illustrated to gain an unsupervised classification of phosphorylated proteins. We perform an analysis that leads to the development of phospho-specific antibodies that may be used as ultrasound stimulation markers in addition to the established phospho-ERK. In addition, we have also identified the activation of Grin2b-Camk2a signaling hub. The validation of this activation is theWestern blot analysis of hippocampal lysates from samples that are either ultrasound simulated or sham treated.The development of phosphorylation markers based on further understanding of signaling hubs activated upon ultrasound can shed light on the therapeutic potential of transcranial ultrasound.

Selected recent publications:

1. Lim J, Tai HH, Liao WH, Chu YC, Hao CM, Huang YC, Lee CH, Lin SS, Hsu S, Chien YC, Lai DM, Chen WS, Chen CC, Wang JL. 2021ASIC1a is required for neuronal activation via low-intensity ultrasound stimulation in mouse brain. Elife10:e61660

2. Lim J, Chu YS, Chu YC, Lo CM, Wang JL. 2020 Low Intensity Ultrasound Induces Epithelial Cell Adhesion Responses. J BiomechEng142:091014

3. Chu YC, Lim J, Lai CH, Tseng MC, Chu YS, Wang JL. 2021 Elevation of Intra-Cellular Calcium in Nucleus Pulposus Cells with Micro-Pipette-Guided Ultrasound. Ultrasound Med Biol47(7):1775-1784

4. Chu YC, Lim J, Tseng MC, Wang JL. 2020 The responses of nucleus pulposus cells to pressure and ultrasound stimulation. J Acoust Soc Am148(4):EL314

5. Chu YC, Lim J, Hwang WH, Lin YX, Wang JL. 2020 Piezoelectric stimulation by ultrasound facilitates chondrogenesis of mesenchymal stem cells. J Acoust Soc Am 148(1):EL58

The responses of N2A cells to piezoelectric stimulation

Yu-Chia Chuang(莊育嘉)
Post-doc fellow, Institute of Biomedical Sciences, Academia Sinica

Ph.D., National Yang-Ming University

Abstract

Piezoelectricity is the ability of the material to generate transient charges in response to the applied mechanical stimulation. Ultrasoundcombined with piezoelectric materials can be exploited to generateindirect electrical stimuli to *in vivo* deep biological tissue, which gives great promise for the development of non-invasive neural regenerative devices and providesexcitingperspectivesin regeneration research and clinical fields. In addition to applications in bioengineering, piezoelectricity is also available in our endogenous body, notably existing in collagen-enriched tissue, such as tendon, ligament, bone, and cartilage.Piezoelectricity, however, has been a much-neglected subject for its physiological role in the past 30 years. It is known that electrical stimulation widely for disparate therapeutic conditions can spur axonal migration to promote nerve regeneration. Whether piezoelectricity could benefit the axon outgrowth and modulate the neural circuit is still unknown. Studies have shown that ultrasonically-induced piezoelectric substrates were used to promote the differentiation of neuron-like PC12 cells. Nevertheless, the inextricable link between ultrasound and ultrasound-mediated piezoelectricity for nerve regeneration leaves knowledge gaps. In this study, we aim to explore the effect of ultrasound and ultrasound-mediated piezoelectricity on neuron behaviors. We designed an ultrasonic live imaging chamber mounted with glass or AT-cut quartz coverslips. The device was utilized to observethe effect of ultrasound or piezoelectric stimulation on the modulation of neuroblastoma N2a cells. Combined with time-lapse confocal imaging, calcium imaging, and immunostaining, the results suggest ultrasound-induced piezoelectricity has benefitin the modulation of actin organization to enhance growth cone activity and neurite dynamics.

Selected recent publications:

1. **Chuang, Y.C.** and Chen, C.C. (2022) The force from filaments: the role of the cytoskeleton and extracellular matrix in the gating of mechanosensitive channels. *Frontiers in Cell and Developmental Biology* (under review)
2. Lin, J.H., Yu, Y.W., **Chuang, Y.C.**, Lee, C.H., and Chen, C.C. (2021) ATF3-expressing large-diameter sensory afferents at acute stage as bio-signatures of persistent pain associated with lumbar radiculopathy. *Cells*, 10(5), 992.
3. Chang, C.T., Fong, S.W., Lee, C.H., **Chuang, Y.C.**, Lin, S.H., Chen, C.C. (2019) Involvement of acid-sensing ion channel 1 1b in the development of acid-induced chronic muscle pain. *Front Neurosci*. 13:124
4. Wu, W. L., Cheng, S. J., Lin, S. H., **Chuang, Y. C.**, Huang, E. Y., Chen, C. C. (2019) The effect of ASIC3 knockout on corticostriatal circuit and mouse self-grooming behavior. *Front Cell Neurosci*. 13:86
5. **Chuang, Y.C.**, Lee, C.H., Sun, W.H., and Chen, C.C. (2018) Involvement of advillin in somatosensory neuron subtype-specific axon regeneration and neuropathic pain. *PNAS*, 115(36): E8557-E8566

Detecting changes: Neurocomputational substrates for under- and overreactions to change

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Institute of Neuroscience

National Yang Ming Chiao Tung University

Ph.D., New York University

Abstract

In an ever-changing world, the ability to correctly detect and respond to changes is key to economic success. For example, a correct and timely detection of change in financial markets allows investors to make the proper adjustments, while an incorrect judgment on change can make all the subsequent responses futile. A decision maker can overreact to change—judging a change has occurred when in fact no change is taking place—and can also underreact to change. But what are the neural mechanisms that give rise to these biases? In a series of fMRI experiments, human participants performed a 'regime-shift' task designed to investigate under- and overreactions to change. At the behavioral level, we found that overreactions are most common in stable environments with noisy signals, whereas underreactions are most common in unstable environments with precise signals. At the neural level, we found that the subjective estimates of change were supported by two distinct functional networks, with the frontoparietal control network involved in the evaluation of sensory signals in light of environmental constraints, and the ventromedial prefrontal cortex in representing the subjects' probability estimates of change. Further, individual differences in the degree of over- and underreactions were represented in the dorsomedial prefrontal cortex (part of the frontoparietal control network) and the striatum. Together, these results indicated that under- and overreactions to change arise from the evaluation of sensory signals in light of environmental constraints, and that the neural implementations for this computation are distinct from probabilistic computations for change estimation.

Selected recent publications:

1. Yang, Y-Y., Wu, S-W. (2020). Base rate neglect and neural computations for subjective weight in decision under uncertainty. *PNAS*, 117(29):16908-16919.

2. Lin, W-H., Gardner, J.L., Wu, S-W. (2020). Context effects on probability estimation. *PLoS Biology*, 18(3): e3000634.

A retrospective and stepwise learning strategy revealed by neuronal activity in the basal forebrain

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Institute of Neuroscience

National Yang Ming Chiao Tung University

M.D., National Taiwan University

Ph.D., Duke University

Abstract

Associative learning is a fundamental cognitive capacity that allows animals and humans to learn the predictive relationship between behavioral events and rewarding outcomes. While the process of learning is commonly conceptualized as a prospective strategy (learning how behavioral events predict future rewards), here we provide behavioral and neurophysiological evidence to show that animals may instead employ a retrospective and stepwise learning strategy (learning how the reward is predicted by preceding behavioral events). In rats learning a new association in which the reward was paired with a sequence of behavioral events, learning started from the event closest to the reward and sequentially incorporated earlier events into animals' internal model. The learning of each behavioral event as a new reward predictor was accompanied by the emergence of basal forebrain (BF) neuronal responses toward that event. BF activities quantitatively conveyed a reward prediction error signal associated with the behavioral event, and promoted reward-seeking behavioral sequences containing the newly learned event. As the internal model incorporated more behavioral events as reward predictors, non-rewarded behavioral sequences that were once compatible with the internal model during early stages of learning became incompatible and were sequentially eliminated. Together, these results demonstrate how the retrospective and stepwise learning strategy can effectively establish animals' internal model during the learning process and lead to the sequential refinement of reward-seeking behaviors. These results also highlight the functional significance of BF neuronal activities, which provided unique insights into the covert dynamics of the learning process in single trials.

Selected recent publications:

1. Manzur HE, Vlasov K, Lin S-C. A retrospective and stepwise learning strategy revealed by neuronal activity in the basal forebrain. bioRxiv. 2022. p. 2022.04.01.486795. doi:10.1101/2022.04.01.486795

2. Mayse JD, Nelson GM, Avila I, Gallagher M, Lin S-C. Basal forebrain neuronal inhibition enables rapid behavioral stopping. Nat Neurosci. 2015;18: 1501–1508.

3. Avila I, Lin S-C. Motivational salience signal in the basal forebrain is coupled with faster and more precise decision speed. PLoS Biol. 2014;12: e1001811.

Aversive prediction errors in pain perception

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National Taiwan University

Ph.D., National Taiwan University

Abstract

The learning of associations between one's actions and their consequences plays a crucial role in decision making, and the difference between the actual outcome and expected outcome (i.e., prediction error) reinforces or extinguishes decisions. Despite a considerable amount of research on reward prediction errors, relatively little is known about the functional significance of aversive prediction errors. In this lecture, I will describe how we used functional neuroimaging techniques to elucidate the role of aversive prediction error signals in human pain perception. Different from the central role for reward prediction errors in updating values related to available actions, we demonstrated that aversive prediction error signals did not update pain expectations, which supported the persistent modulation of expectations on pain throughout the experiment. At the neural level, we showed that positive expectations (i.e., expectations of decreased pain) reduced the perception of pain by enhancing the interaction between the neural system encoding aversive prediction errors and descending pain inhibitory system, whereas negative expectations (i.e., expectations of increased pain) appeared to nonlinearly increase pain by reducing this interaction. In conclusion, we provide evidence that aversive prediction error signals underlie stimulus expectancy effects on pain in humans, with positive and negative expectations engaging dissociable but interrelated neural mechanisms. These mechanisms help to explain why we humans can adapt quickly and appropriately to aversive stimuli whose intensity deviates from our expectations.

Selected recent publications:

1. Cheng-Wei Huang, Chin-Hsien Lin, Yi-Hsuan Lin, Hsin-Yun Tsai, Ming-Tsung Tseng. (2021). Neural Basis of Somatosensory Spatial and Temporal Discrimination in Humans: The Role of Sensory Detection. *Cerebral Cortex*, 32(7):1480-1493.

2. Yao-Wei Shih, Hsin-Yun Tsai, Feng-Sheng Lin, Yi-Hsuan Lin, Chun-Yen Chiang, Zheng-Liang Lu, Ming-Tsung Tseng (2019). Effects of positive and negative expectations on human pain perception engage separate but interrelated and dependently regulated cerebral mechanisms. *The Journal of Neuroscience*, 39(7), 1261-1274.

3. Sung-Ling Yang, Ting-Wei Wu, Ming-Tsung Tseng (2018). Vigilance-related attention systems subserve the discrimination of relative intensity differences between painful stimuli. *Pain*, 159(2):359-370.

4. Ming-Tsung Tseng, Yazhuo Kong, Falk Eippert, Irene Tracey (2017). Determining the neural substrate for encoding a memory of human pain and the influence of anxiety. *The Journal of Neuroscience*, 37(49):11806-11817.

Rethinking policy improvement in reinforcement learning

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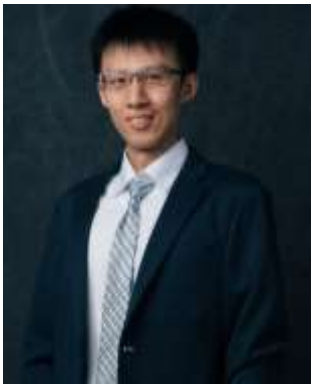

Abstract

Policy improvement is one central component of any reinforcement learning (RL) algorithm, and the most widely-used approach is to leverage the policy gradient (PG) theorem to iteratively improve the learned policies. Despite the success of the PG methods, they could suffer from inefficient training and slow learning progress in various settings. In this talk, we go beyond PG and introduce two new policy improvement frameworks: (i) In the first half, we introduce the action-constrained RL problem and formally discuss the critical "zero-gradient issue" resulting from PG. Then, we present Frank-Wolfe policy optimization (FWPO), which is a decoupling framework that completely resolves the challenging zero-gradient issue and could be combined with neural representation for solving practical RL problems. (ii) Next, we present Hinge policy optimization (HPO), which rethinks policy updates as solving a large-margin binary classification problem with hinge loss. The HPO framework opens up a whole new family of RL algorithms, including the popular heuristic PPO with a clipped surrogate objective (PPO-clip) as a special case. Moreover, we formally prove that HPO attains a globally optimal policy. To our knowledge, this is the first global convergence guarantee for the PPO-clip algorithm. Finally, experimental results in a variety of benchmark environments will also be presented to corroborate the effectiveness of the two frameworks.

Selected recent publications:

1. Bing-Jing Hsieh, Ping-Chun Hsieh, and Xi Liu (2021). Reinforced Few-Shot Acquisition Function Learning for Bayesian Optimization. In *Advances in Neural Information Processing Systems (NeurIPS)*.

2. Khaled Nakhleh, Santosh Ganji, Ping-Chun Hsieh, I-Hong Hou, and Srinivas Shakkottai (2021). NeurWIN: Neural Whittle Index Network For Restless Bandits Via Deep RL. In *Advances in Neural Information Processing Systems (NeurIPS)*.

3. Jyun-Li Lin, Wei Hung, Shang-Hsuan Yang, Ping-Chun Hsieh, and Xi Liu (2021). Escaping from Zero Gradient: Revisiting Action-Constrained Reinforcement Learning via Frank-Wolfe Policy Optimization. In *Uncertainty in Artificial Intelligence* (pp. 397-407). PMLR.

4. Yu-Heng Hung, Ping-Chun Hsieh, Xi Liu, and P. R. Kumar. Reward-Biased Maximum Likelihood Estimation for Linear Stochastic Bandits (2021). In *Proceedings of the AAAI Conference on Artificial Intelligence* (pp. 7874-7882).

5. Xi Liu, Ping-Chun Hsieh, Yu-Heng Hung, Anirban Bhattacharya, and P. R. Kumar. Exploration Through Reward Biasing: Reward-Biased Maximum Likelihood Estimation for Stochastic Multi-Armed Bandits (2020). In *International Conference on Machine Learning* (pp. 6248-6258). PMLR.

Dysregulated affective arousal regulates reward-based decision making in patients with schizophrenia

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Ph.D., Cornell University

Abstract

Schizophrenia is a chronic and severe mental disorder. Dysregulated decision-making and affective processing have been implicated in patients with schizophrenia (SZ) and have significant impacts on their cognitive and social functions. However, little is known about how affective arousal influences reward-based decision-making in SZ. Taking advantage of a 2-choice probabilistic gambling task and utilizing three facial expressions as affective primes (i.e., neutral, angry, and happy conditions) in each trial, we investigated how affective arousal influences reward-related choice based on behavioral, model fitting, and feedback-related negativity (FRN) data in thirty-eight SZ and twenty-six healthy controls (CTRL). We also correlated our measurements with patients' symptom severity. Compared with the CTRL group, SZ expressed blunted responses to angry facial primes. They had lower total game scores and displayed more maladaptive choice strategies (i.e., less win-stay and more lose-shift) and errors in monitoring rewards. Model fitting results revealed that the SZ group had a higher learning rate and lower choice consistency, especially in the happy condition. Brain activity data further indicated that SZ had smaller amplitudes of FRN than their controls in the angry and happy conditions. Importantly, the SZ group exhibited attenuated affective influence on decision-making, and their impairments in decision-making were only correlated with their clinical symptoms in the angry condition. Our findings imply the affective processing is dysregulated in SZ and it is selectively involved in the regulation of choice strategies, choice behaviors, and FRN in SZ, which lead to impairments in reward-related decision-making, especially in the angry condition.

Selected recent publications:

1. Liu, H.H., Liu, C.M., Hsieh, M.H., Chien, Y.L., Hsu, Y.F., Lai, W.S.* Dysregulated affective arousal regulates reward-based decision making in patients with schizophrenia: an integrated study. *Schizophrenia*, 8: 26, 2022 (doi: 10.1038/s41537-022-00234-y).

2. Pei, J.C.#, Luo, D.Z.#, Gau, S.S., Chang, C.Y., Lai. W.S.* Directly and indirectly targeting the glycine modulatory site to modulate NMDA receptor function to address unmet medical needs of patients with schizophrenia. *Frontiers in Psychiatry*, 01 October 2021 (https://doi.org/10.3389/fpsyt.2021.742058).

3. Luo, D.Z.#, Chang, C.Y.#, Huang, T.R., Studer, V., Wang, T.W., Lai, W.S.* Lithium for schizophrenia: supporting evidence from a 12-year, nationwide health insurance database and from Akt1-deficient mouse and cellular models. *Scientific Reports*, 10:647, 2020 (doi: 10.1038/s41598-019-57340-8)

4. Pei, J.C.#, Hung, Wei-Li#, Lin, B.X., Shih, M.H., Lu, L.Y., Luo, D.Z., Tai, H.C., Studer, V., Min, M.Y., Lai, W.S.* Therapeutic potential and underlying mechanism of sarcosine (N-methylglycine) in N-methyl-D-aspartate (NMDA) receptor hypofunction models of schizophrenia. *Journal of Psychopharmacology*, 33(10), 1288-1302, 2019 (doi: 10.1177/0269881119856558).

5. Liu, H.H.#, Hwang, Y.D., Hsieh, M.H., Hsu, Y.F.*, Lai, W.S.* Misfortune may be a blessing in disguise: Fairness perception and emotion modulate decision making. *Psychophysiology*, 54(8), 1163-1179, 2017 (doi:10.1111/psyp.12870; SCI).

Integration between light tough and proprioception: recent advances

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林口長庚紀念醫院/長庚大學

Abstract

Movement of upper limb is an integral behavior across motor and sensation. Proprioceptive inputs provide feedback signals to ensure precise movement trajectories. Even though proprioception is traditionally considered to be obtained through proprioceptive receptors, such as muscle spindles and Golgi tendon apparatus, more and more evidence indicates that cutaneous senses also contribute to the percept of joint position. To this end, cutaneous and proprioceptive inputs are no longer mutually exclusive in terms of their functionality.

A cardinal hallmark of somatosensation is integration across submodalities, such as light touch and proprioceptive inputs. In this talk, we will discuss the evolution of theories regarding the input signals of joint position senses from studies obtained in human and primates. The most important finding is that stretch receptors on the skin is important to determine the percept of joint position, especially in the hand. Another important issue is how joint position and light touch are integrated to yield a holistic percept as we are manipulating an object. Studies performed in our group showed that hand posture affects the perceived feature of stimuli presented on the fingertips. Finally, we will discuss the rule of cutaneous inputs when performing haptic approaches. We will show how cutaneous senses are used as the feedback signals to adjust movement.

Selected recent publications:

1. Pu SW, et al. Decoupling Finger Joint Motion in an Exoskeletal Hand: A Design for Robot-assisted Rehabilitation. IEEE transactions on industrial electronics. 2020 Jan. 67(1) 686-697.
2. Pei Y, et al. Neural mechanisms of tactile motion integration in primary somatosensory cortex. Neuron. 2011; 69(3):536-547.
3. Pei Y, et al. Shape invariant coding of motion direction in primary somatosensory cortex. PLoS Biology. 2010;8(2):e1000305.
4. Pei Y, et al. The tactile integration of local motion cues is analogous to its visual counterpart. Proc Natl Acad Sci USA. 2008 Jun 10;105(23):8130-5.

PROPRIOCEPTION IN RELATION TO NECK PAIN AND DEEP MUSCLE ACTIVATION

Shwu-Fen Wang , Professor

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Abstract

The human musculoskeletal system of spine relies on a proposed bio-tensegrity system to maintain stability and provide mobility. The deep neck muscles, such as multifidus and oblique capitis inferior (OCI), are proposed to work as sensor and tensor, where the proprioception and motor output maintain tension and compression balance in this model. Proprioception is conducted by mechanoreceptor located in muscles and tendons. Proprioceptive functions include reposition accuracy for detecting the length change and tension sensation for detecting the force generated by muscle activation.

Here we report a serious of works that used established proprioceptive tests conducting by ultrasound-based motor analysis system and EMG recording to investigate the relationship between pain, deep muscles activation, and proprioceptive functions of chronic neck pain.

The proprioception of neck declines with age and is further impaired by neck pain. Reposition of neck is affected by age and impaired in chronic neck pain. Pain frequency, neither duration nor intensity, is associated with reposition accuracy. Chronic neck pain also alters EMG patterns of neck muscles during voluntary neck motions. Neck pain causes asymmetric change of OCI thickness in unilateral cervicogenic headache. The change of multifidus thickness is associated with reposition accuracy in chronic neck pain.

In conclusion, aging and pain frequency is related to reposition accuracy of neck. Patients demonstrate higher reposition error, change of motor control pattern and deep muscle thickness. The series studies in cervical proprioception in asymptomatic, aging, and neck pain population have shed light to the role of proprioception in cervical spinal model in relation to the deep muscles, which testing the hypothesis of bio-tensegrity model at macrolevel.

Selected recent publications:

1. Chen, Y. Y., H. M. Chai, C. L. Wang, Y. W. Shau and S. F. Wang (2018). "Asymmetric Thickness of Oblique Capitis Inferior and Cervical Kinesthesia in Patients With Unilateral Cervicogenic Headache." J Manipulative Physiol Ther 41(8): 680-690.

2. Cheng, C. H., J. L. Wang, J. J. Lin, S. F. Wang and K. H. Lin (2010). "Position accuracy and electromyographic responses during head reposition in young adults with chronic neck pain." J Electromyogr Kinesiol 20(5): 1014-1020.

3. Lee, H. Y., J. D. Wang, G. Yao and S. F. Wang (2008). "Association between cervicocephalic kinesthetic sensibility and frequency of subclinical neck pain." Man Ther 13(5): 419-425.

4. Teng, C. C., H. Chai, D. M. Lai and S. F. Wang (2007). "Cervicocephalic kinesthetic sensibility in young and middle-aged adults with or without a history of mild neck pain." Man Ther 12(1): 22-28.

5. Wu, J. P., Tsai, S. Y., Y. W. Shau, C. L. Wang, H. M. Chai and S. F. Wang (2007). "Change of cervicocephalic kinesthetic sensibility in relation to thickness of cervical multifidus in patients with cervical symptoms." Internation conference of Biomechanics

Limb proprioceptive deficits are associated with motor abnormalities in individuals with a developmental coordination disorder

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Abstract

Proprioception refers to the awareness of limb position and motion that is essential for motor control and movement coordination. Individuals with developmental coordination disorder (DCD) primarily exhibit severe motor clumsiness that becomes manifest when executing fine motor skills or as balance and locomotor problems. There has been a long-standing debate, as to whether the motor abnormalities observed in DCD are due to impaired processing of proprioceptive signals required for motor control. Until recently, the available evidence was inconclusive partly because the notion of impaired proprioception was implied indirectly from the resultsof sensorimotor tests, not somatosensory tests. Here, we report a series of our recent work that used established proprioceptive assessments (e.g., psychophysical threshold testing, joint position matching paradigm) to determine upper and lower limb proprioceptive deficits in individuals with DCD. Specifically, we map the magnitude of the abnormal proprioception at the proximal/distal joints and haptic perception, to understand the link between the proprioceptive and movement deficits in DCD.In addition, wediscuss the potential somatosensory-motor training that may be beneficial for limb proprioception in typically and atypically developing children. This presentation highlights scientific evidence of the reciprocal roles of proprioception and motor functionsand offers new insights into clinical implications and future research directions.

Selected recent publications:

1. **Tseng, Y.-T.***, Lin, Y. H., Chen, Y. W., Tsai, C. L., & Chen, F. C. (2022). Impaired wrist position sense is linked to motor abnormalities in young adults with a probable developmental coordination disorder. *Neuroscience Letters. 772, 16, 136446*

2. **Chen, F. C., Pan, C. Y., Chu, C. H., Tsai, C. L., &Tseng, Y. T. (2020). Joint position sense of lower extremities is impaired and related to balance function in children with developmental coordination disorder. *Journal of Rehabilitation Medicine, 52*(8). doi:10.2340/16501977-2720**

3. **Tseng, Y. T.***, Tsai, C. L., & Chen, F. C. (2020). Wrist proprioceptive acuity is linked to fine motor function in children undergoing piano training. *Journal of Neurophysiology*. *124*(6), 2052-2059.

4. **Tseng, Y. T.*,Chen, F. C., Tsai, C. L., &Konczak, J (2019)Position sense dysfunction affects proximal and distal joint in children with developmental coordination disorder. *Journal of Motor Behavior. 51*(1), 49-58.**

5. **Tseng, Y. T.*, Chen, F. C., Tsai, C. L., &Konczak, J (2018). Wrist position**sense acuity and its relation to motor dysfunction in children with developmental coordination**disorder. *Neuroscience Letters.674*, 106-111.**

A Molecular Approach to the Sixth Sense: Proprioception

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生物醫學科學研究所/中央研究院

Abstract

Proprioception, or the integration of somatosensorial information that enables a person to know their body parts' location, movement, and strains at any given time, is the unsung sixth sense of the human body. Proprioceptive afferent data provides the foundation of our spatial and movement awareness and has been suggested as the foundation for self-awareness. Unfortunately, molecular proprioception remains largely unknown, mostly because genetic models to study this sensory modality are lacking. Enter the Acid Sensing Ion Channel (ASIC) family who, being trimeric membrane channels typically known for their function in sensing tissue acidosis, have recently emerged as mammalian dual-functioned, mechano-sensing ion channels. This role is their phylogenic inheritance, for they belong to the ENaC/DEG family of well-known mechanosensors. Our work, spanning electrophysiology, genetics, behavior, imagery and more suggests that the ASIC members play dissimilar and specialized roles in proprioceptor subtypes, mediating specific modalities of proprioception.

This talk will push the idea of using the ASIC family as an approach to probe the specific mammalian proprioceptor classes, with PNS-exclusive ASIC1b at the forefront of the study. The ASICs present themselves as modulators of stretch-induced currents in specific subsets of Parvalbumin-positive proprioceptors. These proprioceptor subtypes are involved in different circuitry, influencing somatosensorial integration, and ultimately leading to observable changes inside and outside of classical proprioception-related behavior.

Selected recent publications:

Astrocytic AhR in Chronic Kidney Disease-Associated Dementia

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Deputy Vice President for Academic Affair, National Yang Ming Chiao Tung University

Ph.D.University of Kansas

Abstract

Chronic kidney disease (CKD)-associated dementia has been attributed to the excessive indoxyl-3-sulfate (I3S) in the brain that is resistant to hemodialysis. I3S is also a tryptophan-derived ligand of the aryl hydrocarbon receptor (AhR). In this study, we investigate the mechanism underlying the role of brain AhR in the CKD-induced brain disorder *in vivo* and *in vitro*. We used 5/6 nephrectomy with an 8-week post-operative period to establish the CKD mouse model, which induced blood and brain I3S elevations, brain AhR activation, increase in anxiety-like behavior and recognition memory impairment. Notably, astrocyte-enriched glutamate transporter 1 (GLT1) was selectively reduced with increased GFAP and neuronal excitation indicator c-Fos in the anterior cortex. Neural lineage-specific as well as astrocyte-specific AhR conditional knockout both attenuated CKD-induced cognitive impairment. These CKD effects in the brain were further investigated *in vitro* using chronic I3S treatment in primary astrocytes and glia-neuron mix cultures, which shows reduction of GLT1 activity, neuron-astrocyte coupling, and loss of excitatory synapses. Pretreatment with an AhR antagonist CH-223191 can alleviate these detrimental effects in both *in vitro* and *in vivo* CKD models. Thus, CKD-associated chronic I3S/AhR activation in the brain causes impaired astrocytic GLT1 activity and neuronal hyperexcitaiton, leading to the CKD-associated synaptotoxicity and cognitive impairment.

Selected recent publications:

1. Chen WC, Chang LH, Huang SS, Huang YJ, Chih CL, Kuo HC, Lee YH*, Lee IH*. (2019) Aryl hydrocarbon receptor modulates stroke-induced astrogliosis and neurogenesis in the adult mouse brain.*J Neuroinflammation.* 16:187.

2. Kuo YM, Hsu PC, Hung CC, Hu YY, Huang YJ, Gan YL, Lin CH, Shie FS, Chang WK, Kao LS, Tsou MY, Lee YH*. (2019) Soluble epoxide hydrolase inhibition attenuates excitotoxicity involving 14,15-epoxyeicosatrienoic acid-mediated astrocytic survival and plasticity to preserve glutamate homeostasis. *Mol Neurobiology*,56:8451-8474.

3. Hung CC, Lin CH, Chang H, Wang CY, Lin SH, Hsu PC, Sun YY, Lin TN, Shie FS, Kao LS, Chou CM,Lee YH* (2016).Astrocytic GAP43 induced by the TLR4/NF-kB/STAT3 axis attenuates astrogliosis-mediated microglial activation and neurotoxicity. *J Neurosci*, 36:2027–2043.

4. Lee YH*, Lin CH, Hsu PC, Sun YY, Huang YJ, Zhuo JH, Wang CY, Gan YL, Hung CC, Kuan CY, Shie FS* (2015). Aryl hydrocarbon receptor mediates both proinflammatory and anti-inflammatory effects in lipopolysaccharide-activated microglia. *GLIA*, 63:1138-1154.

5. Wang CY, Lin HC, Song YP, Hsu YT, Lin SY, Hsu PC, Lin CH, Hung CC, Hsu MC, Kuo YM, Lee YJ, Hsu CY, Lee YH* (2015). PKC-dependent GAP43 phosphorylation regulates gephyrin aggregation at developing GABAergic synapses. *Mol Cell Biol*, 35: 1712-1726.

Mechanism of hyperalgesia priming: role of spinal astrocytes

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Director, Department of Academic Affairs and Instrument Service, Academia Sinica, Taiwan

Ph.D.,University of Illinois, Champaign-Urbana

Abstract

Chronic pain can be initiated by one or more acute stimulations to sensitize neurons into the primed state. In the primed state,the basal nociceptive thresholds of the animal are normal, but, in response to another hyperalgesic stimulus, the animaldevelops enhanced and prolonged hyperalgesia. We have shown that that spinal protein kinase C (PKC)/extracellular signal–regulated kinase (ERK) signal pathway isrequired for neuronal plasticity change, hyperalgesia priming formation, and the development of chronic hyperalgesia usingacid-induced muscle pain model in mice (AIMP). Astrocytes are known as multifunctional cells entirely filling the space between neurons in the central nervous system (CNS), in the CNS astrocytes are active modulators of the brain and spinal cord physiology by carrying out maintaining homeostasis and modulating synaptic transmission. The exact role of astrocytes in hyperalgesia priming remain unknown. I will describe our preliminary results showing that spinal astrocytes are required for the hyperalgesia priming formation. Spinal astrocytes are activated after 1st acid injection in the AIMP model and intrathecal injection of astrocyte-specific toxin L-alpha-aminoadipate (L-AA) could prevent the development of hyperalgesia priming. I will also describe our effort in understanding the signal leading to the astrocyte activation and how this contributes to hyperalgesia priming in AIMP model.

Selected recent publications:

1. Cheng#, Y.F., Chang#, Y.T., Chen, W.H., Shih, H.C., Chen, Y.H., Shyu, B.C. &**Chen, C.C.*** (2017) Cardioprotection induced in mouse model of neuropathic pain via anterior nucleus of paraventricular thalamus. Nat Commun, 8, 826,
2. Chen, W.H., Chang, Y.T., Cheng, S.J. &**Chen, C.C.*** (2018) Spinal PKC/ERK signal pathway mediates hyperalgesia priming. Pain, 159 (5), 907-918.
3. Chang, Y.T., Chen, W.H., Shih, H.C., Shyu, B.C., Min, M.Y. &**Chen, C.C.*** (2019) Anterior nucleus of paraventricular thalamus mediates chronic mechanical hyperalgesia. Pain, 160(5) 1208-1223. (Editor's Choice)
4. Chang, Y.W., Song, Z.H. &**Chen, C.C**.* (2021) FAK regulates cardiomyocyte mitochondrial fission and function through Drp1. FEBS Journal doi: 10.1111/febs.16263.
5. Chen, W.H., Lien, C.C. &**Chen, C.C.*** (2022) Neuronal basis for pain- and anxiety-like behaviors in CeA. Pain 163 (3), e463-e475.

Pericyte and cerebral small vessel diseases

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Abstract

Cerebral small vessel disease (CSVD) is a group of diseasesthat manifests stroke and dementia. It presents lacunes, perivascular spaces, microbleeds, and white matter hyperintensity on brain MRI. Pericytes were associated with the pathogenesis of CSVD because of their unique location in the cerebralcapillary. Pericyte,based in the center of the neurovascular unit (NVU),acts as a totipotent cell. It integrates multiple cell types to maintain blood-brain barrier (BBB) integrity, post-injury regeneration, and angiogenesis. Here I will introduce how cerebral pericytescontribute to the pathogenesis of acquired and hereditary CSVDs through governing BBB and NVU.Type 2 diabetes mellitus (T2DM)-cerebral microangiopathy is a common acquired CSVD. T2DM compromises multiple cellular functions of cerebral pericytes, including angiogenesis, migration, and ischemia-provoked dedifferentiation. These result in the malfunction of BBB and cause excessive vascular leak in very early T2DM, before the CSVD features can be visualized on brain MRI. In addition, maternal T2DM affects the cerebral pericytes of offspring, making their brains more vulnerable to vascular insults and less capable of angiogenesis, even they did not expose to a high-fat diet postnatally. How prenatal hyperglycemia affects pericyte can be shown by the transcriptome analysis of pericytes from offspring's brains. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the commonest hereditary CSVD in Taiwan. The patient's cerebral and retinal small vessels showed a higher leakage and a lower complexity of vascular networks. The variability can be relevant to the various mutant sites.

Selected recent publications:

1. Wu MJ, Liao WA, Lin PY, **Sun YT***. (2022) Muscle Biopsy: A Requirement for Precision Medicine in Adult-Onset Myopathy. *J. Clin. Med.11*(6): 1580

2. Chen YC, Lu BZ, Shu YC, **Sun YT*.** (2022)Spatiotemporal Dynamics of Cerebral Vascular Permeability in Type 2 Diabetes-Related Cerebral Microangiopathy. *Frontiers in Endocrinology (Lausanne).* 12: 805637.

3. Wang HK, Huang CY, Chen YW, **SunYT*.**(2021) Hyperglycemia compromises the ischemia-provoked dedifferentiation of cerebral pericytes through p21–SOX2 signaling in high-fat diet-induced murine model. *Diabetes and Vascular Disease Research,*18(1):1479164121990641.

4. Lin PY, Hung JH, Hsu CK,Chang YT, **Sun YT*** (2021) A novel pathogenic HSPG2 mutation in Schwartz-Jampel Syndrome.*Frontiers in Neurology*12:632336

5. Huang YT, Chen YP, Lin WC, Su WC,**Sun YT***. (2020) Immune Checkpoint Inhibitor-Induced Myasthenia Gravis. *Frontiers in Neurology*, 11:634

Activation of Peripheral TRPM8 Mitigates Ischemic Stroke by Topically Applied Menthol: the roles of astrocytes and microglia

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Abstract

No reports exist as to neuroprotective effects associated with topical activation of transient receptor potential melastatin 8 (TRPM8), a noted cold receptor. In the present study, we identified whether activating peripheral TRPM8 can be an adjuvant therapy for ischemic stroke. Menthol, an agonist of TRPM8, was applied orally or topically to all paws or back of the mouse after middle cerebral artery occlusion (MCAO). We used Trpm8 gene knockout (Trpm8 −/−) mice or TRPM8 antagonist and lidocaine to validate the roles of TRPM8 and peripheral nerve conduction in menthol against ischemic stroke. Application of menthol to paws derma attenuated infarct volumes and ameliorated sensorimotor deficits in stroke mice induced by MCAO. The benefits of topically applied menthol were associated with reductions in oxidative stress, neuroinflammation and infiltration of monocytes and macrophages in ischemic brains. Antagonizing TRPM8 or Trpm8 knockout dulls the neuroprotective effects of topically application of menthol against MCAO. Immunohistochemistry (IHC) analyses revealed significantly higher TRPM8 expression in skin tissue samples obtained from the paws compared with skin from the backs, which was reflected by significantly smaller infarct lesion volumes and better sensorimotor function in mice treated with menthol on the paws compared with the back. Meanwhile, we observed significant therapeutic benefits with the paws dermal application of menthol 16% compared with menthol 8%. Blocking conduction of peripheral nerve in the four paws reversed the neuroprotective effects of topically menthol administrated to paws. On the other hand, oral menthol dosing did not assist with recovery from MCAO in our study. Our results suggested that activation of peripheral TRPM8 expressed in the derma tissue of limbs with sufficient concentration of menthol is beneficial to stroke recovery. Topical application of menthol on hands and foots could be a novel and simple-to-use therapeutic strategy for stroke patients.

Selected recent publications:

1. Huang SS., Su H H, Chien SY, Chung HY, Luo ST., Chu YT., Wang YH., MacDonald I J, Lee HH. and Chen YH* (2022). "Activation of peripheral TRPM8 mitigates ischemic stroke by topically applied menthol." Journal of Neuroinflammation 19(1): 192.

2. Nguyen A, Quach T, Kotha P, Chien SY, MacDonald I, Lane HY, Tu CH, Lin JG*, Chen YH* (2021). Electroacupuncture prevents cocaine-induced conditioned place preference reinstatement and attenuates ΔFosB and GluR2 expression. Sci Rep. 11(1):13694.

3. Chen YH, Lee HJ, Lee MT, Wu YT, Lee YH, Hwang LL, Hung MS, Zimmer A, Mackie K,Chiou LC* (2018) Median nerve stimulation induces analgesia via orexin-initiated endocannabinoid disinhibition in the periaqueductal gray. Proc Natl Acad Sci U S A 115(45):E10720-E10729.

4. Chen YH, Xie SY, Chen CW, Lu DY (2021). Electroacupuncture improves repeated social defeat stress-elicited social avoidance and anxiety-like behaviors by reducing Lipocalin-2 in the hippocampus. Mol Brain, 14(1):150.

5. Huang CC, Ho TJ, Ho HY, Chen PY, Tu CH, Huang YC, Lee YC, Sun MF, Chen YH* (2021). Acupuncture Relieved Chemotherapy-Induced Peripheral Neuropathy in Patients with Breast Cancer: A Pilot Randomized Sham-Controlled Trial. J Clin Med, 10(16):3694.

Deep brain stimulation (DBS) for Psychiatric disorders

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Abstract

Deep brain stimulation (DBS) is an invasive neurosurgical intervention being investigated for several psychiatric disorders, most notably treatment-resistant depression (TRD) and treatment-refractory obsessive-compulsive disorder (OCD), but also Tourette's Syndrome (TS), Alzheimer's dementia (AD), and addiction. The rationale for using DBS in the treatment of psychiatric disorders is based on its effectiveness in several movement disorders and the development of detailed neuroanatomical models for regulating emotion, cognition, and behavior.

In this review, we briefly describe the history of neurosurgery for psychiatric disorders to emphasize that this approach is not new, but has been previously limited by the neuroanatomical models used to select targets and by available neurosurgical techniques. We then describe, with a focus on movement disorders, how the refinement of neuroanatomical models and neurosurgical techniques led to the establishment of ablative neurosurgery and DBS as reasonable approaches for severe, treatment-refractory brain disorders. Next, the available data on the safety and efficacy of DBS for psychiatric disorders are presented and critically evaluation.

Selected recent publications:

1. Lee CC, Yang HC, Lin CJ, Chen CJ, Wu HM, Shiau CY, Guo WY, Hung-Chi Pan D, **Liu KD**, Chung WY, Peng SJ.Intervening Nidal Brain Parenchyma and Risk of Radiation-Induced Changes After Radiosurgery for Brain Arteriovenous Malformation: A Study Using an Unsupervised Machine Learning Algorithm.World Neurosurg. 2019 May;125:e132-e138.

2. Hu YS, Lee CC, Guo WY, Lin CJ, Yang HC, Wu HM, **Liu KD**, Chung WY.Trigeminal Nerve Atrophy Predicts Pain Recurrence After Gamma Knife Stereotactic Radiosurgery for Classical Trigeminal Neuralgia. Neurosurgery. 2019 Apr 1;84(4):927-934.

3. Trifiletti DM, Lee CC, Kano H, Cohen J, Janopaul-Naylor J, Alonso-Basanta M, Lee JYK, Simonova G, Liscak R, Wolf A, Kvint S, Grills IS, Johnson M, **Liu KD**, Lin CJ, Mathieu D, Héroux F, Silva D, Sharma M, Cifarelli CP, Watson CN, Hack JD, Golfinos JG, Kondziolka D, Barnett G, Lunsford LD, Sheehan JP.Stereotactic Radiosurgery for Brainstem Metastases: An International Cooperative Study to Define Response and Toxicity.Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2):280-288.

4. Yang HC, Lin CJ, Luo CB, Lee CC, Wu HM, Guo WY, Chung WY, **Liu KD**.Treatment Outcomes of Cavernous Sinus Dural Arteriovenous Fistulas: Comparison of Radiosurgery and Endovascular Embolisation. Clin Neuroradiol. 2020 Jun;30(2):321-330

5. Lee CC, Sheehan JP, Kano H, Akpinar B, Martinez-Alvarez R, Martinez-Moreno N, Guo WY, Lunsford LD, **Liu KD**.Gamma Knife radiosurgery for hemangioma of the cavernous sinus.J Neurosurg. 2017 May;126(5):1498-1505.

Stereo-EEG the Route to the Field of Neuroscience

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國立陽明交通大學醫學系助理教授, Aug 2018 - present

國際加馬刀研究基金會(IRRF)委員, Jul 2014 - present

亞洲術中神經功能監測學會(AOSIN)委員, Jun 2020 - present

台灣疼痛醫學會監事, May 2021 - present

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Abstract

The effects of epilepsy are felt in multiple aspects of the person's life, including physical and mental health, cognitive function, educational achievements, vocational prospects, and family and peer relations. The successful treatment in patients with refractory epilepsy is the identification and localization of a potential surgical target.

In the past decades, intracranial EEG (iEEG), including subdural grid EEG and stereotactic EEG (sEEG), was used for precise EEG recording. Taipei Veterans General Hospital (TPE-VGH) is the only one center that can perform invasive presurgical evaluation of epilepsy using sEEG. Epilepsy surgery team in TPE-VGH have had the first case of sEEG implantation in 2014. The team also used data from SEEG to explore spreading of seizure activities in the patients with temporal lobe epilepsy, MR negative epilepsy, and epilepsy with migration disorders. The epilepsy surgery team provides good quality of presurgical evaluation and outstanding outcome of epilepsy surgery. In 2015, the team earned the award of "18th National Biotechnology and Medical Care Quality".

More recently, by collaborations with cognitive neuroscientists, several cognitive function including language functions were investigated based on the sEEG recording. Language about lexical tone processing in the brain is a good example. In Mandarin Chinese, there are four tones to distinguish word meaning. By comparing the intracranial EEG recorded under different task demands, the results indicated that EEG recordings from the frontal, temporal, and supramarginal electrodes showed differential responses to different cognitive demands. This is important because we can calculate correlation between electrodes from different brain areas to show how they work in concert to implement a cognitive function. We believe the sEEG is a route can take us on the route to the field of neuroscience.

Selected recent publications:

1. Chou CC, Lee CC*, Lin CF, Peng SY, Hsiao FJ, Yu HY, Chen C, Chen HH, Shih YH: Cingulate gyrus epilepsy: Semiology, invasive EEG, and surgical approaches. Neurosurgery Focus 2020 Apr 1;48(4):E8

2. Lee CC, Hung SC, Chen HH, Chen H, Wu HM, Lin CP, Peng SY: Structural connectivity in children after total corpus callosotomy. Epilepsy Research 2021 (in press)

3. Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, Peng SJ, Liu HL, Yu HY: A Pilot Study of Focused Ultrasound for Drug-Resistant Epilepsy. Epilepsia 2021 Nov 2. [Online ahead of print].

4. Lin FH, Lee HJ, Ahveninen J, Jaaskelainen IP, Yu HY, Lee CC, Chou CC, Kuo WJ: Distributed source modeling of intracranial stereoelectro-encephalographic measurements. Neuroimage 2021 Apr 15;230:117746

Spinal Cord Neuromodulation: from Symptomatic Improvement to Functional Restoration

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Abstract

Spinal cord injury (SCI) usually leads to disconnection between traversing neuronal pathway. The impairment of neural circuitry and its ascending and descending pathway usually leave severe SCI patients with both motor disability and loss of sensory function. In addition to poor quality of life, SCI patients not only have disabling respiratory function, urinary retention, impaired sexual function, autonomic dysregulation but also medical refractory neuropathic pain in the long term. Some translational studies demonstrated that spinal networks possess a dynamic state of synaptic connection and excitability that can be facilitated by epidural spinal cord stimulation. In addition, preliminary human studies also confirmed that spinal cord stimulation enables stepping or standing in individuals with paraplegia as well. During the talk, I will share the plausible interventional mechanisms underlying the effects of epidural spinal cord stimulation in human and animal studies. Following the success of translational research, chronic paralyzed patients due to SCI, defined as motor complete status, regained their voluntary control and function of overground walking and even stepping for some. These progresses lead us into a new hope to help SCI patients to walk and regain their pride and independent life again.

Selected recent publications:

1. Li-Chuan Huang, Li-Guo Chen, Ping-An Wu, Cheng-Yoong Pang, Shinn-Zong Lin, **Sheng-Tzung Tsai**, Shin-Yuan Chen (2021, Oct). Effect of deep brain stimulation on brain network and white matter integrity in Parkinson's disease. CNS neuroscience & therapeutics.

2. Chen, Y. C., S. Y. Chen, T. Y. Chen, J. I. Pan, and **S. T. Tsai.** (2020, Nov). Desflurane and sevoflurane differentially affect activity of the subthalamic nucleus in Parkinson's disease. Br J Anaesth.

3. **Sheng-Tzung Tsai**, Guo-Fang Tseng, Chang-Chih Kuo, Tsung-Ying Chen, Shin- Yuan Chen (2020, Feb). Sevoflurane and Parkinson's Disease: Subthalamic Nucleus Neuronal Activity and Clinical Outcome of Deep Brain Stimulation . Anesthesiology.

4. Chang, T. W., P. H. Tseng, Y. C. Wang, G. F. Tseng, T. L. Chiu, S. Z. Lin, and **S. T. Tsai**. (2020, Apr). Dopaminergic Degeneration and Small Vessel Disease in Patients with Normal Pressure Hydrocephalus Who Underwent Shunt Surgery. J Clin Med.

5. **Sheng-Tzung Tsai**, Shin-Yuan Chen, Shinn-Zong Lin, Guo-Fang Tseng (2020, Mar). Rostral Intralaminar Thalamic Deep Brain Stimulation Ameliorates Memory Deficits and Dendritic Regression in β-Amyloid-Infused Rats. Brain Structure and Function, 225 (2), 751-761. (SCI, 1/21 Anatomy & Morphology).

Non-Invasive Brain Stimulation for Treating Refractory Neuropsychiatric Disorders

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Abstract

A great number of patients with major depressive disorder (MDD) do not improve appreciably after the first-line SSRI antidepressant drug and even fail to respond to several adequate antidepressant trials. Such patients with high medication resistance are defined as treatment-resistant depression (TRD). TRD included a wide range of MDD patients from 1 to several antidepressant failures and is associated with much worse clinical outcomes than non-TRD MDD patients. MDD is considered as a brain disorder. Prefrontal cortex (PFC) and related brain circuits are implicated in TRD. PFC-limbic dysregulation plays an important role in the pathophysiology of MDD and such dysregulation is especially prominent in patients with TRD.

In today's talk, I would first introduce different forms of non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation (rTMS), and theta burst stimulation (TBS) in the treatment of TRD. We also developed a SSRI-resistant animal model to investigate mechanisms of iTBS, finding iTBS involves a normalization of long-term potentiation and depression (LTP and LTD) in the PFC. In addition, NIBS, including rTMS, TBS, transcranial electrical stimulation (tES), and transcranial direct/alternative current stimulation (tDCS/tACS), have been widely studied for treating several refractory illnesses such as chronic pain and tinnitus. In today's talk, I will update recent research results of using NIBS for treating migraine, fibromyalgia, and tinnitus. You would be able to understand evidence-based parameters of NIBS for treating these refractory neuropsychiatric diseases in such examples after the presentation.

Selected recent publications:

1. **Cheng-Ta Li*** et al. Efficacy of Prefrontal Theta-Burst Stimulation in Refractory Depression: A Randomized Sham-Controlled Study. ***Brain,*** 2015 Jul;137(Pt 7):2088-98. (**SCI, IF=15.255**)

2. **Cheng-Ta Li*** et al. Effects of prefrontal theta-burst stimulation on brain function in treatment-resistant depression: A randomized sham-controlled neuroimaging study. ***Brain Stimulation***. 2018;11(5):1054-1062. (**SCI, IF: 9.184**)

3. **Cheng-Ta Li*** et al. Antidepressant Efficacy of Prolonged Intermittent Theta Burst Stimulation Monotherapy for Recurrent Depression and Comparison of Methods for Coil Positioning: A Randomized, Double-Blind, Sham-controlled Study. ***Biological Psychiatry***, Mar. 2020 **(SCI, IF=12.810)**

4. **Cheng-Ta Li***, et al. Global Cognitive Dysfunction and Beta-Amyloid Neuropathology in Late-Life and Treatment-Resistant Depression. ***Psychological Medicine***. 2021 Oct **(SCI, IF=10.592)**

5. Ping-Tao Tseng,..., **Cheng-Ta Li***. Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia: A Systematic Review and Network Meta-analysis. ***JAMA Psychiatry***. 2022 **(SCI, IF=25.911)**

Games of Audio Watermarking: 2002 vs 2022

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Abstract

Watermarking refers to the embedding of hard-to-perceive patterns for communication purposes. When adding a watermark to an audio signal, psychoacoustic principles need to be considered such that perceptible distortions are minimized. These principles include (1) to hide the watermark below the psychoacoustic masking threshold, and (2) to control the frequency or phase shift of tonal components below the just noticeable difference. In this talk, I will review two applications of audio watermarking – namely, copyright protection and audio CAPTCHA (Completely Automated Public Test to Tell Computers and Humans Apart). It turns out that both applications can be formulated as a game between two opponents. In copyright protection, the watermark embedder aims to hide information for the proof of copyright ownership; the attacker's job is to remove the watermark without degrading the sound quality. In the scenario of audio CAPTCHA, I will demonstrate a recent design that utilizes the watermark to fool the neural networks into misjudgment and defend the test from being solved automatically by a "robot". Sound examples will be given throughout the talk to demonstrate the ideas.

Selected recent publications:

1. Chih-Hsiang Huang, Po-Hao Wu, Yi-Wen Liu, Shan-Hung Wu (2021). "Attacking and defending behind a psychoacoustics-based CAPTCHA," *Proc. IEEE ICASSP*, Toronto, June 2021, pp. 895-899.

2. Fu-Rong Yang, Yin-Ping Cho, Yi-Hsuan Yang, Da-Yi Wu, Shan-Hung Wu, and Yi-Wen Liu (2021). "Mandarin singing voice synthesis with a phonology-based duration model," *Proc.APSIPA Annual Summit and Conference*, Tokyo, Japan, pp. 1975-1981.

3. Wei-Chen Hsiao, Yung-Ching Chen, and Yi-Wen Liu (2021). "Measuring distortion-product otoacoustic emission with a single loudspeaker in the ear: Stimulus design and signal processing techniques," *Frontiers in Digital Health* 3:724539.

4. Tzu-Chi Liu, Yi-Wen Liu, and Hau-Tieng Wu (2021). "Denoising click-evoked otoacoustic emission signals by optimal shrinkage," *J. Acoust. Soc. Am.* 149(4), 2659-2670.

5. Yi-Wen Liu, Sheng-LunKao, Hau-Tieng Wu, Tzu-Chi Liu, Te-Yung Fang, and Pa-Chun Wang (2020). "Transient-evoked otoacoustic emission signals predicting outcomes of acute sensorineural hearing loss in patients with Ménière's disease," *Acta Oto-Laryngologica*140(3), 230-235.

Deep-learning-based Speech Enhancement with Its Application to Assistive Oral Communications Devices

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Abstract

Speech enhancement (SE) serves as a key component in most speech-related applications. The goal of SE is to enhance the speech signals by reducing distortions caused by additive and convoluted noises in order to achieve improved human-human and human-machine communication efficacy. In this talk, we will review the system architecture and fundamental theories of deep learning-based SE approaches. Next, we will present more recent advances, including end-to-end and goal-driven based SE systems as well as the SE systems with improved architectures and feature extraction procedures. The reinforcement learning and generative adversarial network (GAN)-based SE methods will also be presented. Finally, we will discuss some applications based on the deep learning SE systems, including impaired speech transformation and noise reduction for assistive hearing and speaking devices.

Selected recent publications:

1. C. Yu, R. E. Zezario, S.-S. Wang, J. Sherman, Y.-Y. Hsieh, X. Lu, H.-M. Wang, and **Y. Tsao***, "Speech Enhancement based on Denoising Autoencoder with Multi-branched Encoders," IEEE/ACM Transactions on Audio, Speech and Language Processing, volume 28, pages 2756-2769, October 2020. (IF=3.919, Ranking=4/31, Citation=16)

2. S.-W. Fu, T.-W. Wang, **Y. Tsao***, X. Lu, and H. Kawai "End-to-End Waveform Utterance Enhancement for Direct Evaluation Metrics Optimization by Fully Convolutional Neural Networks," IEEE/ACM Transactions on Audio, Speech and Language Processing, vol. 26(9), pp. 1570-1584, April 2018. (IF=3.919, Ranking=4/31, Citation=206)

3. S.-W. Fu, C.-F. Liao, **Y. Tsao**, and S.-D. Lin, "MetricGAN: Generative Adversarial Networks based Black-box Metric Scores Optimization for Speech Enhancement," in Proc. ICML 2019, Long Oral Presentation with ICML Travel Grant. (Top conference, citation=112)

4. C.-L. Liu, S.-W. Fu, Y.-J. Li, J.-W. Huang, H.-M. Wang, and **Y. Tsao***, "Multichannel Speech Enhancement by Raw Waveform-mapping using Fully Convolutional Networks," IEEE Transactions on Audio, Speech and Language Processing, vol. 28, pp. 1888-1900, February 2020. (IF=3.919, Ranking=4/31, Citation=28)

5. S.-W. Fu, P.-C. Li, Y.-H. Lai, C.-C. Yang, L.-C. Hsieh, and **Y. Tsao***, "Joint Dictionary Learning-based Non-Negative Matrix Factorization for Voice Conversion to Improve Speech Intelligibility After Oral Surgery," IEEE Transactions on Biomedical Engineering, vol. 64 (11), pp. 2584 - 2594, November 2017. (IF=4.538, Ranking=24/89, Citation=40)

Mapping Spectral and Temporal Information to Complex Pitch Perception

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Abstract

Complex pitch perception is critical for speech, music, and auditory scene analysis. During complex pitch perception, the auditory system filters a sound in a prism-like manner into multiple components at frequency-ordered places along the cochlea. This frequency-ordered organization, tonotopy, plays a critical role in the formation of complex pitch percepts. Altered tonotopy, resulting either from sensorineural hearing loss, psychologicaldisordersor by artificially transposing sounds to arbitrary tonotopic locations on the cochlear, can seriously impact complex pitch perception. This suggests that an accurate mapping between the spectral and temporal information of a soundis crucialinthe computation of complex pitch percepts. In this talk, I will share some of our findings on mapping the contributionfrom spectral and temporal information to complex pitch perception using acoustic signals designed to approximate specific patterns of spectral-temporal cochlear representations.Results from human listeners on aninterrelated series of pitch-relevant tasks will be discussed.I will also describe our efforts in applying a novel signal analysis method to extractparticular features of sound waveforms that may play a deterministic role in regulating the perceived pitch.Implications regarding the relationship between spectral and temporal information in complex pitch perception as well as practical applications for improving the coding of pitch for those with hearing-related disorders or prosthetic hearing devices will also be discussed.

Selected recent publications:

1. **Hsieh, I.***& Yeh, W.T. (2021). The interaction between timescale and pitch contour at pre-attentive processing of frequency-modulated sweeps. *Frontiers in Psychology: Auditory Cognitive Neuroscience*, doi:10.3389/fpsyg.2021.637289.

2. Farda, N.A., Lai, J.Y., Wang, J.C. Lee, P.Y., Liu, J.W. & **Hsieh, I.***(2021). Sanders classification of calcaneal fractures in CT images with deep learning and differential data augmentation techniques. *Injury*, 52(3), 616-624. doi.org/10.1016/j.injury.2020.09.010.

3. Kung, S.J., Wu, D.H., Hsu, C.H. &**Hsieh, I.*** (2020). A minimum temporal window for direction detection of frequency-modulated sweeps: A magnetoencephalography study. *Frontiers in Psychology: Auditory Cognitive Neuroscience*, 11:389.doi:10.3389/fpsyg.2020.00389.

4. **Hsieh, I.*** & Liu, J. (2019). A novel signal processing approach to auditory phantom perception. *Psychonomic Bulletin & Review*, 26(1), 250-260.

5. **Hsieh, I.***, Liu, J., & Liang, Z. (2018). Spectrotemporal window of binaural integration in

6. auditory object formation. *Hearing Research*, 370, 155-167.

Auditory Processing, Phonology and Reading Difficulties in Chinese

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Joint Appointment Research Fellow, Research Center for Information Technology Innovation, Academia Sinica

Ph.D.in Philosophy, University of Cambridge, UK

Abstract

Our work has suggested that there were significant links between Chinese children's perception of speech prosody and their reading abilities. From the behavioral data, our study found that poor auditory frequency processing may associate with Chinese developmental dyslexia with phonological deficits. In support of the phonological deficit hypothesis, what underlies phonological deficit is likely to be auditory-basis. Particularly, Chinese-speaking children with reading difficulties were significantly related to frequency-modulated sweep identification. Lexical tone awareness was significantly associated with basic auditory frequency processing tasks. The biological finding also indicated that auditory sensory processing was affected by both the duration and the direction of a frequency sweep. Therefore, this sensory deficit might be associated with difficulties discriminating frequency contour in Chinese. Finally, we suggest to provide an assistive listening technology to help these children with learning difficulties.

Selected recent publications:

1. Wang, N. Y. H., **Wang, H. L. S.**, Wang, T. W., Fu, S. W., Lu, X., Wang, H. M., & Tsao, Y. (2020). Improving the intelligibility of speech for simulated electric and acoustic stimulation using fully convolutional neural networks. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. https://doi.org/10.1109/TNSRE.2020.3042655

2. Wang, N. Y. H., Chiang, C. H., **Wang, H. L. S.***, & Tsao, Y. (2020). Atypical frequency sweep processing in Chinese children with reading difficulties: evidence from magnetoencephalography. *Frontiers in Psychology, 11,* 1649. https://doi.org/10.3389/fpsyg.2020.01649

3. Chiang, C. H., Hämäläinen, J., Xu, W., &**Wang, H. L.***(2020). Neural responses to musical rhythm in Chinese children with reading difficulties. *Frontiers in Psychology, 11,* 1013. https://doi.org/10.3389/fpsyg.2020.01013

4. **Wang, H. L. S.***, Wang, N. Y. H., Chen, I. C., & Tsao, Y. (2019). Auditory identification of frequency-modulated sweeps and reading difficulties in Chinese. *Research in Developmental Disabilities, 86,* 53-61.

5. **Wang, H. L. S.***, Yeh, F. C., & Wang, N. Y. H. (2019). Specifying the diffusion MRI connectome in Chinese-speaking children with developmental dyslexia and auditory processing deficits. *Pediatrics & Neonatology, 60*(3), 297-304.

Circadian clock and the mood rhythm

Jihwan Myung

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Taipei Medical University

Ph.D. Kyoto University

Abstract

Circadian clocks are oscillatory transcriptional activities that underlie daily rhythms of physiology of the brain and the rest of the body. Although sleep has been traditionally considered the hallmark of the daily change in the brain state, and also a major modulator of the brain physiology that works independently of the circadian rhythm, there remains a possibility that the general state of the brain slowly shifts along with its circadian clock. We have recently discovered that the brain hosts a number of autonomous circadian clocks that keep their own respective time (Myung *et al*, 2018; Chrobok *et al*, 2020). These clocks are not isolated pacemakers and communicate with each other to encode other information of the external day-night cycle such as the day-length (Myung *et al*, 2015) or the period of the cycle (Azzi *et al*, 2017). The extensive communications among clocks appear to extend to the kidney (Myung *et al*, 2019). Under this background, we measured the changes of the mood state in mice with a high temporal resolution across the circadian timespan. By using different experimental paradigms for quantifying affective states, we determine the existence of the circadian rhythm in mood states that are dependent upon internal parameters of age and sex as well as external parameters of temporal light structure.

Selected recent publications:

1. Myung J, Schmal C, Hong S, Tsukizawa Y, Rose P, Zhang Y et al. (2018). The choroid plexus is animportant circadian clock component, *Nature Communications*. 9: 1-13.

2. Chrobok L, Northeast RC, Myung J, Cunningham PS, Petit C, Piggins HD (2020). Timekeeping in the hindbrain: a multi-oscillatory circadian centre in the mouse dorsal vagal complex. *Communications Biology*. 3: 1-12.

3. Myung J, Hong S, DeWoskin D, De Schutter E, Forger DB, Takumi T (2015). GABA-mediated repulsive coupling between circadian clock neurons in the SCN encodes seasonal time, *Proceedings of the National Academy of Sciences*. 112: E3920-E3929.

4. Azzi A, Evans JA, Leise T, Myung J, Takumi T, Davidson AJ, Brown SA (2017). Network dynamics mediate circadian clock plasticity. *Neuron*. 93: 441-450.

5. Myung J, Wu MY, Lee CY, Rahim AR, Truong VH, Wu D, Piggins HD, et al (2019). The kidney clock contributes to timekeeping by the master circadian clock. *International Journal of Molecular Sciences*. 20: 2765.

A working model of the pathophysiology of bipolar disorder

Paola Magioncalda

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M.D., Ph.D., University of Genoa (Italy)

Abstract

Bipolar disorder (BD) is a severe psychiatric disorder that is characterized by the occurrence of active phases of illness - mania and depression, showing opposite clinical symptomatology across the various psychopathological dimensions of psychomotricity, affectivity, and thought - alternated to asymptomatic periods of euthymia. We conducted a series of studies on the neurobiology of BD, by using various magnetic resonance imaging (MRI) modalities, including functional MRI and diffusion MRI, along with laboratory analyses. In the first part of the presentation, we will show a summary of our main results regarding white matter alterations and immunological changes, as well as their relationship, in BD. In the second part of the presentation, we will show a summary of our main results regarding alterations in the functional configuration of large-scale networks at the cortical level and changes in the subcortical-cortical coupling, as well as their potential relationship with neurotransmitter signaling, in BD. Finally, we will integrate all these data on immune dysregulation, structural brain damage, functional brain alterations, and psychopathology in a unified model of the pathophysiology of BD.

Selected recent publications:

1. Magioncalda P and Martino M (2021) A unified model of the pathophysiology of bipolar disorder. Molecular Psychiatry [Online ahead of print]

2. Martino M and Magioncalda P (2021) Tracing the psychopathology of bipolar disorder to the functional architecture of intrinsic brain activity and its neurotransmitter modulation: a threedimensional model. Molecular Psychiatry [Online ahead of print]

3. Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M, Northoff G (2020) Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. Mol Psychiatry 25(1):82-93.

4. Magioncalda P, Martino M, Tardito S, Sterlini B, Conio B, Marozzi V, Adavastro G, Capobianco L, Russo D, Parodi A, Kalli F, Nasi G, Altosole T, Piaggio N, Northoff G, Fenoglio D, Inglese M, Filaci G, Amore M (2018) White matter microstructure alterations correlate with terminally differentiated CD8+ effector T cell depletion in the peripheral blood in mania: Combined DTI and immunological investigation in the different phases of bipolar disorder. Brain Behav Immun 73:192-204.

5. Martino M, Magioncalda P, Huang Z, Conio B, Piaggio N, Duncan NW, Rocchi G, Escelsior A, Marozzi V, Wolff A, Inglese M, Amore M, Northoff G (2016) Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. Proc Natl Acad Sci U S A 113(17):4824-9

A working model of the pathophysiology of bipolar disorder

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M.D., Ph.D., University of Genoa (Italy)

Abstract

Bipolar disorder (BD) is a severe psychiatric disorder that is characterized by the occurrence of active phases of illness - mania and depression, showing opposite clinical symptomatology across the various psychopathological dimensions of psychomotricity, affectivity, and thought - alternated to asymptomatic periods of euthymia. We conducted a series of studies on the neurobiology of BD, by using various magnetic resonance imaging (MRI) modalities, including functional MRI and diffusion MRI, along with laboratory analyses. In the first part of the presentation, we will show a summary of our main results regarding white matter alterations and immunological changes, as well as their relationship, in BD. In the second part of the presentation, we will show a summary of our main results regarding alterations in the functional configuration of large-scale networks at the cortical level and changes in the subcortical-cortical coupling, as well as their potential relationship with neurotransmitter signaling, in BD. Finally, we will integrate all these data on immune dysregulation, structural brain damage, functional brain alterations, and psychopathology in a unified model of the pathophysiology of BD.

Selected recent publications:

1. Magioncalda P and Martino M (2021) A unified model of the pathophysiology of bipolar disorder. Molecular Psychiatry [Online ahead of print]
2. Martino M and Magioncalda P (2021) Tracing the psychopathology of bipolar disorder to the functional architecture of intrinsic brain activity and its neurotransmitter modulation: a threedimensional model. Molecular Psychiatry [Online ahead of print]
3. Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M, Northoff G (2020) Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. Molecular Psychiatry 25(1):82-93.
4. Magioncalda P, Martino M, Tardito S, Sterlini B, Conio B, Marozzi V, Adavastro G, Capobianco L, Russo D, Parodi A, Kalli F, Nasi G, Altosole T, Piaggio N, Northoff G, Fenoglio D, Inglese M, Filaci G, Amore M (2018) White matter microstructure alterations correlate with terminally differentiated CD8+ effector T cell depletion in the peripheral blood in mania: Combined DTI and immunological investigation in the different phases of bipolar disorder. Brain Behav Immun 73:192-204.
5. Martino M, Magioncalda P, Huang Z, Conio B, Piaggio N, Duncan NW, Rocchi G, Escelsior A, Marozzi V, Wolff A, Inglese M, Amore M, Northoff G (2016) Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. Proc Natl Acad Sci U S A 113(17):4824-9.

Depressive rumination is correlated with the self-related process induced brain activity

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Ph.D. National Yang Ming University

Abstract

Rumination, the inclination to dwell on negative self-related thoughts, is a typical symptom of depression. Although rumination has been associated with research-related depressive disorders, the underlying neural mechanism of rumination has not been fully elucidated. Typically, research has focused on the influence of negative emotions rather than the self-related processes on brain activity. According to one working hypothesis, the self-related processes take place within the default-mode network. There have been some fMRI studies which support this hypothesis by showing a strong linkage between the self-related process and several brain regions along the midline of the cortex, including the medial prefrontal cortex, anterior and posterior cingulate cortex. Additionally, the cortical midline structures modulated the activity of other brain regions via slow frequency oscillations. I will share the research findings of our laboratories regarding the relationship between self-related processes and brain activity regardless of negative emotion, and how this relationship differs between people with healthy and people with depression. Additionally, high levels of rumination were associated with hyper-activated midline structures in the cortex, which in turn may reflect difficulties in switching to non-self-related thinking. Similarly, my lab examined this possibility by developing a special task to address this question. Further, I will discuss our findings concerning the switching between self-related and non-self-related processes when individuals have different rumination levels.

Selected recent publications:

Hsu, T.Y.†, Liu, T.L., Cheng, P.Z., Lee, H.C., Lane. T. J.*, Duncan, N.W.* † (2021). Depressive rumination is correlated with the difference between self-oriented decision-making. *Journal of Psychiatry and Neuroscience.* († equal contribution).

Duncan, N.W.*, **Hsu, T.Y.***, Cheng, P.Z., Wang, H.Y., Lee, H.C., and Lane, T.J. (2020). Intrinsic activity temporal structure reactivity to behavioural state change is correlated with depressive symptoms. *European Journal of Neuroscience.* (* First and second authors are equal contribution).

Hsu, T.Y., Lee, H.C., Lane, T.J., Missal, M. (2019). Temporal preparation, impulsivity and short-term memory in depression. *Frontiers in Behavioral Neuroscience.*

Truong, V., Cheng, P. Z., Lee, H.C., Lane, T.J, **Hsu, T.Y.**, Duncan, N.W. (2021). Occipital gamma-aminobutyric acid and glutamate-glutamine alterations in major depressive disorder: An MRS study and meta-analysis. *Psychiatry Research: Neuroimaging.*

Chen, P.H., Ku, H.L., Wang, J.K., Kang, J.H. *, **Hsu, T.Y.** * (2022). EEG microstates are correlated with global functioning in Schizophrenia but not bipolar disorder. *Clinical EEG & Neuroscience.*

Reward valuation in chronic migraine patients with medication overuse

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Abstract

Headaches are often treated with acute abortive medication such as analgesics. However, excessive intake of acute abortive medication may lead to worsening of pre-existing headaches causing the transformation, for example, from episodic to chronic migraine. This type of headache worsening is termed medication-overuse headache (MOH). Despite the addictive-like behaviors in MOH, it is unknown whether MOH is associated with general alterations in reward behavior and brain processing, as is observed in substance use disorders. In this talk, I will present findings from a recent study in which the intertemporal choice task in conjunction with functional magnetic resonance imaging was used to assess temporal discounting and impulsive decision making behavior and the associated brain mechanisms in MOH patients. Furthermore, using models from behavioral economics, brain regions responsible for the encoding of subjective value were evaluated. Based on findings from this analysis, resting-state functional connectivity changes between the affected regions were further explored and dysregulated large-scale brain networks were identified.

Selected recent publications:

1. **Niddam DM**, Wang SJ, Tsai SY*. Pain sensitivity and the primary sensorimotor cortices: a multimodal neuroimaging study. PAIN 2021 Mar 1;162(3):846-855
2. **Niddam DM**, Lai KL, Tsai SY, Lin YR, Chen WT, Fuh JL, Wang SJ. Brain metabolites in chronic migraine patients with medication overuse headache. Cephalalgia 2020 Jul;40(8):851-862
3. **Niddam DM**, Lai KL, Tsai SY, Lin YR, Chen WT, Fuh JL, Wang SJ*. Neurochemical changes in the medial wall of the brain in chronic migraine. Brain 2018 Feb 1;141(2):377-390.
4. **Niddam DM**, Lee SH, Su YT, Chan RC. Brain structural changes in patients with chronic myofascial pain. Eur J Pain 2017 Jan;21(1):148-158.
5. **Niddam DM**, Lai KL, Fuh JL, Chuang CY, Chen WT, Wang SJ. Reduced functional connectivity between salience and visual networks in migraine with aura. Cephalalgia 2016 Jan;36(1):53-66.

Zebrafish Model for Research in Neuroscience

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中央研究院 分子生物所

Ph.D.Univ. Pennsylvania, USA

Abstract

Zebrafish has become a popular research model organism because it offers many excellent research tools. It is amenable to genetic tools such as generation of mutant fish and transgenic fish with fluorescence at desired places. The transparent embryos plus the advanced imaging tools enable detailed cell or gene tracing over time and space. Furthermore, its large clutch size provides easy access of materials for studies. Above all, it is a vertebrate with all features of vertebrates, so that many of the rules in zebrafish also apply to human beings.

Using zebrafish as a model, my laboratory has investigated the molecular mechanism of a disease, spinocerebellar ataxia type 11 (SCA11), characterized by atrophy of granule and Purkinje neurons in the cerebellum. This disease is caused by the mutation of Tau tubulin kinase 2 (TTBK2). We have generated fish with the mutation of ttbk2 genes. We then found that ttbk2 defective fish has problems of ciliopathy, similar to that of human patients. They also have problems in cerebellar development, characterized by the loss of both cerebellar granule neurons and Purkinje cells. These fish thus provide a good tool to understand the molecular basis of the disease.

Selected recent publications:

1. Gibert Y, Chung B-c, "Fish as a model for endocrine systems" ***Mol Cell Endocrinol***531, 11316 (2021).
2. Hsu C-w, Chung B-c, "Evolution, Expression, and Function of Gonadal Somatic Cell-Derived Factor" ***Frontiers Cell Dev Biol*** 9, article 684352, doi: 10.3389/fcell.2021.684352 (2021).
3. Tsai SF; Hung HC; Shih MMC; Chang FC; Chung B-c; Wang CY; Lin YL; Kuo YM, "High fat diet-induced increases in glucocorticoids contribute to the development of non-alcoholic fatty liver disease in mice" ***FASEB J***, doi:10.1096/fj.202101570R (2021).
4. Shih M-C, Huang C-C, Chu H-P, Hsu N-C, and Chung B-c, "Embryonic steroids control developmental programming of energy balance" ***Endocrinology***, 162(12):bqab196. doi: 10.1210/endocr/bqab196. PMID: 34599818. (2021).
5. PanYJ,TongSK,ChungB-c,"Zebrafish establish female germ cell identity by advancing cell proliferation and meiosis"***Frontiers Cell Dev Biol***(2022).

Induced pluripotent stem cells in neurodegenerative disease modelling

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Ph.D.King's College London

Abstract

With their unique features, including self-renewal and pluripotency, pluripotent stem cells are clearly extremely important as they provide not only opportunity to understand the mechanisms underlying cellular differentiation during early development but also hope for the treatment of a wide range of human conditions that can be attributed to the loss or malfunction of specific cell types. A number of devastating diseases, such as neurodegenerative diseases, affect specific neuronal phenotypes. Little is known concerning the molecular pathology underlying these conditions, partly because it has been impossible to access significant quantities of the disease-affected cells or tissues. With recent advances in induced pluripotent stem cell (iPSC) technology, we can now produce large scale of specific neuronal phenotypes and organoids with control and disease genotypes. We use this newly developed in vitro disease modelling system for both mechanistic studies and for the discovery of novel medical intervention. In my presentation, I will demonstrate how we use combined genome editing and organoid technologies to create isogenic human disease models for drug discovery and gene therapy.

Selected recent publications:

1. Wu YY and **Kuo HC*** (2020) Functional roles and networks of non-coding RNAs in the pathogenesis of neurodegenerative diseases, *Journal of Biomedical Science, 27(1):49*

2. Huang HP, Chiang W, Chuang CY, Stone L, Kang CK, Hwu WL, **Kuo HC***. (2019) Using human Pompe Disease induced pluripotent stem cells-derived neural cells for identifying chemicals with therapeutic potential. Molecular Human Genetics, 28(23):3880-3894

3. Chuang CY, Yang CC, Soong BW, Yu CY, Chen SH, Huang HP**, Kuo HC***. (2019)Modeling spinocerebellar ataxias 2 and 3 with iPSCs reveals a role for glutamate in disease pathology. *Scientific Reports, 9(1)1166*

4. Yu CY, Li TC, Wu YY, Yeh CH, Chiang W, Chuang CY, **Kuo HC*.** (2017)The Circular RNA circBIRC6 participates in the molecular circuitry controlling human pluripotency. *Nature Communications.8(1):1149.*

5. Hou PS, Chuang CY, Yeh CH, Chiang W, Liu HJ, Lin TN, **Kuo HC***. (2017) Direct conversion of human fibroblasts into neural progenitors via the use of transcription factors highly enriched in human ESC-derived neural progenitors, *Stem Cell Reports. 8(1):54-68.*

Modeling neurodegeneration using a brain-specific mouse model of myotonic dystrophy

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Associate Research Fellow, Institute of Biomedical Sciences, Academia Sinica

Ph.D., National Yang-Ming University

Abstract

Neurological diseases share many features during disease progression, such as brain atrophy and decline in cognitive function, which suggests a common pathway for developing degenerative features. Cognitive deficits including neurodegeneration are commonly seen in individuals with myotonic dystrophy type 1 (DM1). DM1 is caused by an expansion of CTG repeats in the 3' untranslated region (UTR) of the Dystrophia Myotonica Protein Kinase (*DMPK*) gene. Nuclear accumulation of *DMPK* mRNA containing expanded CUG repeats disrupts the activities of RNA binding protein such as Muscleblind like (MBNL) protein family. The expanded CUG RNA binds and sequesters MBNL proteins resulting in loss of MBNL functions has been implicated in DM1 neural pathogenesis. We generated a brain-specific DM1 mouse model, EpA960/CaMKII-Cre, for expressing expanded CUG RNA in the postnatal brain. We showed that in EpA960/CaMKII-Cre brain, reduced expression of cytoplasmic MBNL1 associated neurotransmission dysfunction occurred before neurodegeneration-reduced MBNL2 expression and aberrant alternative splicing. Investigation of the causal mechanism of neurodegeneration-reduced MBNL2 expression revealed that neurodegeneration conditions, such as glutamate-induced excitotoxicity and dysregulated calcium homeostasis, induced translocation of the cysteine protease calpain-2 into the nucleus, resulting in MBNL2 degradation and reversal of MBNL2-regulated RNA processing to an embryonic pattern. Knockdown of calpain-2 expression or inhibition of calpain-2 nuclear translocation prevented neurodegeneration-reduced MBNL2 expression and dysregulated RNA processing. Increased calpain-2 nuclear translocation associated with reduced MBNL2 expression and aberrant RNA processing also occurred in models for Alzheimer's disease including APP/PS1 and THY-Tau22. Thus, our results suggest that calpain-2–mediated MBNL2 degradation accompanied by re-induction of a developmental RNA processing program may be a converging pathway to neurodegeneration.

Selected recent publications:

1. Wang PY, Lin YM, Wang LH, Kuo TY, Cheng SJ, **Wang GS**. (2017) Reduced cytoplasmic MBNL1 is an early event in a brain-specific mouse model of myotonic dystrophy. *Hum Mol Genet.* 26(12):2247-2257.

2. Wang PY, Chang KT, Lin YM, Kuo TY, **Wang GS**. (2018) Ubiquitination of MBNL1 is required for its cytoplasmic localization and function in promotingneurite outgrowth. *Cell Reports*. 22:2294–2306.

3. Wang LH, Lin CY, Lin YM, Buée L, Sergeant N, Blum D, Chern Y, **Wang GS**. (2022) Calpain-2 mediates MBNL2 degradation and a developmental RNA processing program in neurodegeneration. *J. Neurosci*. (In revision).

Diagnosing nature of disease-associated gene variants in fruit flies

Chi-Kuang Yao(姚季光)
Associate research fellow

Institute of Biological Chemistry, Academia Sinica, Taiwan; Neuroscience Program at Academia Sinica (NPAS), Academia Sinica, Taiwan; Institute of Biosciences, National Taiwan University, Taiwan

Ph.D. National Yang-Ming University, Taiwan

Abstract

Undiagnosed rare diseases are afflicting 3-400 millionof people in the world, and approximately 80% of the cases are estimated as Mentelian disorders. Therefore, there is an urgent need to unravel underpinning gene mutations prior to therapeutic strategy development.*Drosophila melanogaster* (fruit fly), one of popular model organisms, has been actively used to gainrapid and precise *in vivo* diagnosis for establishing the causal relationship between candidate gene mutations and disease phenotypes.The synaptic vesicle (SV) filled with chemical neurotransmitters is the fundamental unit of neuronal communication. The SV releases neurotransmitters when exocytosed. Subsequently, SV endocytosis regenerates new SVs to sustainrepetitive neurotransmitter release duringbrain information processing. Mutations in the genes involved in the SV cycleare emerged to cause a number ofneurological disorders. Our previous studies identified a Ca^{2+} channel named Flower as a key player regulating SV endocytosis in both *Drosophila* and rodent primary cultured neurons. *CACFD1* is the sole human homolog of fly *flower*, yet its mutations have not been associated with any diseases. In collaboration with Undiagnosed Disease Network (UDN),we found a number ofrecessive *CACFD1*variantsin unstudied patients. In this meeting, I will sharehow we used the fly model to decipherthe pathogenic impacts of these uncharacterized *CACFD1*mutations on synaptic transmission.

Selected recent publications:

1. Kim J, Kim S, Nahm M, Li TN, Lin HC, Kim YD, Lee J, Yao CK*, Lee S* (2021) "ALS2 regulates endosomal trafficking, postsynaptic development, and neuronal survival."J Cell Biol.
2. Li TN, Chen YJ, Wang YT, Lin HC, Lu TY, Yao CK* (2020) "A positive feedback loop between Flower and PI(4,5)P2 at periactive zones controls bulk endocytosis in Drosophila." Elife.
3. Lin SS, Hsieh TL, Liou GG, Li TN, Lin HC, Chang CW, Wu HY, Yao CK, Liu YW* (2020) "Dynamin-2 Regulates Postsynaptic Cytoskeleton Organization and Neuromuscular Junction Development." Cell Reports.
4. Peng JJ, Lin SH, Liu YT, Lin HC, Li TN, Yao CK* (2019)"A circuit-dependent ROS feedback loop mediates glutamate excitotoxicity to sculpt the Drosophila motor system." Elife.
5. Yao CK*, Liu YT, Lee IC, Wang YT, Wu PY (2017) "A Ca2+ channel differentially regulates Clathrin-mediated and activity-dependent bulk endocytosis." PLoS biology.

Stereo-EEG the Route to the Field of Neuroscience

Cheng-chia Lee (李政家)

台北榮民總醫院 神經醫學中心 神經外科 主治醫師, Aug 2014 - present

國立陽明交通大學醫學系 助理教授, Aug 2018 - present

國際加馬刀研究基金會(IRRF)委員, Jul 2014 - present

亞洲術中神經功能監測學會(AOSIN)委員, Jun 2020 - present

台灣疼痛醫學會監事, May 2021 - present

台灣中青年神經外科學會理事, Nov 2021 - present

Abstract

. The effects of epilepsy are felt in multiple aspects of the person's life, including physical and mental health, cognitive function, educational achievements, vocational prospects, and family and peer relations. The successful treatment in patients with refractory epilepsy is the identification and localization of a potential surgical target.

In the past decades, intracranial EEG (iEEG), including subdural grid EEG and stereotactic EEG (sEEG), was used for precise EEG recording. Taipei Veterans General Hospital (TPE-VGH) is the only one center that can perform invasive presurgical evaluation of epilepsy using sEEG. Epilepsy surgery team in TPE-VGH have had the first case of sEEG implantation in 2014. The team also used data from SEEG to explore spreading of seizure activities in the patients with temporal lobe epilepsy, MR negative epilepsy, and epilepsy with migration disorders. The epilepsy surgery team provides good quality of presurgical evaluation and outstanding outcome of epilepsy surgery. In 2015, the team earned the award of "18th National Biotechnology and Medical Care Quality".

More recently, by collaborations with cognitive neuroscientists, several cognitive functions including language functions were investigated based on the sEEG recording. Language about lexical tone processing in the brain is a good example. In Mandarin Chinese, there are four tones to distinguish word meaning. By comparing the intracranial EEG recorded under different task demands, the results indicated that EEG recordings from the frontal, temporal, and supramarginal electrodes showed differential responses to different cognitive demands. This is important because we can calculate correlation between electrodes from different brain areas to show how they work in concert to implement a cognitive function. We believe the sEEG is a route can take us on the route to the field of neuroscience.

Selected recent publications:

1. Chou CC, Lee CC*, Lin CF, Peng SY, Hsiao FJ, Yu HY, Chen C, Chen HH, Shih YH: Cingulate gyrus epilepsy: Semiology, invasive EEG, and surgical approaches. Neurosurgery Focus 2020 Apr 1;48(4):E8

2. Lee CC, Hung SC, Chen HH, Chen H, Wu HM, Lin CP, Peng SY: Structural connectivity in children after total corpus callosotomy. Epilepsy Research 2021 (in press)

3. Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, Peng SJ, Liu HL, Yu HY: A Pilot Study of Focused Ultrasound for Drug-Resistant Epilepsy. Epilepsia 2021 Nov 2. [Online ahead of print].

4. Lin FH, Lee HJ, Ahveninen J, Jaaskelainen IP, Yu HY, Lee CC, Chou CC, Kuo WJ: Distributed source modeling of intracranial stereoelectro-encephalographic measurements. Neuroimage 2021 Apr 15;230:117746

Using SEEG to investigate language processing

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Institute of Neuroscience, National Yang-Ming University

Ph.D., National Chung Cheng University

Abstract

More than 50% of languages in the world are tone languages. Tone languages use pitch patterns to distinguish words. For example, in Mandarin Chinese, the syllable /ma/ could mean “mother” when pronounced with a high tone (Tone 1), or “horse” with a falling-rising tone (Tone 3). Therefore, usage of lexical tone is a common practice in human languages rather than exceptional or deviant. Lexical tone has acoustic and articulatory properties distinct from segment (i.e., vowel or consonant). Lexical tone processing creates neural activity patterns distinct from those for processing segment, including higher activities in the right auditory cortex and the right inferior frontal gyrus. In our previous studies, for example, we demonstrated that phonological processing to implement Mandarin lexical tone for production highly correlates with the right inferior frontal gyrus. However, the picture about how it interplays with other language areas in the left hemisphere remains to be elucidated. In this talk, we would like to present you the results of our recent studies in which we used a novel fMRI imaging sequence (10 Hz sampling rate) and SEEG to pin down the possible connections.

Selected recent publications:

1. Claire H. C. Chang, Stanislas Dehaene, Denise H. Wu, Wen-Jui Kuo, Christophe Pallier. 2020. Cortical encoding of linguistic constituent with and without morphosyntactic cues. Cortex (in press).
2. Fa-Hsuan Lin, Yun-Fei Liu, Hsin-Ju Lee, Claire H. C. Chang, Iiro P. Jaaskelainen, Jyh-Neng Yeh, Wen-Jui Kuo. 2019. Differential brain mechanisms during reading human vs. machine translated fiction and news texts. Sci Rep. 2019 Sep 13; 9(1): 13251.
3. Lee SR, Lin FH, Kuo WJ. The neural mechanism underpinning balance calibration between action inhibition and activation initiated by reward motivation. Sci Rep. 2017 Aug 29;7(1):9722.

The human orbitofrontal cortex and subjective value

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Ph.D., New York University

Abstract

In economic choice, evidence from electrophysiological studies in non-human primates and functional magnetic resonance imaging in humans suggested that activity in the orbitofrontal cortex (OFC) encodes the subjective value of options under consideration. Among them, some studies suggested that value representations in the OFC are relative and that the relative representations are affected by the decision makers' recent experience. However, these findings were mainly based on single-unit electrophysiology in non-human primates and have not been widely reported in humans. Using stereo electroencephalography (sEEG), we investigated the neural representations for both the present and past subjective values in the OFC. Patients with epilepsy (n=20) reported his or her willingness to pay—a measure of subjective value—for snack food items in a Becker-DeGroot-Marschack (BDM) auction task. We found that the high frequency power (gamma and high-gamma bands) in the OFC positively correlated with the current subjective value but negatively correlated with the previous subjective value. By contrast, the low frequency power (theta and alpha bands) also represented subjective value, but in opposite encoding directions compared with high-frequency activity. Further, the significant results primarily came from electrode contacts in the central and medial OFC, but not the lateral OFC. Together, these findings indicated that information about the value of the past and present rewards are simultaneously represented in the human OFC, and offered insights into the algorithmic structure for context-dependent computations during economic choice.

Selected recent publications:

1. Yang, Y-Y., Wu, S-W. (2020). Base rate neglect and neural computations for subjective weight in decision under uncertainty. *PNAS*, 117(29):16908-16919.
2. Lin, W-H., Gardner, J.L., Wu, S-W. (2020). Context effects on probability estimation. *PLoS Biology*, 18(3): e3000634.

Functional mapping by direct electrical stimulation in SEEG

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2. Assistant Professor, National Yang Ming Chiao Tung University

3. Secretary General, Taiwan Epilepsy Society

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MS, Institute of Brain Science, National Yang Ming Chiao Tung University

Abstract

Direct electrical stimulation (DES) for localization of brain function, called functional brain mapping, has developed for about 200 years. It was usually performed in the patients with epilepsy in an epilepsy monitoring unit with intracranial electrodes. Not only functional brain mapping, DES can also estimate the functional connectivity, assess the cortical excitability, and provoke the seizures. Fundamentally, DES is a non-physiological method to inhibit or excite local brain functions. Recently, it is applied to perform corticocortical-evoked potentials (CCEPs), which can further express local and distant functional networks.

In this lecture, I will review the history of functional mapping by DES both in the subdural electrodes and in stereo-electroencephalography (SEEG). I will introduce how to adjust parameters of DES in brain mapping. In addition, I will show the clinical results of motor-sensory and language mapping in some cases. In the last part, I will review the update knowledge of CCEPs, and share our preliminary results of CCEPs in functional and epileptic networks.

Selected recent publications:

1. **Chou CC**, Yen DJ, Lin YY, Wang YC, Lin CL, Kao CH. Selective serotonin reuptake inhibitors and poststroke epilepsy: a population-based nationwide study. Mayo Clin Proc. 2017; 92(2):193-199.

2. Peng SJ, **Chou CC**, Yu HY, Chen C, Yen DJ, Kwan SY, Hsu SPC, Lin CF, Chen HH, Lee CC. Ictal networks of temporal lobe epilepsy: views from high-frequency oscillations in stereoelectroencephalography. J Neurosurg. 2018 Nov 1: 1-9 [Epub ahead of print].

3. **Chou CC**, Lee CC, Lin CF, Chen YH, Peng SJ, Hsiao FJ, Yu HY, Chen C, Chen HH, Shih YH. Cingulate gyrus epilepsy: semiology, invasive EEG, and surgical approaches. Neurosurg Focus. 2020 Apr 1;48(4):E8.

4. **Chou CC***, Lin PT, Yen DJ, Yu HY, Kwang SY, Chen C, Liu YT, Shih YC, Ling SY. Acute withdrawal of new-generation antiepileptic drugs in epilepsy monitoring units: Safety and efficacy. Epilepsy Behav. 2021;117:107846.

5. Lee CC, **Chou CC**, Hsiao FJ, Chen YH, Lin CF, Chen CJ, Peng SJ, Liu HL, Yu HY. Pilot study of focused ultrasound for drug-resistant epilepsy. Epilepsia. 2021 63(1):162-175.

Focused Ultrasound and Its CNS Application

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Abstract

The materials consist the review identifying threshold of cavitation-based manipulation for BBBo. To translate BBBo for wider clinical use, a greater understanding of BBBo threshold, monitoring indicators of BBBo, and means to control BBBo stability are needed. BBBo threshold increases with higher frequencies. Critical parameters including the exposure level and microbubble concentration, are about to be summarized and reviewed. Passive cavitation detection to monitor cavitation showed that sub-harmonics can be used as a metric to control BBBo. BBBo based on PCD-feedback control using sub-harmonics, harmonics, and ultra-harmonics is in development, which can be done without MRI. At last, different types of guiding approaches as well as strategies been adopted in clinical practice will be introduced. Clinician relies on engineers dedicating on comprehensive system design to secure focused ultrasound CNS energy delivery and to eventually achieve therapeutic bioeffect. In this presentation, the view angle from the engineering design perspective and clinical application in CNS including essential tremor treatment, as well as developing indications such as blood-brain barrier opening, neuromodulation, and liquid biopsy will be introduced.

Selected recent publications:

1. KT Chen, WY Chai, YJ Lin, CJ Lin, PY Chen, HC Tsai, CY Huang, J Kuo, **HL Liu***, KC Wei*, Neuronavigation-Guided Focused Ultrasound for Transcranial Blood-Brain-Barrier Opening and Immunostimulation in Brain Tumors, Science Advances, Vol. 7, pp. 1-13, eabd0772, 2021.

2. CY Lin, CH Tsai, YC Lin, CY Huang, SR Wu, CM Chen, **HL Liu***, "Ultrasound-Responsive Neurotrophic Factor-Loaded Microbubble-Liposome Complex: Preclinical Investigation for Parkinson's Disease Treatment," Journal of Controlled Release, Vol. 321, pp.519-528, 2020.

3. SG Chen, CH Tsai, CJ Lin, CC Lee, HY Yu, TH Hsieh, **HL Liu***, "Transcranial focused ultrasound pulsation suppresses pentylenetetrazol induced epilepsy in vivo," Brain Stimulation, Vol. 13, pp. 35-46, 2020.

4. CY Lin, CH Tsai, LY Feng, WY Chai, CJ Lin, CY Huang, KC Wei, CK Yeh, CM Chen, **HL Liu***, "Focused Ultrasound-Induced Blood Brain-Barrier Opening Enhanced Vascular Permeability for GDNF Delivery in Huntington's Disease Mouse Model," Brain Stimulation, Vol. 12, No. 5, pp.1143-1150, 2019.

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Combination of navigation-guide focused ultrasound and bevacizumab for patients with recurrent glioblastoma： a phase IIa clinical trial

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Abstract

Introduction: Bevacizumab (BEV), a vascular normalizing therapy that prolongs progression free survival (PFS) for patients with recurrent glioblastoma (rGBM). Focused ultrasound combines with microbubbles (MB-FUS), an emergent technology for targeted blood-brain barrier opening (BBBO), is under investigation for its combinatorial effect with current standard of care for GBM treatment. This study aims to evaluate the safety and efficacy of BEV + MB-FUS for treating patients with rGBM.

Methods: This is a phase IIa, open-label, single-arm clinical trial (NCT04446416). Eligible patients received BEV (10 mg/kg), then MB-FUS with a MB dosage of 0.1 ml/kg and neuronavigation-guided FUS system (NaviFUS-001, NaviFUS, Taiwan). The MB-FUS is planned to be an add-on modality to the bi-weekly BEV therapy for up to 18 sessions (FUS-BEV, 34 weeks).

Results: Six patients underwent total 156 FUS-BEVs (26 times per patients). Three patients (50%) completed the trial protocol, 2 of another 3 patients had disease progression during the treatments, the remaining one patient was in stable disease. The mean progression free survival was 7.5 months. Among the 156 sessions of MB-FUS, there were 3 (1.9%) transient focal scalp pain related to heating. An evaluation of the MB-FUS penetrated regions revealed a significant normalization effect of T2 signal hyperintensity at beam-concentrated areas.

Conclusions: The PFS-6 was 67% in this study. Results have demonstrated the safety, feasibility, and a potential to decrease edema by the mechanism of enhance bevacizumab delivery to the treated site. The preliminary results are encouraging. More data are needed to proof the efficacy of BEV-FUS on rGBM patients.

Selected recent publications:

1. KT Chen, TY Ho, TY Siow, YC Yeh, SY Huang, *Individual cerebrocerebellar functional network analysis decoding symptomatologic dynamics of postoperative cerebellar mutism syndrome.* Cerebral Cortex Communications, (2022), 3, 1-11
2. KT Chen, KC Wei, HL Liu, *Focused ultrasound combined with microbubbles in central nervous system applications.* Pharmaceutics, (2021), 13(7),1084 (2020 IF=6.321)
3. KT Chen, WY Chai, YJ Lin, CJ Lin, PY Chen, HC Tsai, CY Huang, J Kuo, HL Liu*, KC Wei*, *Neuronavigation-Guided Focused Ultrasound for Transcranial Blood-Brain-Barrier Opening and Immunostimulation in Brain Tumors.* Science Advances. (2020) Accepted (IF = 13.116, 5/69 in "Multidisciplinary Science")
4. Po-An Chen, Yi-Chun Chen, Kuo-Chen Wei, Ko-Ting Chen*. *Awake craniotomy for a left pan-hippocampal diffuse low grade glioma in a deaf-mute patient using sign language.* World Neurosurgery. (2020),134:629-634.e1 (2019 IF=1.829)
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Synergic effect of Focused ultrasound and radiation therapy in glioma: a preclinical and upcoming clinical study

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Abstract

The standard treatment of glioblastoma is surgical resection followed by adjuvant chemo/radiotherapy. However, tumor may still recur and resulting in poor survival. In solid tumors, the hypoxia condition presented in most of tumor area may contribute to treatment failure in both adjuvant therapies. It had been proven that systemic delivered oxygen may not sufficient for ionizing radiation to produce cytotoxic effect. A recent study reported using focused ultrasound combined with oxygen-contained microbubbles prior to radiation significantly increased the oxygen content in breast cancers and statistically improved animal survival. Therefore, providing sufficient oxygen in tumor area may be beneficial for radiation therapy. To study the potential role of such strategy for glioblastoma, we used focused ultrasound to treat glioma-bearing animals before radiation therapy. As compared with non-ultrasound treatment groups, the tumor growth rate was significantly inhibited, and the animal survival is prolonged. Furthermore, we found focused ultrasound combined with non-oxygen-containing microbubbles also represented similar results, demonstrate the focused ultrasound induced cerebral vascular permeability increment may also contribute to the radiation therapy effect in glioblastoma. Based on the promising results, the open label, prospective, pilot study will be initiated to investigate the safety and preliminary efficacy of combination of focused ultrasound with re-irradiation in patients with recurrent glioblastoma.

Selected recent publications:

1. **Lin YJ**, Wei KC, Chen PY, Lim M, Hwang TL. Roles of Neutrophils in Glioma and Brain Metastases. Front Immunol. 2021 Aug 13;12:701383.

2. Chen KT, Chai WY, **Lin YJ**, Lin CJ, Chen PY, Tsai HC, Huang CY, Kuo JS, Liu HL, Wei KC. Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors. Sci Adv. 2021 Feb 5;7(6):eabd0772.

3. **Lin YJ**, Mashouf LA, Lim M. CAR T Cell Therapy in Primary Brain Tumors: Current Investigations and the Future. Front Immunol. 2022 Feb 21;13:817296.

4. **Lin YJ**, Huang CY, Shen YC, Wei KC, Chuang CC, Hsu PW, Huang YC, Hwang TL, Chen PY. A manzamine-derived compound as a potential therapeutic agent for glioma by inducing apoptosis and cell cycle arrest. Am J Cancer Res. 2022 Apr 15;12(4):1740-1751.

5. Chen CH, **Lin YJ**, Lin YY, Lin CH, Feng LY, Chang IY, Wei KC, Huang CY. Glioblastoma Primary Cells Retain the Most Copy Number Alterations That Predict Poor Survival in Glioma Patients. Front Oncol. 2021 Apr 26;11:621432.

Using sonobiopsy as a novel noninvasive tool for brain diseases signals detection

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Abstract

Biopsy is one of the important steps for disease diagnosis. Tissue samples are taken from the patient's body by using endoscope, needle puncture or surgery for pathological diagnosis. Due to the high invasive nature and limitation on accuracy and repeated sampling, alternative biopsy method is considered. Recently, the application of liquid biopsy has been highly noted by clinicians. Liquid biopsies use the blood samples collected from patients to analyze the biomarkers, circulating tumor cells and circulating cell free nucleic acids for accurate analysis. With the great advantages such as non-invasive, rapid, accurate and repeated sampling, the utilization rate is increasing in recent years. The key point of liquid biopsy is to analyze biological information in the blood sample, these biomarkers are released from tissues and organs into the blood. However, when applied liquid biopsy for brain diseases, the obstacle is the specialized blood-brain barrier (BBB) which blocks the signals released into the systematic blood flow. BBB protects the brain by limiting macromolecules from entering the brain tissue, in the meantime, it also prevents the brain biological information released into the bloodstream. Therefore, the use of liquid biopsy for brain disease diagnosis is limited. In recent years, transcranial focused ultrasound combined with microbubbles has been proven to non-invasively and accurately open the blood-brain barrier in the brain target area. The application of focused ultrasound to the brain can significantly increase the concentration of extracellular free nucleic acids in the blood, which helps to improve the accuracy of biopsies for brain diseases. Our team take advantage of focused ultrasound to enhance BBB opening, increase the amount of disease-related markers in blood to improve the efficiency and accuracy of brain disease liquid biopsy. With our positive preliminary results, we consider it is possible to extend to practical applications to assist rapid and accurate diagnosis of brain diseases and provide clues for clinical treatment.

Selected recent publications:

1. Yang HW, **Huang CY**, Lin CW, Liu HL, Huang CW, Liao SS, Chen PY, Hsu PW, Lu YJ, Wei KC, Ma CCM. Gadolinium-functionalized nanographene oxide as a nanocarrier for combined drug and microRNA delivery and magnetic resonance imaging. *Biomaterials, 2014 Aug; 35(24): 6534-6542.* (2014). (SCI; IF2019=10.317; Materials science, biomaterials 1/38). **(Co-first author)**

2. Pang HH, **Huang CY***, Chu YW, Lin CJ, Zhou ZL, Shiue YL, Wei KC, Yang HW. Bioengineering fluorescent virus-like particle/RNAi nanocomplexes act synergistically with temozolomide to eradicate brain tumors. *Nanoscale*. 2019 11:8102-8109 (SCI; IF2019=6.895, Physics, applied 23/154) **(Co-first author)**

3. Pang HH, Chen PY, Wei KC, Huang CW, Shiue YL, **Huang CY***, Yang HW. Convection-enhanced delivery of a virus-like nanotherapeutic agent with dual-modal imaging for besiegement and eradication of brain tumors. *Theranostics*. 2019; 9:1752-1763 (SCI; IF2019=8.579; Medicine, research & experimental 8/128) **(Co-corresponding author)**

4. *Hsu WL[1], **Huang CY[1]**, Hsu YP, Hwang TL, Chang SH, Wang HYJ, Feng LY, Tzou SJ, Wei KC, Yang HW. On-skin glucose-biosensing and on-demand insulin-zinc hexamers delivery using microneedles for syringe-free diabetes management. Chemical Engineering Journal. 2020 Oct; 398: 125536.* (SCI; IF2019=10.652; Engineering, environmental 2/52) **(co-first author)**

5. Chen CH, Lin YJ, Lin YY, Lin CH, Feng LY, Chang IYF, Wei KC, **Huang CY***. Glioblastoma primary cells retain the most copy number alterations that predict poor survival in glioma patients. *Frontier in Oncology*. 2021 Apr. 11:1388 **(Corresponding author)**