**Nanosymposium session I**

# Ultrasound Brain Stimulation

Wen-Shiang Chen(陳文翔)
Chair & Professor, Physical Medicine & Rehabilitation, National Taiwan University Hospital and National Taiwan University College of Medicine

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 ($2 \times 10^6$ /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

Chen-Chi Wu(吳振吉)
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.

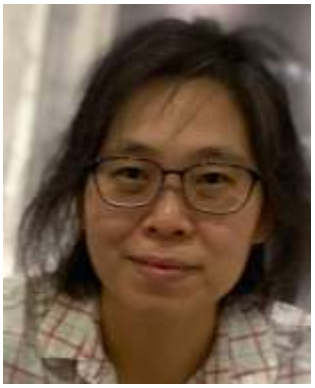
# Low-intensity ultrasound stimulation of mouse brain modulates neurogenesis andregulatesprotein phosphorylation

Jormay Lim(林若梅)

Department of Biomedical Engineering,

College of Medicine and College of Engineering,

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

Shih-Wei Wu (吳仕煒)
Professor

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

hih-Chieh Lin (林士傑)
Professor

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

Ming-Tsung Tseng (曾明宗)

Associate Professor

Graduate Institute of Brain and Mind Sciences

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.

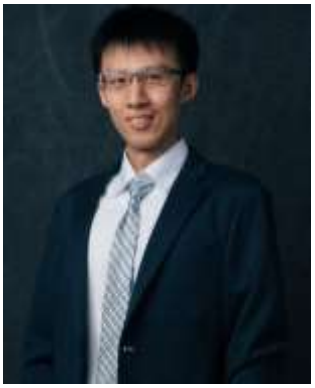
# Rethinking policy improvement in reinforcement learning

Ping-Chun Hsieh (謝秉均)
Assistant Professor

Department of Computer Science

National Yang Ming Chiao Tung University

Ph.D., Texas A&M University



## 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

Wen-Sung Lai (賴文崧)

Professor, Department of Psychology, National Taiwan University

Director, Neurobiology and Cognitive Science Center, National Taiwan University

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

Yu-Cheng Pei, MD PhD (裴育晟)
Current title and affiliation

Professor and Attending Physician at Department of Physical Medicine and Rehabilitation and School of Medicine

復健部部長、主治醫師、教授

Chang Gung Memorial Hospitalat Linkou/Chang Gung University

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

School and Graduate Institute of Physical Therapy, College of Medicine, National Taiwan University, Taipei, Taiwan

## 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

**Nanosymposium session I**

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

Yu-TingTsengPh.D. (曾鈺婷)
Assistant professor

Department of Kinesiology, National Tsing Hua University

助理教授，清華大學運動科學系

## 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

Robert Midence, PhD (康恩宇)

Postdoctoral fellow

博士後研究員

Institute of Biomedical Sciences, Academia Sinica

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

Yi-Hsuan Lee(李怡萱)
Distinguished Professor, Department and Institute of Physiology, National Yang Ming Chiao Tung University

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

Chien-Chang Chen(陳建璋)
Research Fellow, Institute of Biomedical Sciences,

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.

**Nanosymposium session I**

# Pericyte and cerebral small vessel diseases

Yuan-Ting Sun(孫苑庭)
Assistant Professor, Department of Neurology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

MD &Ph.D.National Cheng Kung University

## 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

Yi-Hung Chen(陳易宏)
Director and Professor

Graduate Institute of Acupuncture Science, China Medical University

Ph.D.National Taiwan University

## 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.

**Nanosymposium session I**

# Deep brain stimulation (DBS) for Psychiatric disorders

Kang-Du Liu(劉康渡)

Chief of Functional Neurosurgical department, Neurological Institute, Taipei Veterans General Hospital, Taiwan

## 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

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 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

Sheng-Tzung Tsai(蔡昇宗)

Director and Attending Neurosurgeon, Department of Neurosurgery, Hualien Tzu Chi Hospital

Professor, Department of Surgery

M.D., Ph.D.Tzu Chi University, Hualien, Taiwan

## 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).

**Nanosymposium session I**

# Non-Invasive Brain Stimulation for Treating Refractory Neuropsychiatric Disorders

Cheng-Ta Li (李正達)

Chief, Division of Community & Rehabilitation Psychiatry, Department of Psychiatry, Taipei Veterans General Hospital, Taiwan 台北榮總精神部

Chief, Precision Depression Intervention Center (PreDIC) 情緒精準中心

Professor, Department of Psychiatry and Institute of Brain Science, National Yang Ming Chiao Tung University 國立陽明交通大學醫學系及腦科學研究所

Professor, Institute of Cognitive Neuroscience, National Central University 中央大學認知神經科學研究所

Executive Council member, Taiwanese Society of Psychiatry 台灣精神醫學會

Council member, Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology 台灣生物精神暨神經藥理學會

## 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)**