Clinical applications of transcranial magnetic stimulation
經顱磁刺激的臨床應用

Host: Chi-Chao Chao(趙啟超)、 Der-Sheng Han (韓德生)

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

Time: Sep. 12, 16:45-18:00

Participate societies: Taiwan Neurological Society(台灣神經學學會)、 Taiwan Academy of Physical Medicine and Rehabilitation (台灣復健醫學會)

Neurological or psychiatric disorders often involve abnormal electrical activities in the neural networks, so electro-stimulation has been used to study brain function and as a strategy to diagnose and treat neuropsychiatric diseases. Transcranial Magnetic Stimulation (TMS) applies focal magnetic field-induced current to stimulate the brain and has been widely used in the past 20 years because of its non-invasive nature and its effectiveness in treating neuropsychiatric diseases by modulating the excitability of neural networks. In this nanosymposium, we will report on the clinical applications of TMS in treating neurological diseases and discuss its current limitations and solutions.

新旭生技

Visualizing and Treating Neurodegeneration

專注於神經退化性疾病 ，研發治療藥物與PET影像診斷藥物，
達成腦部精準醫療的目標。

小分子藥物平台

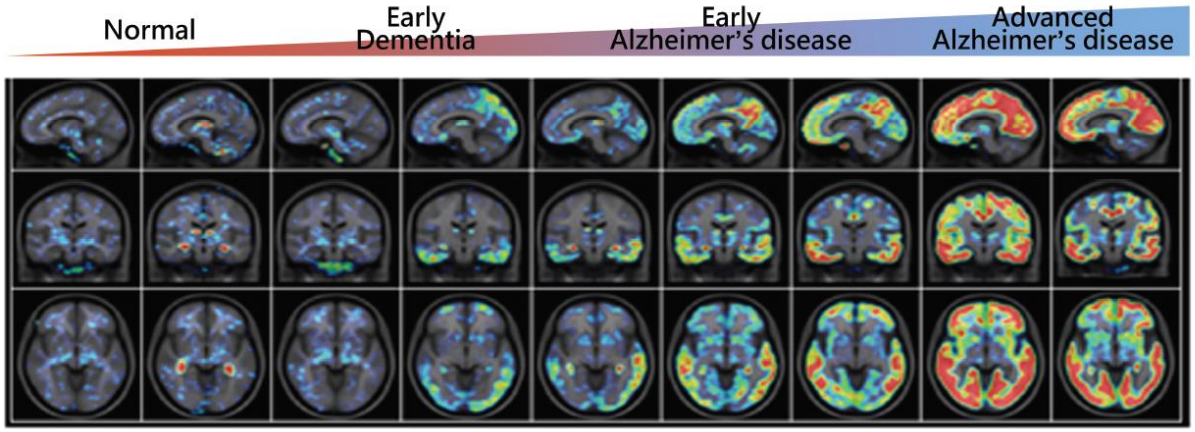
小分子化合物不僅可開發為PET示蹤劑，還可衍生成為治療藥物，改變或清除變異蛋白堆積。

抗體藥物平台

經由新的篩選技術和策略，從抗體庫中篩選出針對特定變異蛋白的單株抗體作為藥物。

Tau PET tracer

^{18}F-APN-1607 PET示蹤劑可以準確量化腦中不正常Tau蛋白堆積。除可分辨正常與失智症患者，同時也可以判斷阿茲海默症病人病情輕重，達成早期精準診斷與預測病情進展的目標。

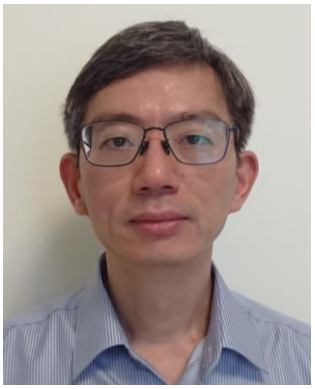


TSfN 跨領域神經科學國際研討會
TSfN Interdisciplinary Neuroscience Congress

APRINOIA Therapeutics

Abnormal motor cortical plasticity in movement disorders

Ming-Kuei Lu (呂明桂)
Attending Physician, Department of Neurology, China Medical University Hospital, Taiwan



MD, China Medical University

PhD, Goethe University

Abstract

Plasticity in motor cortex (M1) plays a pivotal role in motor learning and appropriate motor control in humans. Ample evidences have shown that abnormal M1 plasticity is associated with movement disorders such as Parkinson's disease and dystonia. Currently non-invasive evaluation of M1 plasticity is feasible with transcranial magnetic stimulation (TMS) techniques. By delivering repetitive TMS (rTMS) or paired associative stimulation (PAS) to M1, we can temporarily modulate M1 excitability and study M1 plasticity in the system level. In patients with Parkinson's disease and advanced essential tremor, the long-term potentiation-like M1 plasticity was found significantly impaired. The combined assessment of the microstructure of the corticospinal tract, namely the fractional anisotropy and the mean diffusivity, showed a normal range in the both patient groups. The findings suggested that the impaired M1 plasticity is probably not attributed to the downstream corticospinal tract. In healthy subjects, the corticocortical PAS of cerebellum and M1 can induce spike-timing dependent plasticity in M1. However, this kind of the plasticity was absent in patients with Parkinson's disease and spinocerebellar ataxia type 3. In a patient with gene-proved neurodegeneration with brain iron accumulation type 1, we found that the patient had impaired M1 plasticity and intracortical inhibition. The clinical symptom presented as dystonic tremor can be significantly alleviated by co-contraction of the trapezius muscle at the same side. Intriguingly the excitatory rTMS protocol could restore the intracortical inhibition in this patient, suggesting an association between the 'motor trick' and the intracortical inhibition. In summary, movement disorders can carry aberrant M1 plasticity. A better understanding of the functional role of M1 plasticity in motor control would be with clinical significance.

Selected recent publications:

Chen KH, Tsai CH, Wu RM, **Lu MK** (2016). Neurodegeneration with brain iron accumulation presenting motor trick and impaired motor cortical plasticity. Clin Neurol Neurosurg 141:95-97

Lu MK, Chen CM, Duann JR, Ziemann U, Chen JC, Chiou SM, Tsai CH (2016). Investigation of motor cortical plasticity and corticospinal tract diffusion tensor imaging in patients with Parkinson's disease and essential tremor. PLoS One 11(9):e0162265

Lu MK, Chen JC, Chen CM, Duann JR, Ziemann U, Tsai CH (2017). Impaired cerebellum to primary motor cortex associative plasticity in Parkinson's disease and spinocerebellar ataxia type 3. Front Neurol 8:445

Huang YZ, **Lu MK**, Antal A, Classen J, Nitsche M, Ziemann U, Ridding M, Hamada M, Ugawa Y, Jaberzadeh S, Suppa A, Paulus W, Rothwell J (2017). Plasticity induced by non-invasive transcranial brain stimulation: A position paper. Clin Neurophysiol 128(11):2318-2329

Huang Y, Chen JC, Chen CM, Tsai CH, **Lu MK** (2019) Paired associative electroacupuncture and transcranial magnetic stimulation in humans. Front Hum Neurosci 13:49

Application of repetitive transcranial magnetic stimulation in individuals with incomplete spinal cord injury

Chien-Hung Lai (賴建宏)

Associate Professor, Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taiwan

PhD, Biomedical Engineering, Chung Yuan Christian University

MD., Kaohsiung Medical University

Abstract

People who suffer from spinal cord injury (SCI) usually loss sensory and motor function of extremities that depend on the severity and location of the injury. Following SCI, brain reorganization and motorneuronal connection from brain to spinal cord play a crucial role in the recovery and rehabilitation of sensory and motor dysfunction of distal limbs. Hence, how to strengthen the plasticity of brain and spinal cord to optimize the functional outcome in people with SCI is a challenge.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and painless method to modulate motor cortex excitability and to induce long-lasting changes in cortical and corticospinal transmission. Therefore, rTMS has become one of popular neuroplasticity methods that improve motor function by modulating neuroplasticity of brain and spinal cord and has been applied over the arm and leg representations of the primary motor cortex to treat the consequences of SCI.

Here, I will introduce current evidences that used rTMS in humans with SCI. In addition, non-invasive electrical stimulation also has been used to activate the targeted neural pathways in the spinal cord. Current speech also will discuss the information in combined therapy of rTMS and non-invasive electrical stimulation in persons with incomplete SCI.

Selected recent publications:

Wang T-Y, Chen S-H, Peng C-W, Kang C-W, Chen Y-L, Chen C-L, Chou Y-L, **Lai C-H** (2017). Relevance of Nerve Conduction Velocity in the Assessment of Balance Performance in Older Adults with Diabetes Mellitus. Disabil Rehabil 3:1-9

Lin L-F, Chang K-W, Huang Y-Z, **Lai C-H**, Liou T-H, Lin Y-N (2019). Simultaneous stimulation in bilateral leg motor areas with intermittent theta burst stimulation to improve functional performance after stroke: a feasibility pilot study. Eur J Phys Rehabil Med 55:162-168

Tung Y-C, **Lai C-H**, Liao C-D, Huang S-W, Liou T-H, Chen H-C (2019). Repetitive Transcranial Magnetic Stimulation of Lower-Limb Motor Function in Patients with Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Rehabil 33:1102-1112

Hung E S-W, Chen S-C, Chang F-C, Shiao Y, Peng C-W, **Lai C-H** (2019). Effects of interactive video game–based exercise on balance in diabetic patients with peripheral neuropathy: an open-level, cross-over pilot study. Evid Based Complement Alternat Med 6: 4540709

Lai C-H, Sung W-H, Chiang S-L, Lu L-H, Lin C-H, Tung Y-C, Lin C-H (2019). Bimanual coordination deficits in hands following stroke and their relationship with motor and functional performance. J NeuroEng Rehabil 16: 101

Clinical application of rTMS in the treatment of motor dysfunction in children with cerebral palsy

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Chairman , Professor, Graduate Institute of Early Intervention, Chang Gung University, Taiwan

Abstract

Cerebral palsy (CP) is the most common childhood motor disability. Weakness, spasticity, and loss of dexterity are the major problems in patients with CP. Non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS) and transcranial electric stimulation (TES) has potential to augment the training effects in motor neurorehabilitation via the modulation on neuroplasticity. NIBS in children and adolescents is based on the data from 48 studies involving more than 513 children/adolescents (2.5-17.8 years of age). When safety guidelines are followed, both NIBS are safe modalities in children and adolescents with various neurological conditions and the side effects were mild and transient. Therefore, the rTMS is a safe, non-invasive, well-tolerated and feasible protocol applied to children with CP. rTMS is one of the most promising emerging NIBS that generates magnetic pulses to induce eddy currents in the brain area underlying the stimulation coil. Theta burst stimulation (TBS) is a novel form of rTMS that composed of short and low-intensity bursts of rTMS at 50Hz. Compared to conventional rTMS protocols, TBS yields consistent and long-lasting effects on motor-evoked potentials over a shorter period of time. In addition, TBS has an advantage of shorter treatment time as compared with conventional rTMS. In general, intermittent TBS (iTBS) produces short TBS trains intermittently to facilitate cortical excitability, while continuous (cTBS) represents a longer and continuous TBS train that suppresses cortical excitability. Previous studies showed r-TMS could improve motor function, balance control, gait, and decrease spasticity in children with CP. To the best of our knowledge, no studies had investigated the efficacy of TBS in patients with CP. Therefore, we initiated a study to further clarify the effect of TBS on motor functions in patients with CP.

Selected recent publications:

Chen, C. L. * (2019). Developmental trajectory of self-care in children with cerebral palsy with different manual abilities. *Developmental Medicine & Child Neurology, 61*(5), 508-508.

Chen, C. L. *, Chen, C. Y., Chen, H. C., Wu, C. Y., Lin, K. C., Hsieh, Y. W., & Shen, I. H. (2019). Responsiveness and minimal clinically important difference of Modified Ashworth Scale in patients with stroke. *European Journal of Physical and Rehabilitation Medicine, 55*(6), 754-760.

Chen YJ, Huang YZ, Chen CY, **Chen CL***, Chen HC, Wu CY, Lin KC, Chang TL : Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol*. 2019 Apr 25;19(1):69

Lai, C. J., Chen, C. Y., **Chen, C. L. ***, Chan, P. Y. S., Shen, I. H., & Wu, C. Y. (2017). Longitudinal changes in health-related quality of life in preschool children with cerebral palsy of different levels of motor severity. *Research in developmental disabilities, 61*, 11-18.

Chen HC, Kang LJ, **Chen CL***, Lin KC, Chen FC, Wu KP: Younger Children with Cerebral Palsy Respond Better Than Older Ones to Therapist-Based Constraint-Induced Therapy at Home on Functional Outcomes and Motor Control. *Physical & Occupational Therapy In Pediatrics.* 2016 Apr 36(2) 171-185.

TMS for disease therapy: limitations and possible solutions

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Director, Neuroscience Research Center, Chang Gung Memorial Hospital at Linkou, Taiwan

Professor of Neurology, Chang Gung University, Taiwan

PhD, Institute of Neurology, University College London, UK

MSc, Institute of Biomedical Engineering, National Cheng Kung University, TW

MD., School of Medicine, Taipei Medical University, TW

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has been recently approved for treating drug-resistant depression and some other disorders. However, the effects are known to be variable and responder rate could be low. Moreover, the therapeutic effects on other diseases have been inconsistent and limited. Hence, further improvement for therapy with non-invasive brain stimulation (NIBS) is demanded. For this purpose, three approaches are considered. First, to adjust the therapeutic dose to be optimal: The current dose for therapy could be insufficient for modulating the brain function for good. The conventional rTMS protocol requires 37.5 min for daily session for 4-6 week to treat depression. Theta burst stimulation (TBS) approved by FDA for depression treatment in 2018 shows similar benefits after a 3-min stimulation per day. The much shorter stimulation time leads to the expectation of dose increasing by a longer or multiple session(s) of TBS in one day. Second, to threat the brain as a network: NIBS is usually given to a single location to enhance or suppression the function of that area for disease therapy. However, brain works as a complicated network. Hence, it requires more dedicated and comprehensive studies to understand how to modulate the brain network in a right and efficient way. Third, to develop better techniques: Although rTMS or other techniques, e.g. tDCS, has shown the ability for brain modulation, the modulation is superficially limited to the cortical level and the effects are known variable. A better technique that can reach any location of brain with more consistent effects is required. For example, focused ultrasound at a non-thermal intensity has been demonstrated for neuromodulation on animals and humans without damaging the tissue and is considered a good candidate of the next generation of NIBS. With the help of these developments, hopefully, NIBS will be more efficient and powerful for treating neurological and psychiatric disorders in the future.

Selected recent publications:

Ni HC, Huang J, Wu CT, Wu YY, Chang CJ, Chen RS, **Huang YZ** *. The Impact of Sigle Session Intermittent Theta-Burst Stimulation over the Dorsolateral Prefrontal Cortex and Posterior Superior Temporal Sulcus on Adults with Autism Spectrum Disorder. Front Neurosci. 9;11:255. Doi: 10.3389/fnins.2017.002552017. 2017 May. (SCI)

Huang YZ *, Lu MK, Andrea Antal, Joseph Classen, Michael Nitsche, Ulf Ziemann, Michael Ridding, Masashi Hamada, Yoshikazu Ugawa, Shapour Jaberzadeh, Antonio Suppa, Walter Paulus, John Rothwell. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. Clinical Neurophysiology. 128(11): 2318-2329. doi: doi.org/10.1016/j.clinph.2017.09.007. 2017 Nov. (SCI)

Huang YZ, Chen RS, Fong PY, Rothwell JC, Chuang WL, Weng YH, Lin WY, Lu CS. Inter-cortical modulation from premotor to motor plasticity. Journal of Physiology-London. 2018 Sep;596(17):4207-4217. doi: 10.1113/JP276276. Epub 2018 Jul 5. (SCI)

Li CT*, **Huang YZ***, Bai YM, Tsai SJ, Su TP, Cheng CM. Critical role of glutamatergic and GABAergic neurotransmission in the central mechanisms of theta-burst stimulation. Hum Brain Mapp. 2019 Jan 1. doi: 10.1002/hbm.24485. [Epub ahead of print] (SCI)

Lin WY, Lin MS, Weng YH, Yeh TH, Lin YS, Fong PY, Wu YR, Lu CS, Chen RS, **Huang YZ ***. Association of Antiviral Therapy With Risk of Parkinson Disease in Patients With Chronic Hepatitis C Virus Infection. JAMA Neurology 2019;76(9):1019-1027. doi:10.1001/jamaneurol.2019.1368 (SCI)

Role of Glia in brain health and diseases
膠細胞對大腦健康與疾病的角色

Host: Yi-Hsuan Lee (李怡萱)

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

Time: Sep. 12, 16:45-18:00

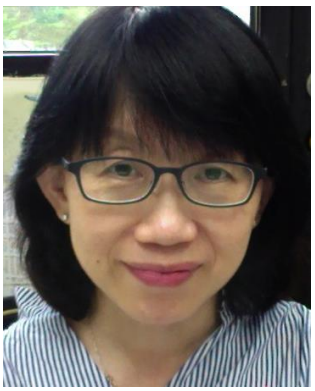
Participate societies: Taiwan Neuroscience Society (台灣基礎神經科學學會)、Taiwanese society of Biological Psychiatry and Neuropsychopharmacology (台灣生物精神醫學暨神經精神藥理學會)

In the vast and complex nervous system, long-distance and short-distance neural connections determine the healthy operation of various organs and the diversity of behavioral activities. Glial cells communicate with neurons and fine-tune the conductivity of neural networks through chemical transmission. In this nanosymposium, we will cover microglia-mediated neuroimmune response, astrocyte-regulated excitatory neurotransmission homeostasis and oligodendrogenesis and the involvement of glial cells in neurodegenerative and psychiatric disorders.

Microglial Galectin-3 as an innate immune response regulator in the brain of Huntington's disease

Yijuang Chern (陳儀莊)
Distinguished Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taiwan

PhD, University of Massachusetts



Abstract

Huntingtin (mHTT) is present in brain cells including microglia, the key innate immune cells of the brain. Galectin-3 (Gal3) is a lectin that binds to β-galactosides. Although Gal3 has been implicated in brain diseases, its function remains elusive. Our findings showed that the plasma Gal3 levels in HD patients and mice were higher than that in controls and correlated with disease severity. The levels of Gal3 in brains of HD patients and mouse models (R6/2) were also higher than those in the controls. The up-regulation of Gal3 by mHTT was cell-autonomous because this phenotype was observed in primary microglia. Further analyses indicate that the up-regulation of Gal3 in microglia contributed to inflammatory responses through NFκB and NLRP3 inflammasome-dependent pathways. Importantly, a portion of Gal3 appeared as puncta on lysosomal vesicles, indicating impairments of lysosomes. Knockdown of Gal3 suppressed inflammation, reduced mHTT aggregation, restored neuronal DARPP32 levels, and ameliorated motor dysfunction and shortened survival in R6/2 mice. Collectively, the suppression of Gal3 normalized the microglia-mediated pathogenesis, which suggests that Gal3 may be a novel therapeutic target for HD and other degenerative diseases as well.

Selected recent publications:

Siew JJ, Chen H-M, Chen H-Y, Chen H-L, Chen C-M, Soong B-W, Wu Yih-Ru, Chang C-P, Chan Y-C, Lin C-H, Liu F-T and **Chern Y**$^{\xi}$ (2019) Galectin-3 is required for the microglia-mediated brain inflammation in Huntington's disease. *Nature Comm* 10, 3473.

Hsu Y-T, Chang Y-G*, Liu Y-C*, Wang K-Y, Chen H-M, Yang S-S, Tsai C-H, Lien C-C$^{\xi}$, and **Chern Y**$^{\xi}$, (2019) Enhanced Na^{+}-K^{+}-$2Cl^{-}$ Cotransporter 1 Underlies Motor Dysfunction in Huntington's Disease. *Mov Disord*, 10.1002/mds.27651. (*These authors contribute equally; $^{\xi}$Co-corresponding authors)

Hsu Y-T, Chang Y-G, Chang C-P, Siew J-J, Chen H-M, Tsai C-H, and **Chern Y**$^{\xi}$ (2017) Altered behavioral responses to gamma-aminobutyric acid pharmacological agents in a mouse model of Huntington's disease. *Mov Disord* 32(11): 1600-1609.

Lin CY, Lai H-L, Chen H-M, Siew J-J, Hsiao C-T, Chang H-C, Liao K-S, Tsai S-C, Wu C-Y, Kitajima K, Sato C, Khoo K-H, **Chern Y**$^{\xi}$(2019). Functional roles of ST8SIA3-mediated sialylation of striatal dopamine D_2 and adenosine A_{2A} receptors. *Translational Psychiatry* 9: 209-221.

Chien T, Weng Y-T, Chang S-Y, Lai H-L, Chiu F-L, Kuo H-C, Chuang D-M, and **Chern Y**$^{\xi}$ (2018) GSK3β negatively regulates TRAX, a scaffold protein implicated in mental disorders, for NHEJ-mediated DNA repair in neurons. *Molecular Psychiatry*, 23:2375-2390.

Negative regulation for innate immunity: from Bedside to Bench

Yi-Yung Hung (洪一永)
Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

PhD, Chang Gung University

MD., Kaohsiung Medical University

Abstract

Depression is a with a high prevalent disease in modern society. Among mood disorder, major depression showed the greatest impact on patients, their families and society. The current mainstream of drug development has gradually changed from serotonin, dopamine, and norepinephrine towards multiple regulation. Among these, the relationship between anti-inflammatory and anti-depression have been extensively studied. Currently known antidepressants for elevating serotonin / norepinephrine have been found to be reduced inflammation. Through our previous research, it is known that patients receiving antidepressants (SSRI but not SNRI) can increase the expression of TNFAIP3. Through investigating negative regulatory system affected by SNRI in patient with major depressive disorder, we found a new possible mechanism for SNRI to decrease TNF-α expression. In addition, we found that the depressive-like behavior decreased after regulating the negative regulatory system.

Selected recent publications:

YY Hung, MK Wu, MC Tsai, YL Huang, HY Kang (2019) Aberrant Expression of Intracellular let-7e, miR-146a, and miR-155 Correlates with Severity of Depression in Patients with Major Depressive Disorder and Is Ameliorated after Antidepressant Treatment Cells 8 (7), 647

KW Huang, MK Wu, **YY Hung** (2019) Elevated TNIP3 mRNA Expression in TNF-α-Secreting Cells from Patients with Major Depressive Disorder. *Neuroimmunomodulation 26 (3), 153-158*

YY Hung, CC Lin, HY Kang, TL Huang. TNFAIP3, a negative regulator of the TLR signaling pathway, is a potential predictive biomarker of response to antidepressant treatment in major depressive disorder. Brain, behavior, and immunity 59, 265-272

Glutamate dysfunction in age-related cognitive decline

Chieh-Hsin Lin (林潔欣)
Chief and attending psychiatrist, Department of General Psychiatry, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

PhD, China Medical University, Taiwan

MD., National Yang Ming University, Taiwan

Abstract

The increasing prevalence of dementia in the elderly is a heavy burden of both patients and their family. Behavioral and Psychological Symptoms of Dementia (BPSD), which is particularly disturbing to caregivers, needs further investigation for its etiology and associative factors. The current main hypothesis for Alzheimer's disease (AD) is the deposit of β–amyloid in the brain. However, most interventions aiming to the clearance of β–amyloid deposit failed to improve the cognitive or global function of AD to date, implying that there should be other more important mechanisms unproven in the course of AD.

NMDA receptor (NMDAR) activation in glutamate neurotransmission plays an important role in learning and memory. NMDARs were found to decrease in the frontal lobe and hippocampus of patients with AD. Our previous study found that NMDAR enhancer-sodium benzoate (a D-amino acid oxidase inhibitor which can elevate D-serine level) can significantly improve the cognitive function of patients with early-phase AD, and also benefit a portion of moderate to severe AD patients. Our preliminary data showed that peripheral D-amino acid oxidase (DAO) levels were higher in patients with BPSD than healthy controls. Moreover, the DAO levels and certain antioxidants were correlated with treatment response of BPSD. Sodium benzoate can alter the levels of some antioxidants. These evidences suggest that the expressions of NMDAR have a potential to be biomarkers for BPSD. Approaches based on NMDAR dysfunction and oxidative stress may have potential to develop novel biomarkers for age-related cognitive decline.

Selected recent publications:

Lin CH, Chen PK, Chang YC, Chou LJ, Chen YS, Tsai G, Lane HY*: Benzoate, a D-Amino Acid Oxidase Inhibitor, for the Treatment of Early-Phase Alzheimer's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. *Biological Psychiatry*. 2014 May 1; 75(9):678-85.

Lin CH, Yang HT, Chiu CC, Lane HY*: Blood levels of D-amino acid oxidase vs. D-amino acids in reflecting cognitive aging. *Scientific Reports* 2017 Nov 1. 7:14849.

Lin CH, Lin CH, Chang YC, Huang YJ, Chen PW, Lane HY*: Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-Blind, placebo-controlled trial. *Biological Psychiatry* 2018 Sep 15;84(6):422-432.

Lin CH, Yang HT, Chen PK, Wang SH, Lane HY*: Sodium Benzoate for the Treatment of Behavioral and Psychological Symptoms of Dementia (BPSD): a Randomized, Double-blind, Placebo-controlled, 6-week Trial. *Journal of Psychopharmacology* 2019 Aug;33(8):1030-1033.

Lin CH, Chiu CC, Huang CH, Yang HT, Lane HY*: pLG72 levels increase in early phase of Alzheimer's disease but decrease in late phase. *Scientific Reports* 2019 Sep 13;9(1):13221.

Regulation of cellular ubiquitination in oligodendrocyte differentiation and myelination

Shun-Fen Tzeng (曾淑芬)
Distinguished Professor, Department of Life Sciences, National Cheng Kung University

PhD, School of Medicine, Virginia Commonwealth University

Abstract

Oligodendrocytes (OLs), a myelin forming glial population in the central nervous system (CNS), are generated from OL precursor cells (OPCs). Although OPCs are observed at the demyelinating site, these cells fail to differentiate into OLs. The metabolism of the myelinated membranes and proteins is critical for demyelinating OLs. We are particularly interested in understanding the regulation of the ubiquitination-associated proteasome and endosomal system in the regulation of OL differentiation and maturation. Our recent study has observed that the disruption of Lys63-linked ubiquitination (K63Ub) in OPCs promotes OL differentiation. However, the downregulation of BRCA1-BRCA2-containing complex subunit 3 (Brcc3), a K63-specific deubiquitinase (DUB), suppressed the differentiation of OPCs to OLs. The higher levels of sphingolipid GalC, MBP and PLP were also detected in K63Ub-immunoprecipitants and in endosome/lysosomal compartments after Brcc3 expression was reduced in OPCs. The in vivo study using an animal model of cuprizone (CPZ)-induced demyelination showed that OL differentiation from implanted Brcc3-KD OPCs into the demyelinating corpus callosum was defective. In comparison with the intact tissues collected from human patients suffering from multiple sclerosis, the lower amount of Brcc3 expressing OLs, but the greater number of OLs expressing high levels of early endosome antigen 1 (EEA1) and K63Ub were observed in the demyelinating tissues. The findings demonstrate that the counterbalance of the K63Ub machinery and DUB machinery for the cellular trafficking of myelin proteins plays the important role in the differentiation of OLs from OPCs in the demyelinating diseases.

Selected recent publications:

Fang KM, Yang CS, Lin TC, Chan TC, **Tzeng SF***. Induced interleukin-33 expression enhances the tumorigenic activity of rat glioma cells. *Neuro Oncol.* 2014; 16(4):552-566.

Wang CY, Yang SH, **Tzeng SF***. MicroRNA-145 as one negative regulator of astrogliosis. *Glia.* 2015; 63(2):194-205.

Wang CY, Deneen B, **Tzeng SF***. MicroRNA-212 inhibits oligodendrocytes during maturation by down-regulation of differentiation-associated gene expression. *Journal of Neurochemistry.* 2017; 143(1):112-125.

Wang CY, Deneen B, **Tzeng SF***. BRCA1/BRCA2-containing complex subunit 3 controls oligodendrocyte differentiation by dynamically regulating lysine 63-linked ubiquitination. *Glia.* 2019; 67(9):1775-1792 (Issue cover).

Sung HY, Chen WY, Huang HT, Wang CY, Chang SB, **Tzeng SF***. Down-regulation of interleukin-33 expression in oligodendrocyte precursor cells impairs oligodendrocyte lineage progression. *Journal of Neurochemistry* 2019;150(6):691-708 (Issue cover).

Neuromodulation
神經調控

Host: Cheng-Chia Lee (李政家)

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

Time: Sep. 12, 16:45-18:00

Participate societies: Taiwan Society for Stereotactic Functional Neurosurgery and Radiosurgery (台灣立體定位功能性神經外科及放射手術學會)、 Taiwanese Society of Biomedical Engineering (中華民國生物醫學工程學會)、 Taiwan Pain Society (台灣疼痛醫學會)

Neuromodulation has always been a mysterious part of neuroscience. Electrical stimulation on specific areas of the nervous system modulates neuronal activity, thereby promoting or inhibiting certain neuronal functions. The typical examples are deep brain stimulation for Parkinson's disease (PD) and spinal stimulator for pain. In recent years, percutaneous magnetic stimulation and focused ultrasound make neuromodulation less invasive. Due to advances in scanning imaging and computer technology, neuromodulation methods continue to develop and advance. In this nanosymposium, we will present the studies of deep brain stimulation for PD, focused ultrasound on epilepsy and spinal stimulator for pain.

Deep Brain Stimulation for Epilepsy

Kang-Du Liu (劉康波)

Chief, Department of Functional Neurosurgery, Neurological Institute, Taipei Veterans General Hospital, Taiwan

Assistant professor, School of Medicine, National Yang-Ming University, Taiwan

Abstract

1: Brain stimulation has been receiving increasing attention as an alternative therapy for epilepsy that cannot be treated by either antiepileptic medication or surgical resection of the epileptogenic focus.

2:The stimulation methods include transcranial magnetic stimulation (TMS) or electrical stimulation by implanted devices of the vagus nerve (VNS) deep brain structure (DBS)(thalamic or hippocampal), cerebellar or cortical areas.

3:TMS is the simplest and least invasive approach. However, the most common epileptogenic areas (mesial temporal structure) probably lie too deep beneath the surface of the skull for effective TMS. The efficacy of VNS in reducing the frequency or severity of seizures is quite variable and depends on many factors which are currently investigated. VNS is well-tolerated and approved in many countries. DBS is much more invasive than either TMS or VNS. Currently, a number of targets for DBS are investigated including caudate, centromedian or anterior thalamic nuclei, and subthalamic nucleus. Direct stimulation of the epileptic cortical focus is another approach to the neuromodulation in epilepsy. Finally, another line of research investigates the usefulness of implantable seizure detection devices (RNS).

4:In this lecture, I will focus on the DBS for epilepsy including the rationale, different targets choice, patient selection and the clinical outcomes. Among the different targets, anterior thalamic nucleus stimulation has demonstrated efficacy and there is evidence to recommend it as the target of choice.

Selected recent publications:

Dr Kang-Du Liu graduated from National Yang-Ming University, and received his neurosurgical residency training in Taipei Veterans General Hospital. After completing the training and acquired Board Certified Neurosurgery qualification, he worked as a visiting fellow in the Neurosurgical Department of UCSF from 2002-2003, Where he had trainings in surgery of Parkinson's disease and movement disorders , and also participated in studies regarding electrophysiology in Parkinson's disease and dystonia . He also got the master degree of Brain Science in the National Yang-Ming University in 2007. He is now the functional neurosurgeon of Neurosurgical Department, Taipei Veterans General Hospital. He also maintained a teaching post at School of Medicine, National Yang-Ming University as assistant professor. Dr Liou's main clinical and academic interests include surgical treatment of Parkinson's disease and movement disorders, interventional pain therapy, and neuromodulation of neurological disorders.

Research Interests: Surgery of Parkinson's disease and movement disorders, microelectrode recording and brain mapping, neuromodulation for neuropathic pain

Preclinical evidence of transcranial focused ultrasound for drug induced epilepsy suppression

Arthur Lung (龍震宇)

General Manager, NaviFUS Corp, Taiwan

PhD, National Yang-Ming University, Taiwan

Abstract

Drug resistant epilepsy is a chronical brain disease which could bother over one million patients now. Using neuromodulation to reduce the epileptic syndrome is achieved through invasive electrical stimulus like DBS, VNS, or RNS. But, all of them have difficulty to support the long-term or noninvasive surgical results. Transcranial focused ultrasound (FUS) is a novel device which can modulate neuron activity and has potential to suppress epileptic signals. We used PTZ and KA animal models to verify that the FUS can reduce the epileptic spikes and no hazard to brain tissue by FUS pulsations interference. In first PTZ model, we review the epilepsy-suppressing effect of various ultrasound parameters while the electroencephalogram (EEG) was concurrently monitored and postoperatively analyzed, animal behavior and histological examination. We observed that FUS exposure contributes to epileptic activity suppression, and this suppression effect depends on the selection of ultrasound parameters. Testing exposure parameters did not to cause tissue damage, inflammatory response, or behavioral abnormalities. In our second study, KA was intrahippocampally injected into rat brain for inducing focal epilepsy. The status epilepticus appeared on the 5th weeks after KA injection. The FUS was used to neuromodulate the hippocampus field in KA animal models on 10th week and 15th week. We found change in EEG and seizure frequency after ultrasound neuromodulation. The FUS inhibited the progression of epileptic signals and had the effect for four weeks. Compared with the FUS treatment group, the EEG signal in the sham group showed a progressive increased pattern after 10th week. These results indicate that the seizure of chronic epilepsy can be effectively inhibited by ultrasound neuromodulation.

Selected recent publications:

Chen, S. G., Tsai, C. H., Lin, C. J., Lee, C. C., Yu, H. Y., Hsieh, T. H., & Liu, H. L. (2020). Transcranial focused ultrasound pulsation suppresses pentylenetetrazol induced epilepsy in vivo. Brain Stimulation, 13(1), 35-46.

Park H, Popescu A, Sponge B (2014) Essential role of presynaptic NMDA receptors in activity-dependent BDNF secretion and corticosteroid LTP. Neuron 84:1009-22

Yang Y, Liu D-q, Sun Y-g, Zuo Y, Sponge B (2016) Remodeling of amygdala-auditory cortex synapses associated with auditory fear learning. Nat. Neurosci 19:1348-55

Spinal cord stimulation: Placement and management

Chung-Ren Lin (林中仁)
Chief, Department of Pain Management, National Cheng-Kung University Hospital, Taiwan

PhD, National Sun Yat-Sen University

MD., National Taiwan University

Abstract

Spinal cord stimulation (SCS) is a neuromodulation technique that is most effective for radicular pain associated with failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), painful ischemic peripheral vascular disease, and ischemic cardiac disease. SCS involves percutaneous or surgical implantation of electrodes in the epidural space, with power supplied by battery-powered implanted pulse generators. In traditional SCS, electrical stimulation modifies the processing of pain in the central nervous system by masking the sensation of pain with a pleasing paresthesia sensation, and this requires an overlapping stimulation-induced paranesthesia with the painful region. Newer forms of SCS (ie, burst and high-frequency HFSCS) do not require paresthesias to be effective, and may provide more effective pain relief for some conditions.

This topic will discuss presurgical psychological evaluation, patient screening, placement of spinal cord stimulators, management of anesthesia for spinal cord stimulator placement, and management of SCS for patients who undergo other surgical procedures. The technique for laminectomy and surgical lead placement, dorsal root ganglion, or peripheral nerve stimulation are discussed separately.

Selected recent publications:

Early high-frequency spinal cord stimulation treatment inhibited the activation of spinal mitogen-activated protein kinases and ameliorated spared nerve injury-induced neuropathic pain in rats. Liao WT, Tseng CC, Wu CH, Lin CR. Neurosci Lett. 2020 Mar 16;721:134763.

Pulsed Radiofrequency Attenuates Complete Freund's Adjuvant-Induced Epigenetic Suppression of Potassium Chloride Cotransporter 2 Expression. Liu CK, Liao WT, Chu YC, Yang CH, Chen KH, Wu CH, Lin CR. Pain Med. 2017 Apr 1;18(4):807-813.

Pulsed radiofrequency attenuates diabetic neuropathic pain and suppresses formalin-evoked spinal glutamate release in rats. Huang YH, Hou SY, Cheng JK, Wu CH, Lin CR. Int J Med Sci. 2016 Dec 8;13(12):984-991.

Epigenetic suppression of potassium-chloride co-transporter 2 expression in inflammatory pain induced by complete Freund's adjuvant (CFA). Lin CR, Cheng JK, Wu CH, Chen KH, Liu CK. Eur J Pain. 2017 Feb;21(2):309-321.

Reduction of spinal glycine receptor-mediated miniature inhibitory postsynaptic currents in streptozotocin-induced diabetic neuropathic pain. Chiu YC, Liao WT, Liu CK, Wu CH, Lin CR. Neurosci Lett. 2016 Jan 12;611:88-93.

The Novel Advances of Spinal Cord Stimulation in Technology, Concept, and Mechanism

Yeong-Ray Wen (溫永銳)

President, Taiwan Pain Society, Taiwan

Chief, Pain Management and Research Center, Dept of Anesthesiology,
China Medical University Hospital, Taichung, Taiwan

Associate Professor,
School of Medicine, China Medical University, Taichung, Taiwan

PhD, Taipei Medical University

Abstract

Spinal cord stimulation (SCS) has been used in pain management for decades and is the last line of choice when conventional medical and/or surgical therapies failed. SCS modulates neural signaling through spinal and supraspinal actions to reduce pain transmission, processing, and plasticity. However, empirical SCS advances have surpassed scientific understanding of mechanisms of action, which strongly limits optimization in SCS effectiveness and progress in device technology.

What exciting, for the past few years, is a beginning of neurostimulation technological advancements. These approaches dramatically improve the clinical efficacy and open up new concepts of clinical neuromodulation. These advancements include novel paradigms, such as Burst-SCS and KHFSCS, innovations in lead design to improve electrostimulation properties, change target to DRG, reduction in IPG capabilities and increase battery lifetime, and a closed-loop system. From a scientific perspective, it is important to know what are the mechanisms behind traditional and novel SCS-induced analgesia, and to which degree placebo effects confound our observations? A clear understanding will greatly improve the quality and efficacy of SCS analgesia and the progress of neuromodulation devices.

In my lecture, I will introduced the novel advances in SCS medicine, including the devices, the concepts, possible neural mechanisms underlying each design, and recent basic studies of SCS-like stimulation as well as derived knowledge in effects on cellular, molecular and circuit system. Besides, I will also introduce a brand-new, Taiwan-oriented SCS device, “Ultrahigh frequency SCS” and our preliminary findings in mechanism from animal studies and analgesic effects from human trials.

Selected recent publications:

Wen YR, Suter MR, Ji RR, Wu YS, Kohno T, Wang KC, Sun WZ, Wang CC. Activation of p38 mitogen-activated protein kinase in spinal microglia contributes to incision-induced mechanical allodynia. Anesthesiology 2009;110:155-65.

Lin ML, W.-T. Lin WT, Huang RY, Chen TC, Huang SH, Chang CH,Tsai SY, Chiu HW, Yeh GC, Lin CW, Wen YR*. Pulsed radiofrequency inhibited activation of spinal mitogen-activated protein kinases and ameliorated early neuropathic pain in rats. Eur J Pain 2014 May; 18: 659–670

Huang RY, Liao CC, Tsai SY, Yen CT, Lin CW, Chen TC, Lin WT, Chang CH, Wen YR*. Rapid and Delayed Effects of Pulsed Radiofrequency on Neuropathic Pain: Electrophysiological, Molecular, and Behavioral Evidence Supporting Long-term Depression. Pain Physician 2017; 20:E269-E283

Chang JH, Tsai SY, Zeng YJ, Liu YC, Li CY, Chen KB, Wen YR*. Ovarian Hormone-dependent and Spinal ERK Activation-regulated Nociceptive Hypersensitivity in Female Rats with Acid Injection-induced Chronic Widespread Muscle Pain. Sci Rep 2019;28;9(1):3077. doi: 10.1038/s41598-019-39472-z).

Huang RY, Poree L, Ho KY, Tsai SY, Liu YC, Tan PH, Wen YR*. Behavioral Survey of Effects of Pulsed Radiofrequency on Neuropathic and Nociceptive Pain in Rats: Treatment Profile and Device Implantation. Neuromoduation 2020; (Accepted)

Rare neurodegenerative disease
罕見神經退化性疾病

Host: Shang-Hsun Yang (楊尚訓)、 Guey-Shin Wang (王桂馨)

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

Time: Sep. 12, 16:45-18:00

Participate societies: Taiwan Neuroscience Society (台灣基礎神經科學學會)、Society for Neurological Rare Disorders-Taiwan (台灣神經罕見疾病學會)

Rare neurodegenerative diseases account for ~1/3 of rare diseases in Taiwan. Many of them currently have no cure and seriously affect patients' nervous functions and life quality. Basic and clinical studies have gradually uncovered the genetic factors, pathogenic mechanisms and new therapeutic options for these diseases. In this nanosympoisum, we will introduce the new treatment strategy for cerebellar atrophy and nucleotide-expansion diseases, the progress of hereditary neuropathy analysis in Taiwan and how genetic and environmental factors affect neurodegenerative diseases.

Therapeutic Development for SCA: Targeting Chaperones-Proteasome Pathway

Chiung-Mei Chen (陳瓊美)
Professor, Department of Neurology, Chang Gung Memorial Hospital, Taiwan

MD., Taipei Medical University, Taipei, Taiwan

Ph.D., Division of Molecular Genetics, Institute of Biochemistry and life Sciences, University of Glasgow, U.K.

Abstract

SCAs types 1, 2, 3, 6, 7, 17, and dentatorubropallidoluy-sianatrophy (DRPLA) as well as Huntington's disease (HD) are a group of neurodegenerative disorders caused by a CAG triplet repeat expansion encoding a long polyglutamine (polyQ) tract in the respective mutant proteins. The cytoplasmic and nuclear aggregate formation, pathological hallmark of polyQ diseases, is likely the initial process to trigger the subsequent pathological events. Transcriptional dysregulation, compromised chaperone-proteasome and autophagy pathway, decreased oxidative stress defense capacity and mitochondrial dysfunction have emerged as contributing factors to the pathogenesis of polyQ diseases. This talk will discuss the roles of impaired chaperone-proteasome pathway and increased oxidative stress in pathogenesis of SCA3 and SCA17 and the therapeutics targeting these pathways.

Selected recent publications:

Lin CY, Lin YC, Huang CY, Wu SR, **Chen CM***, Liu HL*. Ultrasound-responsive neurotrophic factor-loaded microbubble- liposome complex: Preclinical investigation for Parkinson's disease treatment. J Control Release. 2020;321:519-528.

Chen IC, Chang KH, Chen YJ, Chen YC, Lee-Chen GJ, **Chen CM***. Pueraria lobata and Daidzein Reduce Cytotoxicity by Enhancing Ubiquitin-Proteasome System Function in SCA3-iPSC-Derived Neurons. Oxidative Medicine and Cellular Longevity. Volume 2019, Article ID 8130481.

Lin CY, Tsai CH, Feng LY, Chai WY, Lin CJ, Huang CY, Wei KC, Yeh CK, **Chen CM***, Liu HL*. Focused ultrasound-induced blood brain-barrier opening enhanced vascular permeability for GDNF delivery in Huntington's disease mouse model. Brain Stimul. 2019;12(5):1143-1150.

Chang KH, Lee-Chen GJ, Huang CC, Lin JL, Chen YJ, Wei PC, Lo YS, Yao CF, Kuo MW, **Chen CM***. Modeling Alzheimer's Disease by Induced Pluripotent Stem Cells Carrying APP D678H Mutation. Mol Neurobiol. 2019;56(6):3972-3983.

Chen CM, Chen WL, Hung CT, Lin TH, Lee MC, Chen IC, Lin CH, Chao CY, Wu YR, Chang KH, Hsieh-Li HM, Lee-Chen GJ. Shaoyao Gancao Tang (SG-Tang), a formulated Chinese medicine, reduces aggregation and exerts neuroprotection in spinocerebellar ataxia type 17 (**SCA17**) cell and mouse models. Aging (Albany NY). 2019;11(3):986-1007.

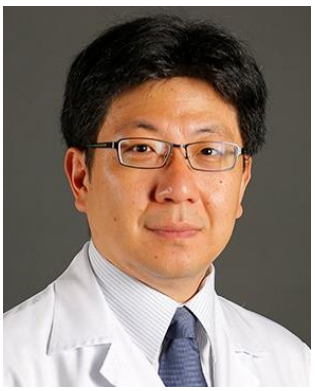
Genetic analysis of patients with inherited neuropathy in Taiwan

Yi-Chung Lee (李宜中)
Director, Division of Peripheral Nerve System Disorders, Neurological Institute, Taipei Veterans General Hospital

Professor, Department of Neurology, National Yang-Ming University

PhD, National Yang-Ming University

MD, National Yang-Ming University



Abstract

Inherited neuropathy is a group of diseases mainly involving peripheral nerves. From 2001 to 2018, we have recruited more than 581 unrelated patients with inherited neuropathy, including 427 with Charcot-Marie-Tooth diseases (CMT), 81 with hereditary neuropathy with liability to pressure palsy (HNPP), 57 with transthyretin-mediated familial amyloidotic polyneuropathy and 16 with distal hereditary motor neuropathy (dHMN) in Taiwan. To elucidate the genetic causes, we firstly screened the CMT patients for *PMP22* duplication and *GJB1* mutations. Then, we screened both CMT and dHMN patients for mutations in 61 neuropathy-implicated genes by a targeted NGS panel. Furthermore, we utilized whole exome sequencing to analyze selected large pedigrees with molecularly unassigned inherited neuropathy. With these strategies, we identified the pathogenic mutations in 312 (73.1%) CMT patients, including 266 (84.4%) patients with demyelinating CMT and 46 (41.1%) patients with axonal CMT, as well as 3 (18.8%) dHMN patients. At the same time, we also identified *GNB4* and *WARS* as novel causal genes for CMT and dHMN and classical axonal CMT as novel disease phenotype for a *TFG* mutation. *In vitro* functional studies also support the pathogenic role of these mutations in neuropathy. Our studies demonstrate the mutational spectrum of inherited neuropathy in Taiwan, expand the list of causal genes of inherited neuropathy and emphasize the importance of *GNB4*, *WARS*, and *TFG* in peripheral nerve functioning.

Selected recent publications:

Lee YC, Chung CP, Chang MH, Wang SJ, Liao YC (2020) *NOTCH3* cysteine-altering variant is an important risk factor for stroke in Taiwanese population. *Neurology* 94:e87-e96.

Hsu YH, Lin KP, Guo YC, Tsai YS, Liao YC, **Lee YC** (2019). Mutation spectrum of Charcot-Marie-Tooth disease among the Han Chinese in Taiwan. *Ann. Clin. Transl. Neurol.* 6:1090-1101.

Lee YC, Chung CP, Chao NC, Fuh JL, Chang FC, Soong BW, Liao YC (2018) Characterization of heterozygous *HTRA1* mutations in Taiwanese patients with cerebral small vessel disease. *Stroke* 49:1593-1601.

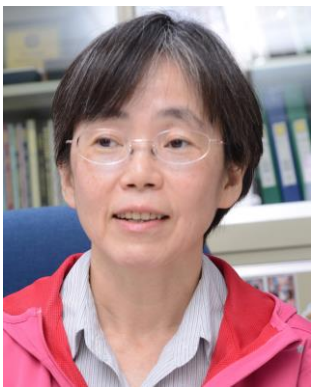
Tsai PC, Soong BW, Mademan I, Huang YH, Liu CR, Hsiao CT, Wu HT, Liu TT, Liu YT, Tseng YT, Lin KP, Yang UC, Chung KW, Choi BO, Nicholson GA, Kennerson ML, Chan CC, De Jonghe P, Cheng TH, Liao YC, Züchner S, Baets J, **Lee YC** (2017) A recurrent *WARS* mutation is a novel cause of autosomal dominant distal hereditary motor neuropathy. *Brain* 140:1252-66.

Tsai PC, Huang YH, Guo YC, Wu HT, Lin KP, Tsai YS, Liao YC, Liu YT, Liu TT, Kao LS, Yet SF, Fann MJ, Soong BW, **Lee YC** (2014) A novel *TFG* mutation causes Charcot-Marie-Tooth disease type 2 and impairs TFG function. *Neurology* 83:903-12.

Vcp overexpression and leucine supplementation increase protein synthesis and improve fear memory and social interaction of *Nf1* mutant mice

Yi-Ping Hsueh (薛一蘋)

Distinguished Research Fellow, Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan



PhD, National Yang-Ming University

Abstract

Neurofibromatosis type I (NF1) is a dominant genetic disorder manifesting, in part, as cognitive defects. Previous study indicated that neurofibromin (*NF1* protein) interacts with valosin-containing protein (VCP)/P97 to control dendritic spine formation, but the mechanism is unknown. Here, using $Nf1^{+/-}$ mice and transgenic mice overexpressing wild-type *Vcp/p97*, we demonstrate that neurofibromin acts with VCP to control ER formation and consequent protein synthesis, and regulates dendritic spine formation, thereby modulating contextual fear memory and social interaction. To validate the role of protein synthesis, we perform leucine supplementation in vitro and in vivo. Our results suggest that leucine can effectively enter the brain and increase protein synthesis and dendritic spine density of $Nf1^{+/-}$ neurons. Contextual memory and social behavior of $Nf1^{+/-}$ mice are also restored by leucine supplementation. Our study suggests that the "endoplasmic reticulum-protein synthesis" pathway downstream of neurofibromin and VCP is a critical regulator of dendritic spinogenesis and brain function.

Selected recent publications:

Shih, P.-Y., Hsieh, B.-Y., Lin, M.-H., Huang, T.-N., Tsai, C.-Y., Pong, W.-L., Lee, S.-P., and **Hsueh., Y.-P.*** (2020) CTTNBP2 controls synaptic expression of zinc-related autism-associated proteins and regulates synapse formation and autism-like behaviors. ***Cell Reports*** (in press)

Huang, T.-N.[#], Hsu, T.-T.[#], Hu, H.-T., Chuang, H.-C., Sun, T.-F., Tao, M.-H., Lin, J.Y., and **Hsueh, Y.-P.*** (2019) Interhemispheric connectivity potentiates the basolateral amygdalae and regulates social interaction and memory. ***Cell Reports*** 29:34-48.

Hung, Y.-F., Chen, C.-Y., Shih, Y.-C., Liu, H.-Y., Huang, C.-M., and **Hsueh, Y.-P.*** (Aug, 2018) Endosomal TLR3, TLR7, and TLR8 control neuronal morphology through different transcriptional programs. ***Journal of Cell Biology*** 217:2727-2742.

Shih, Y.-T. and **Hsueh, Y.-P.*** (2016) VCP and ATL1 regulate endoplasmic reticulum and control protein synthesis for dendritic spine formation. ***Nature Communications*** 7:11020.

Huang, T.-N., Chuang, H.-C., Chou, W.-H., Chen, C.-Y., Wang, H.-F., Chou, S.-J., and **Hsueh, Y.-P.*** (2014) *Tbr1* haploinsufficiency impairs amygdalar axonal projections and results in cognitive abnormality. ***Nature Neuroscience*** 17:240-247.

SUPT4H: a potential therapeutic target against nucleotide repeat expansion disorders

Tzu-Hao Cheng (鄭子豪)

Director, Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taipei, Taiwan

Ph.D., Rutgers University

Abstract

Expression of genes with expanded nucleotide repeats is accounting for a variety of neurodegenerative disorders, such as Huntington's Disease (HD) and familial Amyotrophic Lateral Sclerosis (ALS). HD is caused by CAG tri-nucleotide repeat expansion in the coding sequence of huntingtin gene (*HTT*), with a pathological hallmark of neural atrophy primarily in the striatum of afflicted individuals. In our earlier studies, we demonstrated that the transcription elongation factor SUPT4H is required for the expression of genes containing lengthy nucleotide repeats. When SUPT4H is down-regulated, it results in a decrease of mutant *HTT* expression and a delayed onset of disease of *HD* transgenic *mice.* Analogously, SUPT4H knockdown lowers the expression of mutant *C9ORF72*, a disease allele possessing a long stretch of GGGGCC hexa-nucleotide repeats, and results in a mitigation of mutant-allele-specific phenotypes in a drosophila C9-ALS model. In order to further evaluate the effect of SUPT4H on specimens that recapitulate the pathophysiological conditions of human subjects, induced pluripotent stem cells (iPSCs) collected from HD and C9-ALS patients were differentiated into GABAergic and motor neurons respectively. We found that, upon SUPT4H down-regulation, the abundance of mutant *HTT* in GABAergic neurons and mutant *C9ORF72* in motor neurons was decreased accordingly. Furthermore, the pathological hallmarks of mutant genes were reversed and accompanied with an enhancement of cell viability, supporting the notion that SUPT4H is a valid therapeutic target against HD and C9-ALS.

Selected recent publications:

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

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

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

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

PC Tsai, BW Soong, I Mademan, YH Huang, CR Liu, CT Hsiao, HT Wu, TT Liu, YT Liu, YT Tseng, KP Lin, UC Yang, KW Chung, BO Choi, GA Nicholson, ML Kennerson, CC Chan, PD Jonghe, **TH Cheng**, YC Liao*****, S Züchner, J Baets, and YC Lee***.** (2017). A recurrent WARS mutation is a novel cause of autosomal dominant distal hereditary motor neuropathy. *Brain* 140, 1252-1266

Brain development
大腦發育

Host: Shen-Ju Chou (周申如)

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

Time: Sep. 12, 16:45-18:00

Participate societies: Taiwan Neuroscience Society (台灣基礎神經科學學會)、Taiwan Magnetic Resonance Society (台灣磁共振學會)

A recent explosion in technological advances enables us to study brain in ways never before imagined. In this symposium, leading Taiwanese neuroscientists showcase how new technologies unlock the mysteries of the brain. As many neuropsychiatric diseases, like schizophrenia, autism, and ADHD, have their roots during early brain development, studying how the brain forms and how neurons are born and migrate to the right place and connect to form functional circuits provides a blueprint to help figure out how these processes might go wrong in diseases. This symposium also features the use of state-of-the-art imaging to non-invasively peer into the brain to learn about brain regional activities.

Transcription factors and cortical patterning

Shen-Ju Chou (周申如)
Associate Research Fellow, Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan

PhD, Baylor College of Medicine

Abstract

Mammalian cerebral cortex consists of multiple regions, including neocortex, archicortex, and paleocortex, each with specific functions, cytoarchitectures, gene expression patterns, neuronal properties, and input and output projection patterns. Patterning of the cerebral cortex into distinct cortical regions is an essential process during corticogenesis. It has been well established that patterning transcription factors play important role in setting up the size and position of primary sensory areas within the neocortex. However, how different cortical regions are specified remains unknown. During development, most of the projection neurons in the cerebral cortex arise from common progenitors in the dorsal telencephalon. We will discuss how transcription factors, which are expressed in graded fashion among these dorsal telencephalic cortical progenitors, specify neuronal properties in distinct cortical regions and how the border between cortical regions are established during development.

Selected recent publications:

Hsing HW, Zhuang ZH, Niou ZX, **Chou SJ**. (2019) Temporal differences in interneuron invasion of neocortex and piriform cortex during mouse cortical development. Cerebral Cortex 30:3015-3029.

Wang CF, Hsing HW, Zhuang ZH, Wen MH, Chang WJ, Briz CG, Nieto M, Shyu BC, **Chou SJ**. (2017) Lhx2 expression in postmitotic cortical neurons initiates assembly of the thalamocortical somatosensory circuit. Cell Rep. 18(4):849-856.

Chou SJ, Wang C, Sintupisut N, Niou ZX, Lin CH, Li KC, Yeang CH. (2016) Analysis of spatial-temporal gene expression patterns reveals dynamics and regionalization in developing mouse brain. Sci Rep. 6:19274.

Hsu CL, Nam S, Cui Y, Chang CP, Wang CF, Kuo HC, Touboul J and **Chou SJ**. (2015) Lhx2 regulates the timing of beta-catenin-depedent cortical neurogenesis. Proc Natl Acad Sci U S A. 112(39):12199-204

Chou SJ*, Babot Z*, Leingartner A, Studer M, Nakagawa Y and O'Leary DDM. (2013) Geniculocortical input drives genetic distinctions between primary and higher-order visual areas. Science. 340:1239-42. (*: equal contribution)

Searching for novel genes involved in cortical malformation

Jin-Wu Tsai (蔡金吾)

Associate Professor, Institute of Brain Science (IBS), School of Medicine,

National Yang-Ming University (NYMU), Taiwan

PhD, Columbia University

Abstract

Malformations of cortical development (MCDs) are heterogonous neurodevelopmental disorders that often result in epilepsy and developmental delay in children. To date, the genetic causes of a number of MCDs have been identified, including microcephaly (e.g., MCPH1, ASPM, CPAP, CDK5RAP2, and STIL), lissencephaly (e.g., LIS1, DCX, ARX, and TUBA1A), double cortex (e.g., DCX), periventricular nodular heterotopia (e.g., ARFGEF2), and tuberous sclerosis (e.g., TSC1 and TSC2). However, many genetic mutations involved in MCD pathogenesis still remain unidentified. Here we developed an in vivo genetic screen paradigm that utilizes in utero electroporation of transposons into mouse embryos to induce insertional mutations in neural stem cells (i.e., radial glial cells; RGCs). We identified 33 potential MCD genes, many of which have been previously implicated in neuronal development and related disorders, including holoprosencephaly, microcephaly and mental retardation. Bioinformatics analysis demonstrated that these candidate genes are highly associated with neuronal development and various neuronal disorders. To verify the clinical relevance of these candidate genes, we analyzed somatic mutations in brain tissue from patients with focal cortical dysplasia (FCD) using deep whole exome sequencing (WES) and found multiple mutations in many of these candidate genes. Functional knockdown of these genes in vivo by RNA interference (RNAi) or CRISP/Cas9 technology causes alterations in the distribution of neurons within the developing neocortex that are consistent with the screening results. These findings demonstrate that our new approach is able to mimic MCD pathogenesis and to identify various novel genes and pathways involved in cortical development.

Selected recent publications:

Tsai MH, Muir AM, Wang WJ, Kang YN, Yang KC, Chao NH, Wu MF, Chang YC, Porter BE, Jansen LA, Sebire G, Deconinck N, Fan WL, Su SC, Chung WH, Almanza Fuerte EP, Mehaffey MG, University of Washington Center for Mendelian Genomics, Ng CC, Chan CK, Lim KS, Leventer RJ, Lockhart PJ, Riney K, Damiano JA, Hildebrand MS, Mirzaa GM, Dobyns WB, Berkovic SF, Scheffer IE, **Tsai JW***, Mefford HC* (2020) Pathogenic variants in CEP85L cause sporadic and familial posterior predominant lissencephaly. *Neuron* 106(2):237-245

Ibrahim RB, Yeh SY, Lin KP, Ricardo F, Yu TY, Chan CC, **Tsai JW***, Liu YT* (2020) Cellular secretion and cytotoxicity of transthyretin mutant proteins underlie late onset amyloidosis and neurodegeneration. *Cell Mol Life Sci* 77(7):1421-1434

Chang CH, Zanini M, Shirvani H, Cheng JS, Yu H, Feng CH, Mercier AL, Hung SY, Forget A, Wang CH, Cigna SM, Lu IL, Chen WY, Leboucher S, Wang WJ, Ruat M, Spassky N, **Tsai JW***, Ayrault O* (2019) Atoh1 controls primary cilia formation to allow for SHH-triggered granule neuron progenitor proliferation. *Dev Cell* 48(2):184-199.e5

Lu IL, Chen C, Tung CY, Chen HH, Pan JP, Chang CH, Cheng JS, Chen YA, Wang CH, Huang CW, Kang YN, Chang HY, Li LL, Chang KP, Shih YH, Lin CH, Kwan SY, **Tsai JW*** (2018) Identification of genes associated with cortical malformation using a transposon-mediated somatic mutagenesis screen in mice. *Nat Commun* 9(1):2498

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陳右穎

Abstract

Selected recent publications:

Novel Pathogenic Mechanisms for Neurodevelopmental Disorders

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Abstract

Neurodevelopmental disorders are a group of diseases in which the development of brain is impaired. The pathogenic mechanisms for neurodevelopmental disorders are not well-investigated despite of their high prevalence and social and economic burden. Currently, we focus on three neurodevelopmental disorders with high prevalence rate (PR): epilepsy (PR: 8/1,000), anxiety (PR: 1/50), and autism spectrum disorder (PR: 1/54). We use genetic engineered mice and human-induced pluripotent stem cells (hiPSCs)-derived cortical neurons and cerebral organoids as model organisms to explore novel pathogenic mechanisms for neurodevelopmental disorders in molecular, cellular, circuitry, and behavioral manner. Our long-term goal is to provide novel therapeutic strategies for neurodevelopmental disorders.

Selected recent publications:

Hsu CL, Chou CH, Huang SC, Lin CY, Lin MY, Tung CC, Lin CY, Lai IP, Zou YF, Youngson NA, Lin SP, Yang CH, Chen SK, Gau SS, **Huang HS** (2018) Analysis of experience-regulated transcriptome and imprintome during critical periods of mouse visual system development reveals spatiotemporal dynamics. *Hum Mol Genet* 27 (6):1039-1054.

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