Neuroscience research in primates
靈長類動物的神經研究

Host: Chih-Yang Chen (陳志揚)

Location: 生物醫學科學研究所 B1B會議室
Institute of Biomedical Sciences (IBMS) B1B room

Time: Sep. 13, 11:45-13:00

Participate society: Taiwan Neuroscience Society (台灣基礎神經科學學會)

The most direct way to understand how we see the world, think and act is to study our close relatives, other primates. Primate neuroscience research is very broad, including the studies of sensation, movement, cognition, language, neurological disease and treatment. However, there are very few studies on primates in Taiwan. In this nanosymposium, we will discuss research on the use of macaques and marmosets to study how primates perceive and process visual information, make other-regarding decision and map saccadic representation in the frontal cortex.
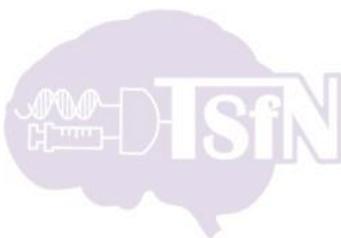
Encoding of color and luminance in macaque primary visual cortex

葉俊毅

Assistant Professor, Department of Psychology, National Taiwan University, Taiwan

PhD, University of Connecticut

Abstract

Contrast between long-wavelength (L-cone) and middle-wavelength (M-cone) signals is one of the channels (the L-M channel) that processes chromatic information in the early visual pathway. Recent studies have found that the weights of L-cone and M-cone inputs in macaque primary visual cortex (V1) are not equal - many V1 neurons prefer red (L-cone) to green (M-cone) stimuli (Conway and Livingstone, 2006; Shirhattia and Ray, 2018). However, the red-green imbalance has not been reported in the lateral geniculate nucleus (Derrington et al, 1984; Gegenfurtner, 2003). Therefore, how the red-over-green preference is generated within V1 remains unclear. We addressed this question by measuring response properties of neurons in different layers of macaque V1 with color sparse noise, which was composed using equiluminant red and green with constant short-wavelength cone weight. We found that red stimuli induced a larger local field potential and a broader visual spread than the green. Spectrum analysis showed a stronger gamma-band (20-60 Hz) power for red than for green. In addition, a higher number of V1 neurons preferred red to green. The magnitude of the red-over-green preference was greater in the output layer 2/3 than in the input layer 4c. Along with the black-over-white bias found previously in the output layer 2/3 of macaque V1 (Yeh et al 2009, Xing et al 2010), the recurrent connection in the superficial layers of macaque V1 is likely the underlying circuitry that amplifies both color and luminance biases and serves as the neuronal basis of perceptual asymmetry of black/white and red/green.

Selected recent publications:

Yeh CI*, Xing D*, Shapley RM (2009). "Black" responses dominate macaque primary visual cortex V1. *Journal of Neuroscience, 29, 11753-11760* (*equal contribution).

Xing D*, **Yeh CI***, Shapley RM (2010). Generation of black-dominant responses in V1 cortex. *Journal of Neuroscience, 30, 13504-13512* (*equal contribution).

Yeh CI, Huang WM, Wu HY, Pei YC (2017). Spatial receptive fields of color-responsive neurons in macaque V1. *Society for Neuroscience Abstract No 57.18*.

Tai W, Wu HY, Huang WM, Pei YC, **Yeh CI** (2017). Synchronous firing of black-dominant and white-dominant cell pairs in macaque V1. *Society for Neuroscience Abstract No 148.23*.

Huang WN, Wu HY, Pei YC, **Yeh CI** (2019). Response asymmetry of red and green in macaque primary visual cortex. *Society for Neuroscience Abstract No 143.09*.
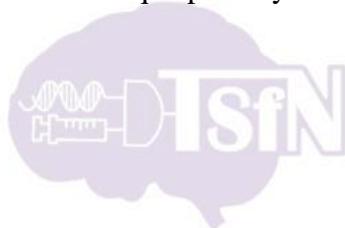
Linking the superior colliculus to pupil size

Chin-An Josh Wang (汪勁安)
Medical researcher, Research Center of Brain and Consciousness and Department of Anesthesiology, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
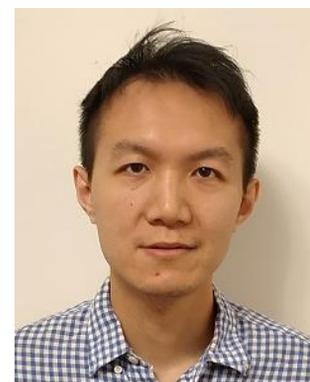
PhD, National Yang-Ming University

Abstract

Pupil size, as a component of orienting, changes rapidly in response to local salient events in the environment. The midbrain superior colliculus (SC), a hub of sensory, cognitive, and motor processing, is hypothesized to encode stimuli based upon saliency to coordinate the orienting response, which includes saccades and pupil dilation. Although the SC is causally involved in saccade generation, its role in coordinating other components of orienting is less understood. Moreover, it remains to be determined whether and how saccades and pupil size are coordinated through the SC. Here, we examined how pupil dynamics are modulated by the SC and stimulus saliency, and the coordination between saccades and pupil responses through the SC. While requiring subjects to maintain central fixation, we presented a salient visual or auditory stimulus. Transient pupil dilation was elicited after presentation of salient stimuli, and the timing and magnitude of evoked pupillary responses were modulated by stimulus contrast, with significantly faster and larger pupillary responses observed for more salient stimuli. Moreover, transient pupil dilation was also elicited by SC microstimulation, and this dilation was qualitatively similar to that evoked by salient stimuli. Varying stimulation parameters systematically modulated evoked saccade as well as pupil responses, with trial-by-trial correlation between two responses. Together, these results demonstrated the saliency modulation of pupillary responses, and the SC coordinates pupillary responses and saccades. Because the SC receives multisensory, arousal, cognitive signals from various cortical and subcortical areas, the SC-pupil pathway provides a novel neural substrate underlying the pupil modulation by various cognitive and arousal processes.

Selected recent publications:

Hsu Y-F, Baird T, **Wang C-A**. (2020). Investigating cognitive load modulation on distractor processing using pupillary luminance responses in the anti-saccade paradigm. *European Journal of Neuroscience*.

Wang C-A, Huang J, Brien DC, & Munoz DP. (2020). Saliency and priority modulation in a popout paradigm: pupil size and microsaccade rate, *Biological Psychology*.

Wang C-A, Munoz DP. (2018). Neural basis of location-specific pupil luminance modulation. *Proceedings of the National Academy of Sciences*, 115(41):10446-10451.

Wang C-A, Baird T, Huang J, Coutinho J, Brien DC, Munoz DP. (2018). Arousal effects in pupil size, heart rate and skin conductance at an emotional face task. *Frontiers in Neurology*, 9, 1029.

Wang C-A, Munoz DP. (2015). A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. *Current Opinion in Neurobiology*, 33:134-140.

Neural mechanism of other-regarding decision and vicarious reward

ChengChi Chu (朱政吉)
Postdoctoral Associate, Yale University

PhD, National Yang-Ming University

Abstract

Neuronal synchrony between social brain regions may play an important role in social decision-making. Previous work found frequency-specific modulations of synchrony between the basolateral amygdala (BLA) and anterior cingulate gyrus (ACCg) when monkey expressed a prosocial decision preference over an antisocial decision preference. Specifically, when monkeys made a decision to donate a reward to the other monkey over an empty bottle, the beta coherence between BLA spikes and ACCg local field potential and the gamma coherence between ACCg spikes and BLA field increased. Here, we further hypothesized that frequency-specific synchronization in the BLA-ACCg circuit is further deployed with respect to social reward outcome. To test this, we examined spike-field coherence in the beta and gamma frequency bands by contrasting different reward outcomes – reward to the self versus the bottle, rewards to both monkeys versus the bottle, and reward to the other monkey versus the bottle. We found that beta coherence between ACCg spikes and BLA field increased around 100-200ms upon the receipt of actor's reward. By contrast, gamma coherence between BLA spikes and ACCg field increased around 350-500ms upon the receipt of other monkey's reward. This increased gamma coherence for other's reward outcome scaled with reward magnitude and could be used to linearly decode the reward magnitude of the actor's reward across contexts. Our findings suggest that frequency-specific neuronal synchrony between BLA and ACCg is involved in the representation of vicarious reward, further supporting the important function of interareal synchrony in guiding social decision-making.

Selected recent publications:

Dal Monte O, **Chu CC**, Nicholas F, Steve Chang (2020) Specialized medial prefrontal-amygdala coordination in other-regarding decision preference. *Nature Neuroscience*
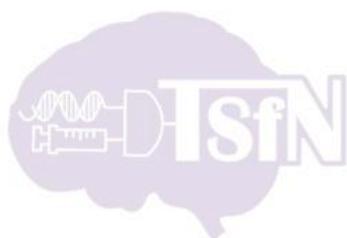
Anatomical and Functional MRI in Non-Human Primate Models

Cecil Yen (顏誠祺)
Staff Scientist, Transgenic Marmoset Core - Imaging Facility, National Institutes of Health, USA

PhD, Bioengineering, University of Pittsburgh

MS, Electrical Engineering, University of Pittsburgh

BS, Physics, National Tsing Hua University

Abstract

Magnetic Resonance Imaging (MRI) has become an indispensable tool to diagram the anatomy and to map the function of the brain. The ubiquitous uses and the noninvasive nature of the MRI make it suitable to image the brain from rodent models to human patients. However, doing MRI in non-human primates, which is an ideal translational model between rodents and humans, was challenging in the past due to technical limitations. Recent advancements in MRI related techniques have opened a new window to study the brain using non-human primates.

In this talk, I will review the latest trends such as high field magnets, customized MRI detectors, and tailored stimulus setups in conducting anatomical and functional MRI in non-human primate models, especially in common marmosets. Marmoset is a rapid-reproductive New World primate with the potential of being transgenesis. Its body size is like a squirrel, which can fit into a preclinical ultra-high field MRI with optimized detectors. Anatomical MRI was routinely performed in anesthetized marmosets to examine brain lesions and to build brain atlas. Functional MRI with somatosensory, visual, auditory stimulations in awake marmosets was available to investigate the brain processes. Anatomical and functional MRI are two complementary techniques to virtual dissect marmoset's brain, which can shed light on our understanding of various neurological disorders and diverse neuroscience questions.

Selected recent publications:

Liu C, Ye FQ, Newman JD, Szczupak D, Tian X, Yen CC, Majka P, Glen D, Rosa MGP, Leopold DA, Silva AC. A resource for the detailed 3D mapping of white matter pathways in the marmoset brain. Nat Neurosci 2020;23(2):271-280.

Liu C, Yen CC, Szczupak D, Ye FQ, Leopold DA, Silva AC. Anatomical and functional investigation of the marmoset default mode network. Nat Commun 2019;10(1):1975.

Yen CC-C, Papoti D, Silva AC. Investigating the spatiotemporal characteristics of the deoxyhemoglobin-related and deoxyhemoglobin-unrelated functional hemodynamic response across cortical layers in awake marmosets. Neuroimage 2018;164:121-130.

Liu C, Ye FQ, Yen CC, Newman JD, Glen D, Leopold DA, Silva AC. A digital 3D atlas of the marmoset brain based on multi-modal MRI. Neuroimage 2018;169:106-116.

Leibovitch EC, Caruso B, Ha SK, Schindler MK, Lee NJ, Luciano NJ, Billioux BJ, Guy JR, Yen C, Sati P, Silva AC, Reich DS, Jacobson S. Herpesvirus trigger accelerates neuroinflammation in a nonhuman primate model of multiple sclerosis. Proc Natl Acad Sci U S A 2018;115(44):11292-11297.

Mapping saccadic representation in the frontal cortex of common marmoset

Chih-Yang Chen (陳志揚)
Project specific assistant professor, Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Kyoto, Japan

PhD, University of Tübingen

Abstract

The frontal cortex in primates has several subregions that are related to saccade generation, e.g., the frontal eye field (FEF) and supplementary eye field (SEF). They are also involved in higher cognitive functions like attention and decision making. In macaques and humans, these regions are easy to identify based on anatomy but are difficult to access because they are in the sulci. In marmosets, although their lissencephalic brains give easy access to these areas, however, these areas are difficult to identify anatomically. Here, I will describe how we spent our effort in utilizing the marmosets for oculomotor and attention research by comparing their saccade behavior to other primates and identifying the frontal saccadic areas them.

We first recorded the marmosets' free-viewing behavior with head-restraining condition and showed that they have similar saccadic kinematics and bottom-up saliency to humans and macaques. We have also trained them on classic visually-guided saccade tasks to show their ability to perform tasks. We further injected viral tracers in the superior colliculus, a known downstream for saccade generation, to trace back to the marmosets' frontal cortex. We identified several potential frontal regions to be FEF and SEF and we electrically microstimulated these areas. We successfully evoked saccades. Finally, we performed calcium imaging in the similar frontal region while the marmoset performing free-viewing task and found saccade related neurons.

We will extend our research using marmosets and prepare for large scale recording and optogenetics to advance our knowledge in the primate oculomotor and attention systems.

Selected recent publications:

Chen C-Y, Hoffmann KP, Distler C, Hafed ZM (2019) The foveal visual representation of the primate superior colliculus. *Curr. Biol* 29:2109-2119

Chen C-Y, Sonnenberg L, Weller S, Witschel T, Hafed ZM (2018) Spatial frequency sensitivity in macaque midbrain. *Nat. Commun* 9:2852

Chen C-Y, Hafed ZM (2017) A neural locus for spatial-frequency specific saccadic suppression in visual-motor neurons of the primate superior colliculus. *J. Neurophysiol* 117:1657-1673

Hafed ZM, **Chen C-Y** (2016) Sharper, stronger, faster upper visual field representation in primate superior colliculus. *Curr. Biol* 26:1647-1658

Chen C-Y, Ignashchenkova A, Thier P, Hafed ZM (2015) Neuronal response gain enhancement prior to microsaccades. *Curr. Biol* 25:2065-2074
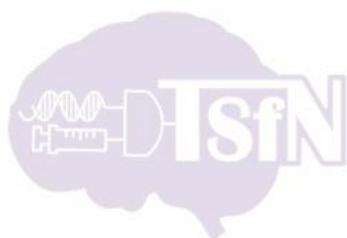
Nutritional neuroscience as mainstream of psychiatry: How omega-3 fatty acids interface mind and body?
營養神經科學作為精神病學的主流：
omega-3脂肪酸如何介導身心

Host: Jane Pei-Chen Chang (張倍禎)

Location:分子生物研究所 Institute of Molecular Biology (IMB)

Time: Sep. 13, 11:45-13:00

Participate societies: Taiwan Society for Nutritional Psychiatry Research (台灣營養精神醫學研究學會)、 Taiwanese society of Biological Psychiatry and Neuropsychopharmacology (台灣生物精神醫學暨神經精神藥理學會)

The recently booming nutritional psychiatry has gradually become the mainstream of psychiatry. In contrast, the "monoamine hypothesis" theory of depression has come to an end in terms of etiology discovery and therapeutic innovation. Accumulating evidence supports the role of inflammation in psychiatric disorders, including depression, attention deficit hyperactivity disorder (ADHD) and dementia. More and more studies found that nutrition and dietary control have an important impact on "body" and "mind", and improve mental health by regulating the immune system and brain-gut-axis. In this nanosymposium, we will report the beneficial effects of omega-3 oil on ADHD, major depression and Alzheimer's disease.
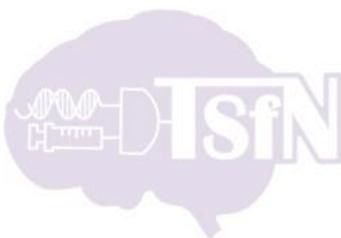
Omega-3 in Attention Deficit Hyperactivity Disorder

Jane Pei-Chen Chang (張倍禎)
Child and Adolescent Psychiatrist, China Medical University Hospital, Taiwan

Visiting Researcher, King's College London, UK

PhD, King's Collge London, UK

MD, China Medical University, Taiwan

Abstract

Omega-3 polyunsaturated fatty acids (PUFAs) are important nutrients for the developing brain. The current literature showed that n-3 PUFAs deficiency may play a role in the pathogenesis of neurodevelopmental disorder, such as attention deficit hyperactivity disorder (ADHD). However, the study findings on the associations between n-3 PUFAs and ADHD have been controversial. Moreover, omega-3 PUFAs have been reported of anti-inflammatory actions, while ADHD has been linked with inflammation and immune dysregulation. However, no studies have focused on the inflammatory status and treatment responses of omega-3 PUFAs in children with ADHD.

The first part of my presentation will provide an overview of our study findings of omega-3 fatty acids and inflammation biomarkers in children with ADHD from cross-sectional, meta-analyses studies. The second part of the presentation will focus on the preliminary findings of our randomized clinical trial of omega-3 PUFAs on the cognitive function in children with ADHD, looking specifically at potential biomarkers such as baseline n-3 PUFAs status.

Selected recent publications:

Chang JP, Mondelli V, Satyanarayanan SK, Yang HT, Chiang YJ, Chen HT, Su KP, Pariante C. Cortisol, inflammation biomarkers and neurotrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan. Brain, Behavior, and Immunity. 2020 (Epub ahead print).

Chang JP, Su KP, Mondelli V, Satyanarayanan SK, Yang HT, Chiang YJ, Chen HT, Pariante CM. High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels. Translational Psychiatry. 2019; 9:303.

Chang JP, Chang SS, Yang HT, Chen HT, Chien YC, Yang B, Su H, Su KP. Omega-3 polyunsaturated fatty acids in cadiovascular diseases comorbid major depressive diosrder-Results from a randomized controlled trial. Brain Behavior and Immunity. 2019. (Epub ahead of Print).

Chang JP, Su KP, Mondelli V, Pariante CM. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder (ADHD): A Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. Neuropsychopharmacology. 2018, 43:534-545.

Chang JP, Jingling L, Huang YT, Lu YJ, Su, KP. Delay Aversion, Temporal Processing, and N-3 Fatty Acids, Intake in Children with Attention-Deficit/Hyperactivity Disorder (ADHD). Clinical Psychological Science 2016, 4:1094-1103.

Inverse correlation between omega-3 concentration and emotional brain response on major depression

Cheng-Hao Tu (杜政昊)
Assistant Professor, Graduate Institute of Acupuncture
Science, China Medical University, Taichung, Taiwan

PhD, National Yang-Ming University, Taiwan

Abstract

Depression is an increasing mental health problem around whole world. Patients with major depression (MDD) have decreased responsiveness to the positive emotion stimuli and/or increased responsiveness to negative emotion stimuli. Recent clinical trials indicated that polyunsaturated fatty acid (PUFA) supplements can improve the symptoms of MDD, with the higher treatment efficacy of eicosapentaenoic acid (EPA) than of docosahexaenoic acid (DHA). However, the possible central mechanisms of EPA and DHA treatment remained unexplored. Twenty-four MDD patients have been participated in this double-blind, randomized-controlled study. All patients have been randomly allocated into EPA or DHA group for a 12-week treatment session. The 21-item Hamilton depression rating scale has been used to assess the depressive symptoms as clinical outcomes. Blood samples from vein have been taken to measure the membrane PUFA level on erythrocyte by gas chromatography of methyl esters. The brain responses to emotional picture stimuli have been measured by a 3T MRI scanner. The results showed that EPA may have more clinical efficacy than DHA on MDD patients. The EPA level was significantly increased after the treatment of EPA but not DHA, while the DHA level was both significantly increased after the treatment of EPA and DHA. The improvement of clinical symptoms has a trend to negative correlated with EPA level within EPA group, while neither significant correlation between DHA level within EPA group nor both EPA and DHA within DHA treatment group has been found. Imaging results further revealed that change of EPA level was negatively correlated with the changes of activity of right ventrolateral prefrontal cortex and anterior insula cortex when processing positive emotion stimuli with EPA treatment, whereas the DHA level was also negatively correlated with the activity of left anterior insula and right dorsolateral prefrontal cortex when processing negative emotion stimuli with DHA treatment. These results raised a possible role of docosapentaenoic acid, an intermediary metabolite between EPA and DHA, on the PUFA treatment of MDD subjects.

Selected recent publications:

Cheng-Hao Tu, Iona MacDonald, and Yi-Hung Chen* (2019). The Effects of Acupuncture on Glutamatergic Neurotransmission in Depression, Anxiety, Schizophrenia, and Alzheimer's Disease: A Review of the Literature. *Frontiers in Psychiatry* 14: 1-12

Ching-Yuan Lai, Jen-Huan Chiang, Jaung-Geng Lin, Hung-Rong Yen, **Cheng-Hao Tu***, Yi-Hung Chen* (2018). Chinese herbal medicine reduced the risk of stroke in patients with Parkinson's disease: A population-based retrospective cohort study from Taiwan. *PLoS One* 13: e0203473

Jaung-Geng Lin, Yu-Chen Lee, **Cheng-Hao Tu**, Iona MacDonald, Hsin-Yi Chung, Sih-Ting Luo, Shih-Ya Hung*, Yi-Hung, Chen* (2018). Histamine H1 Receptor Antagonists Facilitate Electroacupuncture Analgesia. *American Journal of Chinese Medicine* 46: 55-68

Neuroimaging as a predictor to evaluate the effect of omega 3 FUFA on the brain

Chun-Ming Chen (陳君明)
Postdoctoral Research Fellow, Department of Medical Imaging, China Medical University Hospital, Taiwan

PhD, National Chung Hsing University

Abstract

Neuroimaging has been broadly used to observe brain alterations between patients with mental disorders and healthy ones. Various imaging and data processing methods, including voxel-based morphometry (VBM), cortical thickness, diffusion tensor imaging (DTI), or functional magnetic resonance imaging (fMRI) provide complementary information to get more understanding to the diseases.

Omega-3 fatty acids were well known as its benefit to health, such as reducing the risk of cardiovascular disease, prevent or treat depression or other mood disorders. Here, I would like to apply a mini-review to the recent progress of MRI studies related to major depression and discuss if any potential imaging biomarkers could be used as predictors to monitor the effect of Omega-3 fatty acid.

Selected recent publications:

Chia-Chun Hung, Sheng Zhang, Chun-Ming Chen, Jeng-Ren Duann, Ching-Po Lin, Tony Szu-Hsien Lee, Chiang-Shan R. Li, Striatal functional connectivity in chronic ketamine users: a pilot study, Am J Drug Alcohol Abuse. 2019 Jul 2:1-13. doi: 10.1080/00952990.2019.1624764

Shin-Lei Peng*, Chun-Ming Chen, Chen-You Huang, Cheng-Ting Shih, Chiun-Wei Huang, Shao-Chieh Chiu, Wu-Chung Shen, Effects of hemodynamic response function selection on rat fMRI statistical analyses. Front. Neurosci., 2019 Apr 30. doi: 10.3389/fnins.2019.00400

Yi Huang, Jui-Cheng Chen, Chun-Ming Chen, Chon-Haw Tsai and Ming-Kuei Lu*, Paired Associative Electroacupuncture and Transcranial Magnetic Stimulation in Humans. Front. Hum. Neurosci., 12 February 2019. doi.org/10.3389/fnhum.2019.00049

Chun-Ming Chen, Yen-Chih Huang, Cheng-Ting Shih, Yung-Fang Chen, Shin-Lei Peng, MRI-based measurements of whole-brain global cerebral blood flow: Comparison and validation at 1.5T and 3T. JMRI 25 Feb. 2018 https://doi.org/10.1002/jmri.25989

Ming-Kuei Lu*, Jui-Cheng Chen, Chun-Ming Chen, Jeng-Ren Duann, Ulf Ziemann, Chon-Haw Tsai*. Impaired Cerebellum to Primary Motor Cortex Associative Plasticity in Parkinson's Disease and Spinocerebellar Ataxia Type 3. Front Neurol. 2017; 8: 445. Published online 2017 Aug 29. doi: 10.3389/fneur.2017.00445

Omega-3 polyunsaturated fatty acids promote brain-to-blood clearance of β-Amyloid in a mouse model with Alzheimer's disease

Huanxing Su (蘇煥興)
Institute of Chinese Medical Sciences, University of Macau, Macao, China

PhD, University of Hong Kong

MD., Zhejiang University

Abstract

Amyloid-β (Aβ) plaques is one of the typical pathological hallmark of Alzheimer disease (AD). Accumulating evidence suggests that the imbalance between Aβ production and clearance leads to extracellular Aβ accumulation in the brain. It is reported that the blood-brain barrier (BBB) transport plays a predominant role in Aβ clearance from brain to blood. In the present study, we investigated dynamic alterations of BBB transport function in the early disease stage of AD using APPswe/PS1dE9 C57BL/6J (APP/PS1) transgenic mice. Our results showed that the expression of lipoprotein receptor-related protein 1 (LRP-1), a main efflux transporter of BBB, started to decrease at the age of 4 months old. Interestingly, supplementing with fish oil which is rich in omega-3 polyunsaturated fatty acids (PUFAs) significantly enhanced the expression level of LRP-1 and promoted Aβ clearance from the bran to circulation, as revealed by reduced soluble/insoluble Aβ levels and senile plaques in the brain parenchyma and a corresponding increase of Aβ levels in plasma. Besides, fish oil supplement significantly inhibited the NF-κB activation, reduced the expression of interleukin-1β and tumor necrosis factor-α, and suppressed the glial activation in APP/PS1 mice. The results of the study provide evidence that BBB transport function could be impaired at a very early disease stage, which might contribute to Aβ pathological accumulation in AD, and omega-3 PUFAs intervention could be an effective strategy for the prevention of the progression of AD through promoting Aβ clearance from brain-to-blood.

Selected recent publications:

Ke M, Chong CM, Zeng H, Huang M, Huang Z, Zhang K, Cen X, Lu JH, Yao X, Qin D*, Su H*. Azoramide protects iPSC-derived dopaminergic neurons with PLA2G6 D331Y mutation through restoring ER function and CREB signaling. Cell Death Dis. 2020 Feb 18;11(2):130.

Chong CM, Ke M, Tan Y, Huang ZJ, Zhang K, Ai N, Ge W, Qin DJ, Lu JH, Su H*. Presenilin 1 deficiency suppresses autophagy in human neural stem cells through reducing γ-secretase-independent ERK/CREB signaling. Cell Death Dis. 2018 Aug 29;9(9):879.

Luo C, Ren H, Yao X, Shi Z, Liang F, Kang JX, Wan JB, Pei Z, Su KP, Su H*. Enriched Brain Omega-3 Polyunsaturated Fatty Acids Confer Neuroprotection against Microinfarction. EBioMedicine. 2018 Jun;32:50-61.

Huang X, Chen Y-Y, Shen Y, Cao Y, Li A, Liu Q, Li Z, Zhang L-B, Dai W, Tan T, Arias-Carrion O, Xue Y-X, Su H* and Yuan T-F*. Methamphetamine abuse impairs motor cortical plasticity and function. Molecular Psychiatry 2017 Sep;22(9):1274-1281.

Ren H, Luo C, Feng Y, Yao X, Shi Z, Liang F, Kang JX, Wan JB, Pei Z, Su H*. Omega-3 polyunsaturated fatty acids promote amyloid-β clearance from the brain through mediating the function of the glymphatic system. FASEB J, 2017 Jan;31(1):282-293.

Prolotherapy
增生療法

Host: Der-sheng Han (韓德生)、 Yeong-Ray Wen (溫永銳)

Location:　跨領域大樓
　　　　　Interdisciplinary Research Building for Science and Technology (IRB)

Time: Sep. 13, 11:45-13:00

Participate societies: Taiwan Academy of Physical Medicine and Rehabilitation (台灣復健醫學會)、 Taiwan Pain Society (台灣疼痛醫學會)

Prolotherapy is the treatment of local injection of glucose solution and has a long-standing history to exert certain effect on the repair of soft tissues (muscles, tendons, sarcolemma, ligaments, joints, nerves, etc.) and pain control. In 2018, the New England Journal of Medicine has an article discussing prolotherapy. However, how local injection of glucose can relieve pain and repair damaged soft tissues remains unanswered. In this nanosymposium, we will report on the clinical applications of prolotherapy in pain relief, Carpal tunnel syndrome and intradiscal regeneration and discuss the possible mechanism underlying the therapeutic power of prolotherapy.
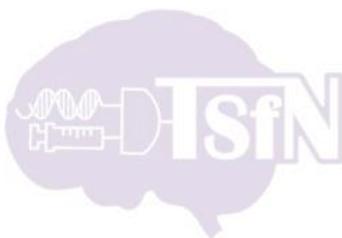
Junctional Regenerative Medicine:
The Future of Prolotherapy

Pan, Jen-Li (潘健理)
Attending Physician, Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei, Taiwan

Medical Director, PAN Regenerative Pain Clinic, Taipei, Taiwan

EMBA, National Taiwan University

MD, National Taiwan University

Abstract

In the field of regenerative pain medicine, especially prolotherapy, the anatomical continuity of human connective tissue system is the building block of the "Biotensegrity" theory. This whole tensegrity chain or network involve multiple types of connective tissues, including bone, cartilage, ligament, tendon, fat, nerve, vessels, fascia, etc. As various tissues are integrated together in this system, there will definitely be many forms of tissue junctions: myo-tendinous, neuro-muscular, chondro-osseous, to name a few. Across these junctions, not only mechanical forces are transduced, but nutrition, sensory sensory information, cell migrations, etc, are also in action, either unidirectional or bidirectional. To maintain the integrity of these junctions, both structurally and functionally, are crucial to a healthy biotensegrity system.

Disruptions of some interfaces within these junctional transitions, therefore, may usually be the root cause of pain and dysfunctions. Traditional prolotherapy has been focusing on fibro-osseous junctions (entheseal organs) as the major treatment targets; and dextrose, platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), exosomes, are some injectants among the candidates to repair or regenerate these fibro-osseous disruptions. However, there are still other junctional disruptions other than entheses that can cause pain, and there may be other pathophysiologies which might be totally different to that of the entheses. Hence, rregenerative interventions, either via conservative (nutritional), mini-invasive or surgical approaches, may be beneficial in restoration of these junctional disruptions, therefore relieve pain and improve function of the whole biotensegrity system.

Selected recent publications:

Simon F Tang, Carl P Chen, **Jen-Li Pan**, Jean-Lon Chen, Chau-Peng Leong, Ngok-Kiu Chu **The Effects of a New Foot-Toe Orthosis in Treating Painful Hallux Valgus** Arch Phys Med Rehabil. 2002 Dec;83(12):1792-5.

梁秋萍(Chau-Peng Leong) ； 周適偉(Shih-Wei Chou) ； 林聰樺(Tsong-Hwa Lin) ； 潘健理(Jen-Li Pan) ； 裴育晟(Yu-Cheng Pei) ； 朱岳喬(Ngok-Kiu Chu) ； 黎建中(Kin-Chung Lai) ； 杜國賢(Kuo-Hsien Tu) ； 鄧復旦(Simon F.T. Tang) 身心障礙者對於個別化醫療復健輔助器具設計服務需求暨市場供需調查 Taiwan J Phy Med Rehab 2004 32(1): 1-10

何春生(Chun-Sheng Ho) ； 張權維(Chein-Wei Chang) ； 謝有丁(Eou-Ting Hsieh) ； 潘健理(Jen-Li Pan) 外傷性腦傷併股骨骨折之多處異位性骨化症：個案報告 Taiwan J Phy Med Rehab 2010 38(3): 195-200
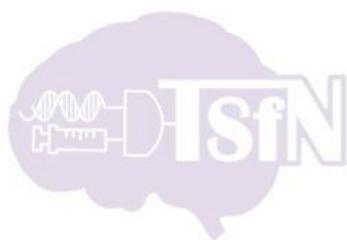
Prolotherapy and Biotensegrity

Chia-Hung Lin (林家弘)
President, Taiwan Association of Prolotherapy and Regenerative Medicine

Director, Immanuel Regenerative Care Clinic

Prolotherapy specialist, VS, mini-invasive orthopedic center, Tong Hospital, Taiwan

MD. Yang-Ming University

Abstract

Prolotherapy has been introduced to this world since 1930 by Dr. Hackett, which is described as injection of irritating substance to fibro-osseous junction of tendon and ligament to stimulate the tissue regeneration. In the theory, the most cause of chronic musculoskeletal pain may come from ligament laxity, and prolotherapy can tighten the ligament to restore stability to treat the pain.

Dextrose became the most popular injectate in prolotherapy for safety, effectiveness, easy to prepare and the cost, etc. Other effective injectates were proposed, such as PRP, then prolotherapy gradually was referred as hypertonic dextrose injection, while PRP, stem cell, etc. are referred as Regenerative Injection Therapy (RIT).

Biotensegrity was proposed by Dr. Stephen Levin in mid 1970s, and he described the force in oour body was transmitted all around in a tensegrity way. There are only tension and compression elements in tensegrity system. Prolotherapy can be applied to fascia attachment or septum when the fascia is lax or torn, and in clinical practice, it provides good results. Prolotherapy can also be done intraosseusly and also into vertebral disc, and that completes the model of biotensegriy by treating fascia, tendon, ligament, jointm, disc and bone. Reconstruction of biotensegrity could be the way to treat chronic pain when using prolotherapy as a tool.

Selected recent publications:

Tsai SW, **Lin CH**.(2010) Treatment of atlantoaxial rotatory fixation with botulinum toxin muscle block and manipulation. *Journal of Chinese Medical Association,*73:222-224

Chang ST, **Lin CH** (2014) Cigarette smoking dose as a predictor of need for surgical intervention in patients with lumbar disk herniation. *Journal of Medical Sciences* 34(1):23-29

Carpal tunnel syndrome and prolotherapy

Yung-Tsan Wu (吳永燦)

Attending Physician and Associate Professor, Department of Physical Medicine & Rehabilitation, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

MD., National Defense Medical Center (NDMC)

Abstract

Carpal tunnel syndrome (CTS) is the most common peripheral entrapment neuropathy. Although many conservative treatments are available, their therapeutic effect is rather insignificant and of short duration. The concept of prolotherapy is used in management of many musculoskeletal disoders in recent years and is regarded as regenerative therapies because of its potential for promotion of soft tissue regeneration. Nowadays, prolotherapy is used to treat CTS (known as neural prolotherapy or perineural injection therapy) with outstnading effect. Both hyposmolar dextrose (5% dextrose) and platelet-rich plasma (PRP) are the most used injectate for perineural injection in clinical practice. The 20th edition of Harrison's Principles of Internal Medicine textbook recommend this novel technique as a first-line conservative treatment for CTS. This simple and novel treatment can significantly improve successful rate of conservative treatments and decrease further surgical rate of CTS.

Selected recent publications:

Wu YT, Ke MJ, Ho TY, Li TY, Shen YP, Chen LC (2018). Randomized double-blinded clinical trial of 5% dextrose versus triamcinolone injection for carpal tunnel syndrome patients. Annals of Neurology. 84(4):601-610 (IF: 10.244, Rank: 8/197, Clinical neurology)

Wu YT, Ho TY, Chou YC, Ke MJ, Li TY, Tsai CK, Chen LC (2017). Six-month efficacy of perineural dextrose for carpal tunnel syndrome: a prospective randomized double-blind controlled trial. Mayo Clinic Proceedings. 92:1179-1189 (IF=7.199, Rank: 11/154, MEDICINE, GENERAL & INTERNAL)

Li TY, Chen SR, Shen YP, Chang CY, Su YC, Chen LC, **Wu YT**. Long-term outcome after perineural injection with 5% dextrose for carpal tunnel syndrome: a retrospective follow-up study (2020). Rheumatology (Accept) (IF: 5.149, Rank: 4/31, Rheumatology)

Chen LC, Ho TY, Shen YP, Su YC, Li TY, Tsai CK, **Wu YT**. Perineural Dextrose and Corticosteroid Injections for Ulnar Neuropathy at the Elbow: A Randomized Double-blind Trial (2020). Arch Phys Med Rehabil (IF: 2.697, Rank: 10/65, Rehabilitation)

Shen YP, Li TY, Chou YC, Ho TY, Ke MJ, Chen LC, **Wu YT**.Comparison of perineural platelet-rich plasma and dextrose injections for moderate carpal tunnel syndrome: A prospective randomized, single-blind, head-to-head comparative trial. J Tissue Eng Regen Med. 2019 Nov;13(11):2009-2017 (IF=3.319, Rank: 23/80, Engineering, Biomedical)

Intradiscal Prolotherapy

Tsung-Ju Wu (吳宗儒)
Director, Chief, Department of Physical Medicine and Rehabilitation, Yuanlin Christian Hospital, Changhua, Taiwan

PhD, China Medical University

MD., Kaohsiung Medical University

Abstract

The lumbar discogenic pain is one of the most common causes of low back pain. The diagnosis is made by discography to reproduce the concordant pain. Treatment modalities include noninvasive treatments such as drug therapy, multiple physical modalities, and multidisciplinary biopsychosocial rehabilitation. In recent years, intradiscal injection therapy with platelet-rich plasma (PRP) or stem cells has been demonstrated as an effective treatment on these patients.

The common treatment targets of US-guided treatment on the lumbar spine include facet joints, medial branches, and inter-lamina epidural space. And these procedures are mostly performed under fluoroscopy or computed tomography (CT) guidance. Recently, ultrasound (US) has been an emerging tool utilized in the performance of chronic pain interventions as it is easily available, free of radiation and offers real-time guidance.

Selected recent publications:

Ultrasound-Guided Lumbar Intradiscal Injection for Discogenic Pain: Technical Innovation and Presentation of Two Cases. **Wu TJ**, Hung CY, Lee CW, Lam S, Clark TB, Chang KV. J Pain Res. 2020 May; Volume 2020:13 Pages 1103—1107

Glucose enhances aggrecan expression in chondrocytes via the PKCα/p38-miR141-3p signaling pathway. **Wu TJ**, Fong YC, Lin CY, Huang YL, Tang CH. J Cell Physiol. 2018 Sep;233(9):6878-6887. doi: 10.1002/jcp.26451. Epub 2018 Mar 25.

Glucose suppresses IL-1β-induced MMP-1 expression through the FAK, MEK, ERK, and AP-1 signaling pathways. **Wu TJ**, Lin CY, Tsai CH, Huang YL, Tang CH. Environ Toxicol. 2018 Oct;33(10):1061-1068. doi: 10.1002/tox.22618. Epub 2018 Aug 11.
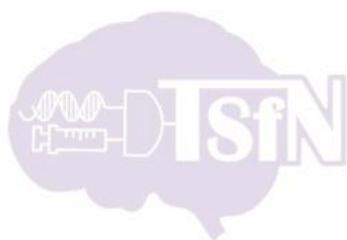
Neurodynamics and technologies for prevention, diagnosis, and treatment of neurological disorders

神經動力學和技術在預防，診斷和治療神經系統疾病的應用

Host: Li-Wei Ko (柯立偉)

Location:生物醫學科學研究所 B1C會議室
Institute of Biomedical Sciences (IBMS) B1C room

Time: Sep. 13, 11:45-13:00

Participate societies: Taiwan Society of Cognitive Neuroscience (台灣認知神經科學學會)、 Taiwan Academy of Physical Medicine and Rehabilitation (台灣復健醫學會)、 Taiwan Neurological Society (台灣神經學學會)

In recent years, interdisciplinary research and innovative medicine have been actively promoted for the goal of "smart healthcare". We will share our achievements, including (1) the brain computer interface alarming system for assisting migraine prediction and treatment, (2) the objective analysis of pain perceptions in migraine patients, (3) the early warning system for sleep disorders, (4) the integration of augmented reality, posture- and brain wave-sensing to improve post-stroke rehabilitation, and (5) interactive balance rehabilitation training by electro-stimulation to enhance the brain activity and postural stability in patients with bilateral vestibular dysfunction.

Innovative BCI technology in pain sensitivity measurement and prediction

Li-Wei KO (柯立偉)PhD.

Professor, Institute for Bioinformatics and Systems Biology, College of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan.

Jointly Appointed Professor, Drug Development and Value Creation Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan.

Chair, IEEE Computational Intelligence Society, Taipei Chapter, Taipei, Taiwan.

Deputy Director, Center for Smart Healthcare, National Chiao Tung University, Hsinchu, Taiwan.

Director, Interdisciplinary Neuroscience Ph.D. Program, University System of Taiwan, Taiwan

Abstract

Inherent fuzzy entropy is an objective measurement of electroencephalography (EEG) complexity reflecting the robustness of brain systems. In this study, we present a novel application of multiscale relative inherent fuzzy entropy using repetitive steady-state visual evoked potentials (SSVEPs) to investigate EEG complexity change between two migraine phases, i.e., interictal (baseline) and preictal (before migraine attacks) phases. We used a wearable headband EEG device with O1, Oz, O2, and Fpz electrodes to collect EEG signals from 80 participants [40 migraine patients and 40 healthy controls (HCs)] under the following two conditions: During resting state and SSVEPs with five 15-Hz photic stimuli. We found a significant enhancement in occipital EEG entropy with increasing stimulus times in both HCs and patients in the interictal phase, but a reverse trend in patients in the preictal phase. In the 1st SSVEP, occipital EEG entropy of the HCs was significantly lower than that of patents in the preictal phase (FDRadjusted $p < 0.05$). Regarding the transitional variance of EEG entropy between the 1st and 5th SSVEPs, patients in the preictal phase exhibited significantly lower values than patients in the interictal phase (FDR-adjusted $p < 0.05$). Furthermore, in the classification.

Selected recent publications:

H. Y. Zhang, C. Stevenson, T. P. Jung, and **L. W. Ko***, "Resting and pre-stimulus EEG spectra predict the SNR of SSVEPs and BCI performance," accepted by *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, May 2020.

C. R. Phang and **L. W. Ko***, "Global Cortical Network Distinguishes Motor Imagination of the Left and Right Foot," accepted by *IEEE Access*, May 2020.

L. W. Ko*, O. Komarov, W. K. Lai, W. G. Liang, and T. P. Jung, "Eyeblink Recognition Improves Fatigue Prediction from Single-Channel Forehead EEG in a Realistic Sustained Attention Task," accepted by *Journal of Neural Engineering*, May 2020.

R. K. Chikara, W. C. Lo, **L. W. Ko***, "Exploration of Brain Connectivity during Human Inhibitory Control," *Sensors*, vol. 20, no. 6, March 2020.

O. Komarov, **L. W. Ko***, and T. P. Jung, "Associations among emotional state, sleep quality, and resting-state EEG spectra: a longitudinal study in graduate students," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, DOI: 10.1109/TNSRE.2020.2972812, vol. 28(4), pp. 795-840, APRIL 2020.

Multimodal Pain Sensitivity in Migraine

Shuu-Jiun Wang (王署君)
Director, Neurological Institute, Taipei Veterans General Hospital

Director, Brain Research Center, National Yang-Ming University

MD., School of Medicine, National Yang-Ming University

Abstract

Previous studies regarding the quantitative sensory tests (QST) are inconsistent in migraine. We hypothesized that the QST results were influenced by headache frequency or migraine phase. This study recruited migraine patients with different headache frequencies and in different phases as well as healthy controls (HCs). Participants underwent QST, including heat, cold, and mechanical punctate pain thresholds (HPT, CPT, and MPT) at the supraorbital area (V1 dermatome) and the forearm (T1 dermatome). Prospective headache diaries were used to record headache frequency and migraine phase when QST was performed. Twenty-eight CM patients, 64 EM patients, and 32 HCs completed the study. Significant higher MPTs were found in only EM group compared with HCs. The MPTs decreased as headache frequency increased and nadired. In EM group, MPT was the highest ($p < 0.05$) in those in the inter-ictal phase and declined when approaching the ictal phase. Linear regression analyses showed that in those with EM, headache frequency and phase were independently associated with MPTs and accounted for 29.7% and 38.9% of the variance in V1 ($p = 0.003$) and T1 ($p < 0.001$) respectively. Of note, unlike MPT, our study did not demonstrate similar findings for HPT and CPT in migraine patients. In conclusion, our study provides new insights into the dynamic changes of QST, especially MPT in patients with migraine. MPTs vary depending on headache frequency and migraine phase, providing an explanation for the inconsistency across studies.

Selected recent publications:

Cao ZH, Lin CT*, Lai KL, Ko LW, King JT, Liao KK, Fuh JY, Wang SJ*. Extraction of SSVEPs-based Inherent Fuzzy Entropy Using a Wearable Headband EEG in Migraine Patients. IEEE Trans Fuzzy Syst 2020;28:14-27.

Pan LLH, Wang YF, Lai KL, Chen WT, Chen SP, Ling YH, Chou LW, Treede RD, Wang SJ*. Mechanical Punctate Pain Threshold is Associated with Headache Frequency and Phase in Patients with Migraine. Cephalalgia 2020 May16:333102420925540. (Epub ahead of print)

Benoliel Rq, Svensson Pq, Evers Sq, Wang SJq, Barke A, Korwisi B, Rief W, Treede RD, The IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic secondary headache or orofacial pain. Pain 2019;160:60-8. (Narrative review) (Co-first author)

Chen SP*, Fuh JL, Chou KH, Huang YH, Huang CC, Lirng JF, Wang YF, Lin CP, Wang SJ*. Dynamic changes in white matter hyperintensities in reversible cerebral vasoconstriction syndrome. JAMA Neurol 2018;75(9):1106-13.

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;141:377-90.

The circadian rhythm and its disorders: from bench to bedside

Chung-Yao Hsu (徐崇堯)

Chief, Department of Neurology, Kaohsiung Medical University Hospital

Chief, Department of Neurology, Kaohsiung Medical University

Director, Sleep Disorders Center, Department of Neurology, Kaohsiung Medical University Hospital

EDUCATION:

M.D., Department of Medicine, Kaohsiung Medical University, Taiwan

Ph.D., Department of Medicine, the University of Edinburgh, United Kingdom

Abstract

Circadian rhythms are physical and behavioral changes following a roughly 24-hour cycle and responding primarily to light and darkness of the environment. Circadian rhythm is controlled by a central clock located in the suprachiasmatic nuclei (SCN) of hypothalamus and also by many peripheral clocks in most peripheral tissues. These central and peripheral clocks work though the expression of clock genes and their proteins, which have both positive and negative feedback loops. Disrupted clock

genes have revealed alterations in circadian rhythmicity as well as changes in sleep duration and sleep architecture. Circadian rhythm sleep disorders are a group of sleep disorders affecting the timing of sleep onset and wake-up. People with circadian rhythm sleep disorders are unable to sleep and wake up according to the schedule of the environment so they can suffer from both insomnia and hypersomnia. Their total sleep time is generally adequate if they are allowed to sleep and wake at the times according to their body clocks. The peak incidence of mortality in patients with end stage renal disease exhibits diurnal variation. The aim of our human study was to assess the effect of hemodialysis schedule on sleep quality and daytime symptoms. We prospectively selected 150 hemodialysis (HD) patients in three groups (morning, afternoon, and evening dialysis) and gave them a sleep questionnaire, the Epworth sleepiness scale and the Pittsburgh sleep quality index. Our results showed the evening dialysis group experienced more sleep time in bed, required less hypnotic medication, had fewer daytime symptoms, and experienced less daytime sleepiness. Our human study indicates a beneficial effect of evening HD on sleep quality and reduction of daytime symptoms. The aim of our animal study was to clarify the role of circadian rhythm in the pathogenesis of sleep disturbance in patients with chronic kidney disease (CKD). Sixteen Sprague-Dawley rats (eight from 5/6 nephrectomized CKD group and eight from control group) were used for electroencephalography and electromyography recording. Eight rats (four from CKD and four from control group) were sacrificed at six Zeitgeber time (ZT) points and determined the mRNA expression of clock genes, rPer1, rPer2 and rBMAL1b in the hypothalamus. Our results showed that both slow wave sleep and rapid eye movement sleep were significantly increased in the ZT22–24 of the dark period in the CKD rats when compared with those sleep architectures obtained from the control rats. The CKD-induced sleep disruptions were associated with significant up-regulations of rPer1 and rPer2 mRNA expression in the hypothalamus. Our animal study indicates that disrupted circadian rhythm plays a role in the pathogenesis of sleep disturbance in patients with CKD.

Selected recent publications:

YC Chuang, SD Chen, SB Jou, TK Lin, SF Chen, NC Chen, **CY Hsu*** (2019, Jul). Sirtuin 1 Regulates Mitochondrial Biogenesis and Provides an Endogenous Neuroprotective Mechanism Against Seizure-Induced Neuronal Cell Death in the Hippocampus Following Status Epilepticus. International journal of molecular sciences, 20(14). pii: E3588.

MN Wu, CL Lai, CK Liu, CW Yen, LM Liou, CF Hsieh, MJ Tsai, SC Chen, **CY Hsu*** (2018, Dec). Basal Sympathetic Predominance in Periodic Limb Movements in Sleep after Continuous Positive Airway Pressure. Sleep & breathing, 22(4), 1005-1012.

VC Chen, YH Yang, TY Kuo, KY Huang, YC Huang, Y Lee, RS McIntyre, YS Huang, **CY Hsu*** (2018, Sep). Increased Incidence of Obstructive Sleep Apnea in Hospitalized Children following Enterovirus Infection: A Nationwide Population-Based Cohort Study. The Pediatric infectious disease journal, 37(9), 872-879.

MN Wu, CL Lai, CK Liu, LM Liou, CW Yen, Sharon CJ Chen, CF Hsieh, SW Hsieh, FC Lin, **CY Hsu*** (2015, Oct). More severe hypoxemia is associated with better subjective sleep quality in obstructive sleep apnea. BMC pulmonary medicine, 15:117.

MN Wu, CL Lai, CK Liu, CW Yen, LM Liou, CF Hsieh, MJ Tsai, SC Chen, **CY Hsu*** (2015, Jun). Basal sympathetic predominance in periodic limb movements in sleep with obstructive sleep apnea. Journal of Sleep Research, 24(6), 722-9.

The application of mixed-reality music rehabilitation system for the hemiplegic lower limb in stroke patients

Chia-Hsin Chen (陳嘉炘)MD, PhD.

Director, Department of Physical Medicine and Rehabilitation,

Kaohsiung Medical University Hospital

Professor, School of Medicine, College of Medicine,

Kaohsiung Medical University,

Abstract

Stroke remains the third leading cause of death in Taiwan after cancer and heart disease. The stroke patients receive the low rehabilitation programs due to insufficient rehabilitation services. Some creative approaches have been proposed to accelerate or make the process more intriguing, such as virtual reality (VR) or robotic exoskeletons. In order to promote the rehabilitation efficacy and to adopt the mixed-reality (MR) system instead of VR environment, we design an innovative mixed-reality music rehabilitation (MR2) system. The system contents MR goggle and HoloLens. While performing the training program, the system can monitor patient's both gait information and electroencephalographic (EEG) signals. The gait data was gained by with IMU-based wearable motion capture device. The sampling rate of the sensors was 40 Hz. The EEG signals were recorded by the wet-electrode EEG cap, NuAmp to understand the rehabilitation performance in the central nervous system. In the stroke group, two different procedures with the stroke patients were used to validate the performance of MR music rehabilitation system. The non-MR patient group was performed by the stroke patient compared with the MR patient experiment. The results show that the patient's motor function is significantly activated when wearing the MR2 system during the ambulation. The gait analysis results also present significantly increased angle in hemiplegic hip and knee flexion during walking following the tempo of the MR music exercise. EEG power decrease in delta, alpha, and lower beta band were explored at Cz channel during the healthy subject experiment. EEG power also show difference between MR patient group and non-MR group.

Selected recent publications:

Hsiao YH, Chien SH, Tu HP, Fu JC, Tsai ST, Chen YS, Chen YJ, Chen CH*. (2019, Nov). Early Post-Operative Intervention of Whole-Body Vibration in Patients After Total Knee Arthroplasty: A Pilot Study.. Journal of clinical medicine, 7;8(11). pii: E1902.

Chen YJ, Chang WA, Wu LY, Huang CF, Chen CH*, Kuo PL. (2019, Jul). Identification of Novel Genes in Osteoarthritic Fibroblast-Like Synoviocytes Using Next-Generation Sequencing and Bioinformatics Approaches.. International journal of medical sciences, 21;16(8):1057-1071.

Chen CH, Lin YH, Chen CH, Wang YH, Yeh ML, Cheng TL, Wang CZ. (2018, Oct). Transforming growth factor beta 1 mediates the low-frequency vertical vibration enhanced production of tenomodulin and type I collagen in rat Achilles tendon. . PLoS One, 11;13(10):e0205258.

Chen YJ, Chang WA, Wu LY, Hsu YL, Chen CH*, Kuo PL. (2018, Jul). Systematic Analysis of Differential Expression Profile in Rheumatoid Arthritis Chondrocytes Using Next-Generation Sequencing and Bioinformatics Approaches. International journal of medical sciences, 13;15(11):1129-1142..

Wang YH, Wu JY, Kong SC, Chiang MH, Ho ML, Yeh ML, Chen CH*. (2018, Apr). Low power laser irradiation and human adipose-derived stem cell treatments promote bone regeneration in critical-sized calvarial defects in rats. . PLoS One, 5;13(4):e0195337

Developing Hyperscanning Brain-Computer Interfaces with AR/VR Technology to Decipher Inter-Brain Signatures of Spatial Navigation

Chun-Hsiang Chuang (莊鈞翔)

Assistant Professor

College of Education/Research Center for Education and Mind Sciences

National Tsing Hua University, Taiwan

Ph.D., National Chiao Tung University

Abstract

Spatial navigation is a central human cognitive skill across the entire lifespan. For adolescents, spatial ability can predict who will go into STEM fields. For elders, spatial navigation deficit is a cognitive marker for Alzheimer's disease. It is thus particularly urgent for us to understand the complex cognitive functions subserving spatial orientation, and to enhance spatial abilities in general. The overarching goal of this research is to explore the future of mutual understanding between humans teaming up to find a win-win solution to complex problem solving and augment human behavioral performance. In this talk, we will introduce: a VR environment with an omnidirectional treadmill, enabling users to walk endlessly in any direction; a brain dynamic rendering and interaction in an augmented reality mobile system; an experimental paradigms for spatial navigation studies; a robust hyperscanning EEG system that can carry out multisubject recording of different subjects with zero phase-lag synchronization. Some other studies relevant to the combination of VR/AR and EEG technology such as multitasking and mindfulness practice will be also introduced. We believe this technology could contribute to the tool development for the prevention and treatment of neurological disorders.

Selected recent publications:

CH **Chuang**, JT King, BS Wu, ZH Cao, YK Wang, CT Lin, 2018, March, 'Brain electrodynamic and hemodynamic signatures against fatigue during driving', *Frontiers in Neuroscience*, 1-12.

TN Do, **CH Chuang**, SJ Hsiao, CT Lin, YK Wang, 2019, June, 'Neural comodulation of independent brain processes related to multitasking', *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 1160-1169.

CT Lin, TY Hsieh, YT Liu, YY Lin, CN Fang, YK Wang, G Yen, N Pal, **CH Chuang*,** 2018, May, 'Minority oversampling in kernel adaptive subspaces for class imbalanced datasets', *IEEE Transactions on Knowledge and Data Engineering*, 950-962.

Z Cao, CT Lin, **CH Chuang**, KL Lai, SJ Wang, 2018, June, 'Exploring resting-state EEG complexity before migraine attacks,' *Cephalalgia,* 1296-1306.

CT Lin, **CH Chuang*,** S Kerick, T Mullen, TP Jung, LW Ko, SA Chen, JT King, K McDowell, 'Mind-wandering tends to occur under low perceptual demands during driving', *Scientific Reports* 2016, 6, 1-11.
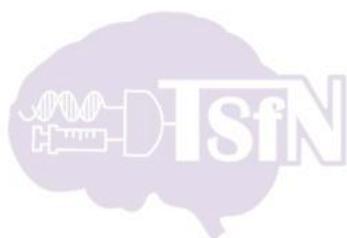
Normal pressure hydrocephalus:
A treatable disease presents like dementia
水能載舟，亦能覆舟

Host: Ko-Ting Chen (陳科廷)

Location: 細胞與個體生物研究所
Institute of Cellular and Organismic Biology (ICOB)

Time: Sep. 13, 11:45-13:00

Participate societies: Taiwan Neurological Society (台灣神經學學會)、 Taiwan Neurosurgical Society(台灣神經外科醫學會)

Normal pressure hydrocephalus (NPH) is a disease in elder population (age > 60 years) and has a clinical triad of gait unsteadiness, urinary incontinence and cognitive decline. However, since the neural function also start to decrease in this group of elder people, some patients with NPH may be mis-identified as degenerative dementia without being treated properly. On the contrary, there may be other patients treated as NPH who were actually degenerative dementia. In this nanosymposium, we will discuss clinical obstacles on diagnosis and treatment of NPH and share our experience in using brain metabolic imaging techniques to distinguish hydrocephalus from neurodegenerative dementia.

Toward diagnosing and understanding patients with normal pressure hydrocephalus

Ko-Ting Chen (陳科廷)

Attending physician, Brain Tumor Division, Department of Neurosurgery,

Chang Gung Memorial Hospital, Taoyuan, Taiwan

PhD candidate, Biomedical Engineering, Chang Gung University

MD, School of Medicine, National Yang Ming University

Abstract

Normal pressure hydrocephalus (NPH) is a mysterious disease resulting from impaired absorption of cerebrospinal fluid (CSF). The mysterious part is that "how and why" dysregulation of non-cellular fluid result in a global cerebral function decline. Since we humans are the only species of complicated higher cortical functions, one may understand the mystery only through examine patients with NPH. Since a "definite" diagnosis of idiopathic NPH can only be made until a patient's symptoms improved after the shunt procedure based on Japanese or International guidelines, a critical step is to identify the best candidates for shunting the overly accumulated CSF "preoperatively". Disproportionately enlarged subarachnoid space hydrocephalus (DESH) on magnetic resonance imaging or computed tomography has been proposed to be a noninvasive image marker with both diagnostic and prognostic values. Nevertheless DESH, as with other modalities such as CSF tap test, provides no functional information. Positron emission tomography (PET) uses radioisotope fluorodeoxyglucose (18F-FDG) which is uptake in brain regions and represents regional metabolism. Researchers are actively exploring this method especially in differentiating NPH from other neurodegenerative diseases. Today, I will discuss the dilemma and outlet of diagnosing patients with NPH and the potential advantages by having 18F-FDG PET in understanding patients with NPH.

Selected recent publications:

Ko-Ting Chen, Ya-Jui Lin, Wen-Yen Chai, Chia-Jung Lin, Pin-Yuan Chen, Chiung-Yin Huang, John S. Kuo, Hao-Li Liu, Kuo-Chen Wei. Neuronavigation-guided focused ultrasound (NaviFUS) for transcranial blood-brain barrier opening in recurrent glioblastoma patients: clinical trial protocol. *Annals of Translational Medicine*. (2020) doi: 10/21037/atm-20-344

Ko-Ting Chen, Kuo-Chen Wei, Hao-Li Liu. Theranostic strategy of focused ultrasound induced bloodbrain barrier opening for CNS disease treatment. *Frontiers in Pharmacology*. (2019) 10:86. 3. Po-An Chen, Yi-Chun Chen, Kuo-Chen Wei, **Ko-Ting Chen**. Awake craniotomy for a left panhippocampal diffuse low grade glioma in a deaf-mute patient using sign language. *World Neurosurgery*. (2019) doi: https://doi.org/10.1016/j.wneu.2019.11.129.

Ko-Ting Chen, Shih-Tseng, Chieh-Tsai Wu. The Clinical Value of Intraoperative Mobile Computed Tomography in Managing High-Risk Surgical Patients with Traumatic Brain Injury – A Single Tertiary Trauma Center Experience. *World Neurosurg* (2017) 98:727-733.e3

Ko-Ting Chen, Tai-Wei Erich Wu, Chi-Cheng Chuang, Yung-Hsin Hsu, Peng-Wei Hsu, Yin-Cheng Huang, Tzu-Kang Lin, Chen-Nen Chang, Shih-Tseng Lee, Chieh-Tsai Wu, Chen-Kan Tseng, Chun-Chieh Wang, Ping-Ching Pai, Kuo-Chen Wei, Pin-Yuan Chen. Corpus Callosum Involvement and Postoperative Outcomes of Patients with Gliomas. *J Neurooncol* (2015) 124:207-214

Normal pressure hydrocephalus, a reversible dementia

Yi-Chun Chen (陳怡君)

Chief, Dementia Branch, Department of Neurology, Chang Gung Memorial

Hospital, Linkou Medical center, Taiwan

Associate Professor, College of Medicine, Chang-Gung University

MD., Chung Shan Medical University

Abstract

The prevalence of dementia is increasing as global populations are rapidly aging. The number of people affected by dementia is expected to reach 131 million in the year 2050. Dementia is a clinical syndrome of cognitive and functional impairment. Age-standardized prevalence of dementia for those aged 60 years or older was estimated to be 5% to 7% in most world regions. Dementia is a heterogeneous disease entity. The most common forms of dementia are caused by neurodegeneration, such as Alzheimer's disease, Lewy body dementias, vascular dementia, and frontotemporal dementia. However, not all the people with cognitive impairment have neurodegeneration. There are a number of underlying diseases for cognitive impairment are potentially treatable and curable; the condition is so-called reversible dementia. Idiopathic normal pressure hydrocephalus (iNPH) is one of the clinical treatable conditions that are needed to be excluded by laboratory and imaging before the diagnosis of irreversible neurodegeneration is made. iNPH is a complex neurologic condition in which the CSF fails to drain properly and causes ventricle enlargement and cortical atrophy. In addition to the clinical triad of iNPH, i.e. urinary incontinence, unsteady and magnetic gait, and cognitive impairment, there are differences in the clinical and cognitive profile between neurodegenerative dementia and iNPH. Both clinical and imaging data are crucial for the diagnosis of iNPH, but the potential overlapping with neurodegenerative diseases make the differential diagnosis difficult. I will discuss the clinical hallmarks of iNPH and focus on the neuropsychological assessment in the differential diagnosis of iNPH.

Selected recent publications:

Chen YC, Tsao HH, Chu YC, Wang JJ, Lee JD, Chang PY, Hsu WC (2018) Exploring the spectrum of subcortical hyperintensities and cognitive decline. *J Neuropsychiatry Clin Neurosci* 30:130-8

Chen YC, Chiu YJ, Lin CH, et al. (2019) Indole compound NC009-1 augments APOE and TRKA in Alzheimer's disease cell and mouse models for neuroprotection and cognitive improvement. *Journal of Alzheimer's Disease* 67, 737-56.

Chen YC, Chou WH, Tsou HH, et al. (2019) A Post-hoc Study of D-amino Acid Oxidase in Blood as an Indicator of Post-stroke Dementia. *Frontiers Neurology* 26:10:402.

Chen YC, Liu YL, Tsai SJ, Kuo PH, Huang SS, Lee YS (2019) LRRTM4 and PCSK5 Genetic Polymorphisms as Markers for Cognitive Impairment in A Hypotensive Aging Population: A Genome-Wide Association Study in Taiwan. *J Clin Med.* 8, 1124.

Chen YC, Hsiao CC, Zheng WD, Lee RG, Lin R (2019) Artificial neural networks-based classification of emotions using wristband heart rate monitor data. *Medicine* 98:e16863.

Identifying Treatable Cognitive Impairment Patients with 18F-FDG PET

Tsung-Ying Ho (何宗穎)

Attending Physician, Department of Nuclear Medicine,

Chang Gung Memorial Hospital, Taoyuan, Taiwan

MD, Chang Gung University

Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is considered a treatable neurologic impairment. Patients with iNPH may sometimes have clinical cognitive symptoms that are difficult to differentiate with other age-related disorders such as dementia. 18F-FDG PET has shown its value in diagnosing and differentiating several types of dementia, including Alzheimer's disease, Dementia with Lewy Body (DLB), and behavioral variant frontotemporal dementia (bvFTD). In this talk, we will demonstrate the 18F-FDG PET hypometabolic patterns in patients with cognitive impairment and the role of selecting patients with iNPH for surgical intervention. Comparison of patients' 18F-FDG PET studies before and after surgical treatment and the corresponding interval change of clinical symptoms will be also discussed.

Selected recent publications:

Ho, T. Y., Chao, C. H., Chin, S. C., Ng, S. H., Kang, C. J., & Tsang, N. M. (2020). Classifying Neck Lymph Nodes of Head and Neck Squamous Cell Carcinoma in MRI Images with Radiomic Features. Journal of Digital Imaging, 1-6.

Guo, D., Jin, D., Zhu, Z., **Ho, T. Y.**, Harrison, A. P., Chao, C. H., ... & Lu, L. (2020). Organ at Risk Segmentation for Head and Neck Cancer using Stratified Learning and Neural Architecture Search. In Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition (pp. 4223-4232).

Jin, D., Guo, D., **Ho, T. Y.,** Harrison, A. P., Xiao, J., Tseng, C. K., & Lu, L. (2019, October). Accurate esophageal gross tumor volume segmentation in pet/ct using twostream chained 3d deep network fusion. In International Conference on Medical Image Computing and Computer-Assisted Intervention (pp. 182-191). Springer, Cham.

Cheng, C. T., **Ho, T. Y.**, Lee, T. Y., Chang, C. C., Chou, C. C., Chen, C. C., ... & Liao, C. H. (2019). Application of a deep learning algorithm for detection and visualization of hip fractures on plain pelvic radiographs. European radiology, 29(10), 5469-5477.

Ho, T. Y., Chou, P. C., Yang, C. T., Tsang, N. M., & Yen, T. C. (2015). Total lesion glycolysis determined per RECIST 1.1 criteria predicts survival in EGFR mutationnegative

patients with advanced lung adenocarcinoma. Clinical Nuclear Medicine, 40(6), e295-e299.

Metabolic Brain Network for 18F-FDG PET Imaging

Sheng-Yao Huang (黃聖堯)

Postdoctoral Research Fellow, Molecular Medicine Research

Center, Chang Gung University, Taiwan

PhD, National Yang-Ming University

Abstract

Normal pressure hydrocephalus (NPH) is an accumulation of cerebrospinal fluid (CSF) that causes the ventricles in the brain to become enlarged, sometimes with little or no increase in intracranial pressure (ICP). In most cases of NPH, the cause of blockage to the CSF absorptive pathways is unclear. Normal pressure hydrocephalus (NPH) is an important and treatable cause of neurologic impairment. Diagnosis is complicated due to symptoms overlapping with other neurodegenerative diseases. The pathophysiology underlying NPH is not well understood. In recently study, some study reports a FDGPET pattern of hypometabolism and this pattern may differentiate NPH from degenerative diseases and has the potential to serve as a biomarker for NPH in future studies. In future, we will used the graph theory technique to provides functional interregional connectivity information and to explore the underlying pathophysiological mechanisms of NPH. In this report, I will review our past findings in metabolic brain network analysis. We found two major key metabolic network patterns in different stages of Alzheimer's disease (AD). Metabolic brain network analysis has drawn attention as a tool to help with a clinical diagnosis and the evaluation of neuropsychiatric disease.

Selected recent publications:

S. Y. Huang, C.Y. Wu, K.J. Lin, I.T. Hsiao (2017) Difference in metabolic connectivity using 18F-FDG PET in MCI and Alzheimer's Disease. *Neurological Sciences* 381:259

S.Y. Huang, J.L. Hsu, K.J. Lin, H.L. Liu, S.P. Wey, I.T. Hsiao (2018) Characteristic patterns of interand intra-hemispheric metabolic connectivity in patients with stable and progressive mild cognitive impairment and Alzheimer's disease. *Scientific Reports* 8(1):13807

Wu KY, Hsiao IT, Chen CH, Liu CY, Hsu JL, **Huang SY**, Yen TC, Lin KJ, (2018) Plasma Aβ analysis using magnetically-labeled immunoassays and PET 18F-florbetapir binding in non-demented patients with major depressive disorder. *Scientific Reports* 8(1):2739

Wu KY, Lin KJ, Chen CH, Chen CS, Liu CY, **Huang SY**, Yen TC, Hsiao IT (2018) Diversity of neurodegenerative pathophysiology in nondemented patients with major depressive disorder: Evidence of cerebral amyloidosis and hippocampal atrophy. *Brain Behav* 8(7)

Sheng-Yao Huang, Jung-Lung Hsu, Kun-Ju Lin, and Ing-Tsung Hsiao, the Alzheimer's Disease Neuroimaging Initiative (2020) A Novel Individual Metabolic Brain Network for 18F-FDG PET Imaging. *Front Neurosci.* 14: 344.