Neurofilament light chain: emerging evidence in neuropsychiatric disorders

Yu-Li Liu(劉玉麗)
Investigator, Center for Neuropsychiatric Research, National Health Research Institutes, Miaoli County, TAIWAN

Ph.D., East Tennessee State University

Abstract

Neurofilament light chain (NFL) is a protein located mainly in the axon region of myelinated brain neuron. This small protein has been studied intensively for its characteristic of sending brain neuronal damage messages toward the peripheral blood. It makes diagnoses of brain injuries possible through taking peripheral blood rather than cerebral spinal fluid. Using single molecule array method for NFL concentration measurement as an in vitro diagnostic device for neurodegenerative diseases, such as dementia, amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease, has already been approved in Europe. Recent studies have also shown that peripheral blood NFL level may indicate the severity of psychiatric diseases, including schizophrenia, major depressive disorder, and substance use. In this report session, the researchers will report the discovery of NFL in psychiatric diseases and its role in the pathological symptom. I will summarize recent literature reports on NFL that reveal its potential applications for both basic and clinical research.

Selected recent publications:

1. Huang, MC, Chung, RH, Lin, PH, Kuo, HW, Liu, TH, Chen, YY, Chen, ACH, **Liu, YL**. (correspondence) (2022) Increase in plasma CCL11 (Eotaxin-1) in patients with alcohol dependence and changes during detoxification. Brain Behavior and Immunity. 99:83-90.

2. Chen, MH, **Liu, YL**, Kuo, HW, Tsai, SJ, Hsu, JW, Huang, KL, Tu, PC, Bai, YM. (2022) Neurofilament light chain is a novel biomarker for major depression and related executive dysfunction. Int J Neuropsychopharmacol.25(2):99-105.

3. Chang, HM, Chen, PY, Fang, CP, Liu, TH, Wu, CT, Hsu, YC, Kuo, HW, **Liu, YL,** (correspondence), Huang, MC. (2021/7) Increased nectin-4 levels in chronic ketamine abusers and the relationship with lower urinary tract symptoms. Environ ToxicolPharmacol. 87:103714.

4. **Liu, YL**, Bavato, F., Chung, AN, Liu, TH, Chen, YL, Huang, MC, Quednow, B. B. (2021) Neurofilament light chain as novel blood biomarker of disturbed neuroaxonal integrity in patients with ketamine dependence. World J Biol Psychiatry. 27:1-9.

5. Fang, CP, Liu, TH, Chung, RH, Tsou, HH, Kuo, HW, Wang, SC, Liu, CC, Liu, SC, Chen, ACH, **Liu, YL**. (correspondence) (2020) Genetic variants in NECTIN4 encoding an adhesion molecule are associated with continued opioid use. PLoS One. 15(6), e0234549.

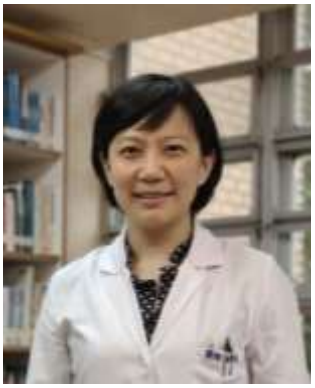
Exploring the role of neurofilament light chain in addiction

Ming-Chyi Huang(黃名琪)

Chief and Staff Psychiatrist, Department of Addiction Sciences, Taipei City Psychiatric Center, Taipei City Hospital, Taipei, TAIWAN

Adjunct Professor, Department of Psychiatry, Taipei Medical University, Taipei, Taiwan

M.D., Ph.D.,



Abstract

Substance use disorders have been associated with persistent neurocognitive impairment and structural brain abnormalities. Because brain imaging facilities are not universally available for healthcare systems, it may be feasible to look for a reliable and adequate substitute indicator for clinicians to evaluate and monitor the neurotoxicity severity. We examined the level of NFL in patients with ketamine dependence (KD) and alcohol dependence (AD) the explored its relationship with clinical characteristics. We found significantly increased NFL levels following chronic and heavy ketamine or alcohol use. In patients with KD, we found pronounced increase of NFL levels in the those comorbid with MDD. The observation warrants further investigation of a potential neuroaxonal vulnerability of depressed patients to prolonged ketamine exposure. In addition, NFL level might be a novel indicator for AD and reflect clinical severity in craving and psychological symptoms (anxiety and depression). Also, the aldehyde dehydrogenase gene polymorphism rs671 seemed to influence the level of NFL. These observations collectively indicate NFL levels may serve as a potential indicator for neurotoxicity related to addictive disorders.

Selected recent publications:

1. **Huang, MC,** Chung, RH, Lin, PH, Kuo, HW, Liu, TH, Chen, YY, Chen, ACH, Liu, YL. (correspondence) (2022) Increase in plasma CCL11 (Eotaxin-1) in patients with alcohol dependence and changes during detoxification. *Brain Behavior and Immunity*.Jan;99:83-90.

2. Liu, YL, Bavato, F., Chung, AN, Liu, TH, Chen, YL, **Huang, MC*,**Quednow, B. B. (2021) Neurofilament light chain as novel blood biomarker of disturbed neuroaxonal integrity in patients with ketamine dependence. *World J Biol Psychiatry*. 27:1-9.

3. **Huang MC,** Chen CH, Chen LY, Chang HM, Chen CK, Lin SK, Xu K. (2020) Chronic Ketamine Abuse Is Associated with Orexin-A Reduction and ACTH Elevation. *Psychopharmacology*, Jan, 237 (1), 45-5

4. Cheng WJ, Chen CH, Chen CK, **Huang MC***, Pietrzak RH, Krystal JH, Xu K. (2018) Similar psychotic and cognitive profile between ketamine dependence with persistent psychosis and schizophrenia. *Schizophr Res*, 2018 Sep;199:313-318

5. Wang LJ, Chen CK, Lin SK, Chen YC, Xu K, **Huang MC***. (2018) Cognitive profiles of ketamine-dependent patients in comparisons to healthy controls and methamphetamine abusers. *Psychopharmacology*, Jul; 235(7):2113-21.

Neurofilament Light Chain Is a Novel Biomarker for Major Depression and Related Executive Dysfunction

Mu-Hong Chen
Attending Psychiatrist, Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

Department of Psychiatry, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

M.D., Ph.D., National Yang Ming Chiao Tung University.

Abstract

Background: Evidence suggests that major depressive disorder is related to neuroaxonal injury and that neurofilament light chain (NfL) is a biomarker of neuroaxonal injury. In addition, proinflammatory cytokines have been reported to be associated with major depression and neuroaxonal injury. **Methods:** Forty patients with major depression and 40 age- and sex-matched healthy control subjects were enrolled for the measurement of NfL and proinflammatory cytokines and assessment of executive function. General linear models were used to examine the association between NfL levels, proinflammatory cytokine levels, and executive function. **Results:** Patients with major depressive disorder exhibited significantly higher NfL levels ($p = 0.007$) than the control subjects. NfL levels were positively related to log-transformed levels of tumor necrosis factor (TNF)-α ($p = 0.004$). Higher levels of NfL ($p = 0.002$) and TNF-α ($p = 0.013$) were associated with greater deficits in executive function. **Discussion:** NfL was a novel biomarker for major depressive disorder and related executive dysfunction. Further studies are necessary to elucidate the role of NfL in the pathophysiology of major depression and related cognitive impairment.

Selected recent publications:

1. **Chen MH**, Chang WC, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, Huang WS, Su TP. Functional dysconnectivity of frontal cortex to striatum predicts ketamine infusion response in treatment-resistant depression. Int J Neuropsychopharmacol. 2020 Jul 30:pyaa056.

2. **Chen MH**, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, Hong CJ, Tu PC, Cheng CM, Su TP. Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression. J Clin Psychiatry. 2020 Nov 10;81(6):20m13232.

3. **Chen MH**, Kao CF, Tsai SJ, Li CT, Lin WC, Hong CJ, Bai YM, Tu PC, Su TP. Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. Genomics. 2020 Dec 25:S0888-7543(20)32077-2.

4. **Chen MH**, Cheng CM, Gueorguieva R, Lin WC, Li CT, Hong CJ, Tu PC, Bai YM, Tsai SJ, Krystal JH, Su TP. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. Neuropsychopharmacology. 2019 Aug 17.

5. **Chen MH,** Liu YL, Kuo HW, Tsai SJ, Hsu JW, Huang KL, Tu PC, Bai YM. Neurofilament Light Chain Is a Novel Biomarker for Major Depression and Related Executive Dysfunction. Int J Neuropsychopharmacol. 2022 Feb 11;25(2):99-105.

The Interplay of Stress, Inflammation, and Nutrition in Depression

Kuan-Pin Su(蘇冠賓)

Professor and Deputy Superintendent, An-Nan Hospital, China Medical University, Tainan, Taiwan

PI, Mind-Body Interface (MBI-Lab), Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

M.D., Kaohsiung Medical College, Kaohsiung, Taiwan

Ph.D. Institute of Psychiatry, King's College London, UK

Abstract

The increasing global burden calls for the development of novel approaches to tackle unmet needs in prevention and treatment of depression underlying biological, psychological and social dysregulations. Depressed patients with chronic low-grade inflammation might be classified as a subgroup of major depressive disorder (MDD); therefore, looking for antidepressant therapies from anti-inflammatory pathways could improve treatment effectiveness for this subgroup of patients. Omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) are anti-inflammatory both in peripheral organs and central nervous systems and have clinically applied in the treatment and prevention of depression, cardiovascular diseases, dyslipidaemia, diabetes and arthritis. Anthropological studies suggest that human beings evolved to a modern diet with less than one-tenth of omega-3 to omega-6 PUFAs intake ratio, which leads to a constitutional bias toward chronic systemic inflammatory status to explain dramatically increasing of depression and chronic medical illnesses in modern world. The presentation is to provide our recent clinical and pre-clinical studies and an overview about the role of inflammation in "mind-body" comorbidity and present anti-inflammatory mechanisms by which n-3 PUFAs may orchestrate the molecular and cellular functions and facilitate the therapeutic pathways in chronic medical illnesses and depression.

Selected recent publications:

1. Yang CP, Chang CM, Yang CC, Pariante CM,Su KP*. Long COVID and long chain fatty acids (LCFAs): Psychoneuroimmunity implication of omega-3 LCFAs in delayed consequences of COVID-19. **Brain Behavior and Immunity** 2022 Apr 4;103:19-27.

2. Cheng SW, Li JX, Chien YC, Chang JP, Shityakov S, Huang SY, Galecki P, Su KP*. Genetic Variations of Ionotropic Glutamate Receptor Pathways on Interferon-α-induced Depression in Patients with Hepatitis C Viral Infection. **Brain Behavior and Immunity** 2021 Mar; 93:16-22.

3. Yang B, Lin L, Bazinet RP, Chien YC, Chang JPC, Satyanarayanan SK, Su HX, Su KP*. Clinical efficacy and biological regulations of omega-3 PUFA-derived endocannabinoids in major depressive disorder. **Psychotherapy and Psychosomatics** 2019;88(4):215-224.

4. Bosini A, Nicolaou A, Camacho-Munoz MD, Kendall A, Di Benedetto MG, Giacobbe J, **Su KP***. Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. **Molecular psychiatry** 2020Nov;26(11):6773-6788.

5. Lin YW, Wu AIC, Su HX, **Su KP***. Transient receptor potential V1 (TRPV1) modulates the therapeutic effects for comorbidity of pain and depression: The common molecular implication for electroacupuncture and omega-3 polyunsaturated fatty acids. **Brain Behavior and Immunity** 2020 Oct; 89: 604-614.

Loss of Functionof Shaker type Potassium Channels caused Epileptic Encephalopathy

Meng-Han Tsai(蔡孟翰)
Professor, Department of Neurology

Director, Division of Epilepsy and Brain Function

Director, Genomics and Proteomics Core Laboratory

Deputy Director, Department of Medical Research

M.D. Ph.D.Kaohsiung Chang Gung Memorial Hospital,

Chang Gung University, Taiwan

Abstract

Potassium (K+) channels are essential for the regulation of neuronal membrane potential and electrophysiological excitability. The Shaker-type potassium channels (Kv1) family contains 8 members including Kv1.1-Kv1.8. Six were prominently expressed in the CNS (Kv1.1-6). Hitherto, two of the Kv1 genes(*KCNA1* and *KCNA2*)have been reported to cause human epilepsies. In this study, we identified three patients with de novo missense pathogenic variants in three additional Shaker-type channel genes (*KCNA3*, *KCNA4*, and *KCNA6*). All variants were located in important functional domains such as the selectivity filter or the S6 hinge responsible for gating. Clinically, they presented as early-onset epileptic encephalopathy which subsided after the infantile period. Electrophysiological studies demonstrated loss of function effects in two of the variants, which could impair repolarization of the action potentials causing hyperexcitable neuronal activities. The disease course coincided with the age-related expression of these genes. Our findings expand the list of potassium channels genes, especially the Shaker-type, that cause human epilepsies.

Selected recent publications:

1. Pathogenic Variants in CEP85L Cause Sporadic and Familial Posterior Predominant Lissencephaly. M.-H. H. Tsai, A. M. Muir, W.-J. J. Wang, Y.-N. N. Kang, K.-C. C. Yang, N.-H. H. Chao, et al. *Neuron* 2020 Vol. 106 Issue 2 Pages 237--245.e8

2. Impairment in dynein-mediated nuclear translocation by BICD2 C-terminal truncation leads to neuronal migration defect and human brain malformation. M. H. Tsai, H. Y. Cheng, F. S. Nian, C. Liu, N. H. Chao, K. L. Chiang, et al. *Acta neuropathologica communications* 2020 Vol. 8 Issue 1 Pages 106

3. PRRT2 missense mutations cluster near C-terminus and frequently lead to protein mislocalization. M. H. Tsai, F. S. Nian, M. H. Hsu, W. S. Liu, Y. T. Liu, C. Liu, et al. *Epilepsia*2019 Vol. 60 Issue 5 Pages 807—817.

4. Etiology of hippocampal sclerosis: evidence for a predisposing familial morphologic anomaly. M. H. Tsai, H. R. Pardoe, Y. Perchyonok, G. J. Fitt, I. E. Scheffer, G. D. Jackson, et al. *Neurology* 2013 Vol. 81 Issue 2 Pages 144-9

5. Clinical genetic study of the epilepsy-aphasia spectrum. M. H. Tsai, D. F. Vears, S. J. Turner, R. L. Smith, S. F. Berkovic, L. G. Sadleir, et al. *Epilepsia* 2013 Vol. 54 Issue 2 Pages 280-7.

EpileptogenesisIn Cerebral Cavernous Malformations: Genomic Landscape, Biomarkers And Neuroplasticity

Yo-Tsen Liu(劉祐岑)MD, PhD
台北榮民總醫院神經醫學中心神經內科癲癇科主治醫師

Division of Epilepsy, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan.

國立陽明交通大學醫學系兼任副教授

School of Medicine, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan.

Abstract

Cerebral cavernous malformation (CCM), characterized by enlarged, blood-filled endothelial compartments within the venous-capillary vascular bed, is the most frequent epileptic substrate of cerebral vascular malformations.Epilepsy is the leading clinical manifestation of CCM, observed in 50% of patients.However, the clinical behavior of a CCM lesion could be highly variable and it is quite challenging to predict the epilepsy risk and outcome of different lesions.The uncertainty thus leads to the consensus of ideal treatment for CCMremains inconclusive.Familial CCM and some sporadic cases caused by loss-of-function mutations in one of the three genes, *CCM1*, *CCM2* and *CCM3*, with the hallmark of multiple lesions, have significant higher risk of CCM-related epilepsy (CRE).Recently, the substantial contribution of somatic mutations to the epileptogenetic mechanism of CCM has been recognized.Understanding the genomic landscape is essential to decipher the mechanisms of the development and progression of CRE. It is also important to search biomarkers from the transcriptome, proteome and connectome of CCM which can correlate with the patient's seizureoutcome and other clinical relevant phenotypes. Further, the key molecules shaping the CCM microenvironments and the whole picture of the crosstalk between abnormal vasculogenesis and altered neuronal plasticity could be unraveled. The goal is to improve precision treatment of CCM.

Selected recent publications:

1. Clinical characteristics and long-term outcome of cerebral cavernous malformations-related epilepsy. Shih YC, Chou CC, Peng SJ, Yu HY, Hsu SPC, Lin CF, Lee CC, Yang HC, Chen YC, Kwan SY, Chen C, Wang SJ, Lin CJ, Lirng JF, Shih YH, Yen1 DJ, Liu YT*. Epilepsia, April 19, 2022 accepted.

2. Novel Lissencephaly-Associated DCX Variants in the C-terminal DCX Domain Affect Microtubule Binding and Dynamics. Lin JR#, Cheng JF#, **YT Liu**, Hsu TR, Lin KM, Chen C, Lin CL, Tsai MH, Tsai JW*, Epilepsia, Feb 22, 2022 accepted.

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

4. Biophysical characterization and pharmacological modulation of Transthyretin Ala97Ser mutant. **YT Liu**, YJ Yen, F Ricardo, Y Chang, PH Wu, SJ Huang, KP Lin*, TY Yu*. Ann Clin Transl Neurol. 2019 Oct;6(10):1961-1970. doi: 10.1002/acn3.50887. Epub 2019 Sep 10.

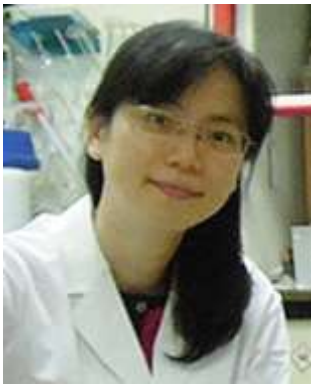
5. PRRT2 mutations lead to neuronal dysfunction and neurodevelopmental defects. **Liu YT**, Nian FS, et al, Soong BW*, Tsai JW*. Oncotarget. 2016 Jun 28;7(26):39184-39196.

Deciphering age-dependent neuronal hyperexcitability caused by CDKL5 deficiency

Wenlin Liao (廖文霖)

Professor, Institute of Neuroscience, National Cheng-Chi University

Ph.D. National Yang-Ming University



Abstract

Cyclin-dependent kinase-like 5 (CDKL5) is a serine-threonine kinase, localized primarily in the nucleus to control gene expression and neuronal development by regulating protein phosphorylation. Mutations in *CDKL5* gene cause CDKL5 deficiency disorder (CDD), a developmental and epileptic encephalopathy characterized by severe early-onset seizures, developmental delay and intellectual disability. Despite well-defined genetic cause, children with CDD are resistant to most of the anti-epileptic drugs and the pathogenic mechanisms for early-onset seizures in CDD remain unclear.

Through longitudinal EEG recordings coupled with videotaping in preweaning mouse pups, we found that *Cdkl5* null pups displayed increased EEG discharges at postnatal day 12 (P12) compared to their wild-type (WT) littermate controls. The increased burst discharges in mutants returned to the comparable pattern of WT mice after P14, suggesting that CDKL5 deficiency may increase neuronal excitability in an age-dependent manner. Through electrophysiological study and whole-genome RNA sequencing, we further revealed that CDKL5 ablation increases firing rate of neurons and down-regulates genes for tangential migration in dorsal hippocampus at P7. By contrast, the transcript levels of marker genes for GABAergic interneurons, such as parvalbumin and somatostatin, were up-regulated in cortical tissue of mutants at the age of P17 and 3-month, consistent to the increased number of parvalbumin-positive neurons found in the primary motor cortex of adult *Cdkl5* null mice. Our results demonstrate that CDKL5 is required to preserve gene expression essential for interneuronal migration during early postnatal age. Loss of CDKL5 may affect tangential migration of interneurons that leads to hyperexcitability soon after birth. Our discoveries may provide a basis to develop therapeutics for early-onset seizures in developmental disorders, including CDD.

Selected recent publications:

1. Su SH, Kao FC, Huang YB, **Liao W** (2015) MeCP2 in the rostral striatum maintains local dopamine content critical for psychomotor control. *The Journal of Neuroscience*, 35:6209-6220.

2. Kao FC, Su SH, Carlson GC, **Liao W** (2015) MeCP2-mediated alterations of striatal features accompany psychomotor deficits in a mouse model of Rett syndrome. *Brain Structure and Function*, 220: 419-434

3. Jhang CL, Huang TN, Hsueh YP and **Liao W** (2017) Mice lacking cyclin-dependent kinase-like 5 manifest autistic and ADHD-like behavior. *Human Molecular Genetics*, 26(20): 3922-34.

4. **Liao W** (2019) Psychomotor Dysfunction in Rett Syndrome: Insights into the Neurochemical and Circuit Roots. *Developmental Neurobiology*, 79(1): 51-59.

5. Jhang CL, Lee HY, Chen JC and **Liao W** (2020) Dopaminergic loss of cyclin-dependent kinase-like 5 recapitulates methylphenidate-remediable hyperlocomotion in mouse model of CDKL5 deficiency disorder. *Human Molecular Genetics*, 29(14): 2408-19.

Cellular and molecular mechanisms for malformations in cortical development

Jin-Wu Tsai(蔡金吾)

Distinguished Professor, Institute of Brain Science (IBS), College of Medicine, National Yang Ming Chiao Tung University (NYCU), Taiwan

Dean of Research and Development, NYCU, Taiwan

Adjunct Professor, Department of Biological Science & Technology, NYCU, Taiwan

Ph.D., Columbia University

Abstract

Neural developmental disorders are divesting neurological diseases resulting from defects in neural progenitor proliferation, neuronal migration and connections during development. These defects may lead brain malformations, including microcephaly, lissencephaly, double cortex, and focal cortical dysplasia. The patients often suffer from epilepsy, developmental delay, and cognitive impairments. To date, the genetic causes of a number of brain malformations have been identified, such as LIS1, DCX, ARX, TUBA1A, NDE1, KATNB1, and CDK5. Using in utero electroporation to knock down these genes and monitoring cellular and subcellular events with live cell imaging in brain slices, we found that LIS1 together with dynein facilitates centrosomal and nuclear movements during neuronal migration. Using whole exome sequencing (WES) in a cohort of patients with cortical malformation, we further identified variants in novel genes, CEP85L and BICD2, that cause lissencephaly. However, many genetic mutations involved in cortical malformations still remain unidentified. Recently, 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 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. In this presentation, molecular mechanisms of thesegenes in cortical malformation will be discussed.

Selected recent publications:

1. Lin JR, Cheng JF, Liu YT, …, Tsai JW* (2022) Novel lissencephaly-associated *DCX* variants in the C-terminal DCX domain affect microtubule binding and dynamics, ***Epilepsia***, *in press*.

2. Tsai MH, Muir AM, WangWJ, Kang YN, Yang KC, Chao NH, Wu MF, …, Dobyns WB, BerkovicSF, SchefferIE, Tsai JW*, MeffordHC* (2020) Pathogenic variants in CEP85L cause sporadic and familial posterior predominant lissencephaly. ***Neuron***, 106(2):237-245.

3. Tsai MH, Cheng HY, Nian FS, Liu C, Chao NH, Chiang KL,…,Tsai JW* (2020) Impairment in dynein-mediated nuclear translocation by BICD2 C-terminal truncation leads to neuronal migration defect and human brain malformation. ***Acta NeuropatholCommun***, 8(1):106.

4. Chang CH, ZaniniM, ShirvaniH, Cheng JS, Yu H, Feng CH, Mercier AL, Hung SY, Forget A, …, Spassky N, Tsai JW*, Ayrault O* (2019) Atoh1 controls primary cilia formation to allow for SHH-triggered granule neuron progenitor proliferation. ***DevCell***, 48(2):184-199.e5.

5. Lu IL, …,Tsai JW* (2018) Identification of genes associated with cortical malformation using a transposon-mediated somatic mutagenesis screen in mice. ***Nat Commun***, 9(1):2498.

Application of hUCMSC Exosomes in Neuropathic Pain and Spinal Cord Injury Models

Jen-Kun Cheng(鄭仁坤)
Senior Attending Anesthesiologist,

Mackay Memorial Hospital

Professor/Discipline Director of Anesthesiology,

Mackay Medical College

M.D., National Yang-Ming Medical College

Ph.D., National Taiwan University

Abstract

In the past decades, exosomes derived from mesenchymal stem cells have been used as therapeutics in various fields. Recently, we first demonstrated the antinociceptive effects of human umbilical cord mesenchymal stem cell (hUCMSC) exosomes, given intrathecally, in the L5/6 spinal nerve ligation neuropathic pain model. The therapeutic effects were associated with anti-inflammatory and neurotrophic effects of exosomes. We then further tested locally applied exosomes, embedded in alginate scaffold, in the pain model and found similar analgesic and neurotrophic effects. To further extent the application of exosomes, we examined the use of exosomes, embedded in gelfoam, in T9 spinal cord hemisection injury model. Our recent work demonstrated the nerve regenerative and motor function-improving potential of hUCMSC exosomes in the spinal cord injury model.

Selected recent publications:

1. Poongodi R, Chen YL, Yang TH, Huang YH, Yang KD, Lin HC, **Cheng JK** (2021) Bio-Scaffolds as Cell or Exosome Carriers for Nerve Injury Repair. *International Journal of Molecular Sciences* 22:13347.
2. Hsu JM, Shiue SJ, Yang KD, Shiue HS, Hung YW, Pannuru P, Poongodi R, Lin HY,**Cheng, J. K** (2020) Locally applied stem cell exosome-scaffold attenuates nerve injury-induced pain in rats. *Journal of Pain Research* 13:3257-68.
3. Shiue SJ, Rau RH, Shiue HS, Hung YW, Li ZX, Yang KD, **Cheng, JK** (2019) Mesenchymal stem cell exosomes as a cell-free therapy for nerve injury–induced pain in rats. *Pain*, 160: 210-23.
4. Shiue SJ, Peng HY, Lin CR, Wang SW, Rau RH, **Cheng JK** (2017) Continuous intrathecal infusion of cannabinoid receptor agonists attenuates nerve ligation-induced pain in rats. *Regional Anesthesia and Pain Medicine* 42:499-506.
5. Chen YL, Tsaur ML, Wang SW, Wang TY, Hung YC, Lin CS, Chang YF, Wang YC, Shiue SJ**Cheng JK** (2015) Chronic intrathecal infusion of mibefradil, ethosuximide and nickel attenuates nerve ligation-induced pain in rats. *British journal of anaesthesia* 115:105-11.

Nutrition interventionfor neuropathic,muscular and acute pain

Jen-Yin, Chen(陳貞吟)
Professor and Chair

Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan

Ph.D.National Chung Hsing University

Abstract

Vitamin D and vitamin C are essential micronutrients for human health. In cell and animal models, vitamin D has concentration-dependent anti-inflammatory effects through inhibiting the production of nitric oxide. Nitric oxide increases phosphorylated N-methyl-D-aspartate receptors in spinal dorsal horn neurons leading to central sensitization and mechanical allodynia. Vitamin D deficiency induces excessive reactive oxygen species resulting in cold pain,produces a marked dysbiosis and alters nociception via molecular mechanisms involving the endocannabinoid and related mediator signaling system. Clinically, we discovered that patients with neuropathic pain had a high prevalence of hypovitaminosis D which was associated with increased spontaneous cold pain and brush-evoked painbased onthe DN4 questionnaire. Vitamin C exerts antinociception and neuromodulation. Spontaneous pain symptoms include tingling, prickling, pins and needles sensation, as wellas electric shock, bursting, jumping, shooting, stabbing and burning pain. We discovered that the patients' plasma vitamin C concentrations were negatively correlated with spontaneous pain and with tingling, prickling or pins and needles sensation by the LANSS Questionnaire.Intravenous high-dose vitamin C relieved spontaneous pain effectively but not brush-evoked pain in patients with neuropathic pain. We will describe the findings in patients with muscular pain as well.A pneumatic tourniquet involving a previous exsanguination is often used in total knee arthroplasty. The procedures induce muscle ischemia leading to tissue acidosis and aching sensation (soreness,sngception). Sngception depends on the proton-sensing neurons and is a specific somatosensory function that transmits the aching sensation from the peripheral to the central nervous system when the tissue acidosis. High-dose vitamin C pretreatment reduces exercise-induced muscle soreness, oxidative stress and with little loss on muscle function.The benefits of intravenous high-dose vitamin C in patients with total knee arthroplasty will be reported.

Selected recent publications:

1. Hung KC, Wang LK, Lin YT, Yu CH, Chang CY, SunCK, **Chen JY** (2022) Association of preoperative vitamin D deficiency with the risk of postoperative delirium and cognitive dysfunction: A meta-analysis. *Journal of Clinical Anesthesia* 79:110681.
2. **Chen JY**, Lin YT, Wang LK, HungKC, LanKM, Ho CH, ChangCY (2019). Hypovitaminosis D in postherpetic neuralgia-High prevalence and inverse association with pain: A retrospective study. *Nutrients*11:2787.
3. Wang LK, Lin YT, Hung KC, Chang CY, Wu ZF, Hu ML, **Chen, JY** (2020). Plasma Vitamin C Concentrations Were Negatively Associated with Tingling, Prickling or Pins and Needles Sensation in Patients with Postherpetic Neuralgia. *Nutrients* 12:2384.
4. Wang LK, Chuang CC, **Chen, JY** (2018) Relief of acute herpetic pain by intravenous vitamin C: The dosage may make a difference. *Annals of Dermatology* 30:262-63.
5. **Chen JY**, Chu CC, Lin YS, So EC, Shieh JP, Hu ML (2011). Nutrient deficiencies as a risk factor in Taiwanese patients with postherpetic neuralgia. *British journal of nutrition* 106:700-07

New advances in myofascial pain syndrome

Li-Wei Chou(周立偉)

Professor and Director, Departmentof PhysicalTherapy and Graduate Institute of Rehabilitation Science, China Medical University, Taiwan.

Director, Departmentof PhysicalMedicineandRehabilitation, Asia University Hospital, AsiaUniversity,Taiwan.

M.D., Ph.D.China Medical University

Abstract

Myofascial pain syndrome, characterized by the presence of myofascial trigger points (TrPs), is recognized as a common source of musculoskeletal pain. Myofascial TrP is a hyperirritable spot within a taut band of skeletal muscle that is painful on compression, stretch, overload, or contraction of the tissue which usually responds with a referred pain that is perceived distant from the spot.Several needling therapies are proposed for treatment of myofascial pain syndrome. In fact, two different needling applications can be used to inactivate TrP: wet needling (injections) or dry needling.Fu's subcutaneous needing (FSN) is one of the newly invented dry needling methods. The treated target is tightened muscle (the muscle including TrPs). The soft tissue pain diseases might be treated via FSN combined the special techniques (swaying movement and reperfusion approach).

The application of TrP needlingtherapy is able to reduce this excitability by reducing peripheral nociception from the TrP, by reducing dorsal horn neuron activity, and by modulating brainstem areas. However, effects are only seen at short-term and effect sizes are small, pointing to a particular role that TrPs play within the complex chronic pain experience.When providing needling therapy to chronic pain patients, therapists are advised to integrate contemporary pain neurosciences when providing the treatment. This implies applying evidence-based recommendations; therefore, TrP needling therapy can be part of, but should never be, the only treatment plan for individuals with chronic pain. A comprehensive management program should include neuroscience pain education,exercise programs,self-management (including graded activity),stress management (psychological),sleep management,and other individuallytailored aspects of self-management.

Selected recent publications:

1. Huang CH, Lin CY, Sun MF, Fu Z, **Chou LW** (2022) Efficacy of Fu's Subcutaneous Needling on Myofascial Trigger Points for Lateral Epicondylalgia: A Randomized Control Trial. *Evidence-Based Complementary and Alternative Medicine* 2022:5951327.

2. Dommerholt J, Hooks T, Thorp JN, **Chou LW** (2019) A critical overview of the current myofascial pain literature–July 2020. *Journal of Bodywork and Movement Therapies* 24:307-20.

3. **Chou LW,**Hong CZ (2019) Needling Therapy for Myofascial Low Back Pain. *Journal of the Formosan Medical Association* 23:335-45.

4. Hsieh YL, Hong, CZ, Liu SY, **Chou LW**, Yang, CC (2016) Acupuncture at distant myofascial trigger spots enhances endogenous opioids in rabbits: a possible mechanism for managing myofascial pain. *Acupuncture in Medicine* 34:302-09.

5. **Chou LW**, Hsieh YL, Kuan TS, Hong CZ (2014) Needling therapy for myofascial pain: recommended technique with multiple rapid needle insertion. *BioMedicine* 4:13.

Mechanism of prolotherapy and ultrasound in chronic muscle pain

Der-Sheng Han(韓德生)

Medical Director, National Taiwan University Hospital Beihu Branch.

Clinical Associate Professor, Department of Physical Medicine and Rehabilitation, College of Medicine, National Taiwan University.

Director, Taiwan Academy of Physical Medicine and Rehabilitation

Director, Taiwan Osteoporosis Association

Director, Taiwan Society of Neurorehabilitation

Education Committee, ISPRM

PhD.Graduate Institute of Clinical Medicine, National Taiwan University, Taiwan.

Abstract

Prolotherapy is widely used in pain control and tissue repair in pain medicine. The classical mode is injection with hypertonic dextrose in muscle or perimysium. However, the analgesic mechanism is still not known. Here we successfully established dextrose-mediated analgesia in a mouse model of fibromyalgia. The analgesic effects of dextrose injections were evaluated in a mouse model of fibromyalgia, in which bilateral chronic mechanical hyperalgesia was induced by unilateral intramuscular acid injection. The injectant (dextrose), dose (≥ 5%) and volume (>10 uL) but not osmolarity were essential for the prolotherapy. Further studies showed that activation of acid-sensingion channel 1a (ASIC1a), neural activation, and the release of substance P from muscle afferents were required in the dextrose-induced analgesia. Both pharmacological blockade and genetic deletion of ASIC1a or substance P as well as lidocaine abolished the dextrose-induced analgesia in mice with chronic hyperalgesia. Moreover, intramuscular dextrose injection induced phosphorylated extracellular signal-regulated kinase (pERK) expression in dorsal root ganglia neurons expressing substance P; the pERK expression was inhibited by the ASIC1a antagonist PcTx1. The optimal settings for prolotherapy in fibromyalgia-like pain are dextrose- and volume-dependent, and the peripheral analgesia involves ASIC1a and substance P signaling in muscle afferents. We suggest a possible mechanism of action of dextrose prolotherapy in noninflammatory muscle pain such as fibromyalgia and provides insights for treating other types of chronic pain.

Selected recent publications:

1. **Han DS**, Lee CH, Shieh YD, Chang CT, Li MH, Chu YC, Wang JL, Chang KV, Lin SH, Chen CC (2022) A role for substance P and acid-sensing ion channel 1a in prolotherapy with dextrose-mediated analgesia in a mouse model of fibromyalgia. *Pain*163:E622-33.

2. Hsu WH[*], **Han DS**[*], Ku WC[*], Chao YM, Chen CC[#], Lin YL[#](2022) Metabolomic and proteomic characterization of sng and pain phenotypes in fibromyalgia.European Journal of Pain 26:445-62. ([*]equal contribution, [#]correspondence)

3. Chang KV, Hung CH, Sun WZ, Wu WT, Lai CL, **Han DS[*]**, ChenCC[*] (2020) Evaluating soreness symptoms of fibromyalgia: Establishment and validation of the Revised Fibromyalgia Impact Questionnaire with Integration of Soreness Assessment. *Journal of the Formosan Medical Association* 119:1211-18.([*] co-correspondence)

4. **Han DS**, Lee CH, Shieh YD, ChenCC (2019) Involvement of substance P in the analgesic effect of low-level laser therapy in a mouse model of chronic widespread muscle pain. *Pain Medicine*20:1963-70.

5. Lin JH[*], Hung CH[*], **Han DS**[*], Chen ST, Lee CH, Sun WZ, Chen CC (2018) Sensing acidosis: nociception or sngception? *Journal of Biomedical Science*25:85. ([*] equal contribution)

Inflammation and Nutrition in Child Mental Health: Focus on ADHD

Jane Pei-Chen Chang
Director,Child Psychiatry Division, Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan

Assistant Professor, College Medicine, China Medical University, Taichung, Taiwan

M.D., China Medical University, Taichung, Taiwan

M.Sc., China Medical University, Taichung, Taiwan

Ph.D., Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, UK

Abstract

Inflammation and deficiency of omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been suggested to play a role in attention deficit hyperactivity disorder (ADHD). Studies have suggested that children with ADHD tend to have higher inflammatory biomarkers and less intake and lower blood levels of n-3 PUFAs. This talk will provide a brief overview focused on personalized medicine of n-3 PUFAs in ADHD with the most updated research findings supported by cross-sectional studies, meta-analyses and randomised controlled trials.

Selected recent publications:

1. **Chang JP,*** Su KP, Mondelli V, Pariante CM. Cortisol and Inflammatory Biomarker Levels in Youths with Attention Deficit Hyperactivity Disorder (ADHD): Evidence from a Systematic Review with Meta-analysis. Translational Psychiatry. 2021; 11(1):430.

2. **Chang JP.** Personalised medicine in child and adolescent psychiatry: Focus on omega-3 polyunsaturated fatty acids and ADHD. Brain, Behavior and Immunity-Health. 2021; 16:100310.

3. **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.

4. **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.

5. **Chang JP**, Mondelli V, Satyanarayanan SK, Chiang YJ, Chen HT, Su KP, Pariante CM. Cortisol, inflammatory biomarkers and neutrophins in children and adolescents with attention deficit hyperactivity disorder (ADHD) in Taiwan. Brain, Behavior and Immunity. 2020;88:105-113.

Effects of Anthocyanin-rich Mulberry Milk on Working Memory and Mental Wellbeing in Healthy Working Population

Pongsatorn Paholpak
Associate Profressor, Department of Psychiatry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Research Institute for High Human Performance and Health Promotion, Khon Kaen University, Khon Kaen, Thailand

MD. Khon Kaen University

Abstract

Anthocyanins from various types of berries have been investigated for positive effects on cognitive, mood, anxiety, and stress symptoms. Our group conducted an open-labelled study in 300 healthy volunteers to consume either 1 or 2 servings of the anthocyanin-rich mulberry milk daily for 6 weeks. We monitored performances on 7 computerized working memory tests, General Health Questionnaire-28 (GHQ-28), Hospital Anxiety and Depression Scale (HADS), saliva activity levels of acetylcholinesterase (AchE), monoamine oxidase (MAO), and cortisol at the baseline and after 6 weeks. We found significant improvement of performances on all working memory tasks, significantly decreased GHQ-28 and HADS total scores and all their subscales, and significantly decreased activity levels of AchE, MAO-A, MAO-B, and cortisol in both groups (all $p < 0.05$). We speculated that a daily consumption of anthocyanin-rich mulberry milk improved psychological and somatic symptoms via suppressions of AchE, MAO and cortisol activity.

Selected recent publications:

1. Thukham-Mee WWattanathorn J, **Paholpak P**, Rangseekajee P, Piyavhatkul N.The Positive Modulation Effect of a 6-Week Consumption of an Anthocyanin-Rich Mulberry Milk on Working Memory, Cholinergic, and Monoaminergic Functions in Healthy Working-Age Adults . Oxid Med Cell Longev. 2021 Aug 31;2021:5520059. doi: 10.1155/2021/5520059. eCollection 2021

2. Rangseekajee P, Aphisitphinyo S, Paholpak P, Piyavhatkul N, Vadhanavikkit P, Manasawee K, **Paholpak P**.Mobile Application for Monitoring Behavioral and Psychological Symptoms of Dementia in Patients with Moderate to Severe Dementia. Geriatr Gerontol Int. 2021 Apr 13. doi: 10.1111/ggi.14164 PMID: 33851502

3. .Fong SS, **Paholpak P**, Daianu M, Deutsch MB, Riedel BC, Carr AR, Jimenez EE, Mather MM, Thompson PM, Mendez MF.The attribution of animacy and agency in frontotemporal dementia versus Alzheimer'sdisease. Cortex. 2017 Jul;92:81-94. doi: 10.1016/j.cortex.2017.03.019. Epub 2017 Apr 8. PMID: 28458182

4. Person-Based Versus Generalized Impulsivity Disinhibition in Frontotemporal Dementia Alzheimer Disease.**Paholpak P**, Carr AR, Barsuglia JP, Barrows RJ, Jimenez E, Lee GJ, Mendez MF.J Geriatr Psychiatry Neurol. 2016 Sep 19. DOI: 10.1177/0891988716666377 PMID: 27647788

5. **Paholpak P**, Li-Jung L, Carr DR, Jimenez E, Barrows RJ, Sabodash V, Mendez MF. Prolonged Visual Facial Grasp in Frontotemporal dementia..J Alzheimers Dis. 2016 May 7;53(1):327-35. doi: 10.3233/JAD-150864.PMID: 27163801

Brain Ageing: Potential Avenue for Antioxidant Compounds?

Hanafi Ahmad Damanhuri
Associate Professor, Department of Biochemistry, Faculty of Medicine, The National University of Malaysia

Ph.D., Macquarie University, Australia

Abstract

Brain aging is a continuous and complex multifactorial process manifested by physiological and cognitive deterioration, ultimately leading to death. Brain aging influences mental health and affects individuals' ability to carry out their daily routines. For the past decades, research has been conducted to understand how the ageing process affects the brain, from the molecule to the functional perspective. Despite the aggressive effort, many more questions are being raised and fail to clearly explain how the actual process occurs during brain ageing. It was further supported by the fact that the numbers of drugs or natural products extract results in inconclusive findings in delaying brain ageing progression in various contexts. Several questions remain unsolved and require extensive investigation. The controversies and relevant issues will be discussed further in the presentation.

Selected recent publications:

1. Aslina Pahrudin Arrozi, Wan Zurinah Wan Ngah, Hanafi Ahmad Damanhuri and Suzana Makpol (2021) Modulatory Effects of Alpha- and Gamma-Tocopherol on the Mitochondrial Respiratory Capacity and Membrane Potential in an In Vitro Model of Alzheimer's Disease. Frontiers in Pharmacology 12: 69883 (1-11).
2. Nur Fathiah Abdul Sani, Ahmad Imran Zaydi Amir Hamzah, Zulzikry Hafiz Abu Bakar, Yasmin Anum Mohd Yusof, Suzana Makpol, Wan Zurinah Wan Ngah and Hanafi Ahmad Damanhuri(2021) Gene expression profile in different age groups and its association with cognitive function in healthy Malay adults in Malaysia. Cells 10: 1611 (1-25).
3. Nur Zuliani Ramli, Mohamad Fairuz Yahaya, Ikuo Tooyama and Hanafi Ahmad Damanhuri (2020) A mechanistic evaluation of antioxidant nutraceuticals on their potential against age-associated neurodegenerative diseases. Antioxidants 9 (10): 1019 (1-39).
4. Zulzikry Hafiz Abu Bakar, Hanafi Ahmad Damanhuri, Suzana Makpol, Wan Mohd Aizat, Nur Fathiah Abdul Sani, Ahmad Imran Zaydi Amir Hamzah, Khairun Nain Nor Aripin, Mohd Dzulkhairi Mohd Rani, Nor Azila Noh, Rosdinom Razali, Musalmah Mazlan, Hamzaini Abdul Hamid, Mazlyfarina Mohamad and Wan Zurinah Wan Ngah (2019) Effect of Age on the Protein Profile of Healthy Malay Adults and its Association with Cognitive Function Competency. Journal of Alzheimer's Disease 70: S43–S62.
5. Wan Nurzulaikha Wan Nasri, Suzana Makpol, Musalmah Mazlan, Ikuo Tooyama, Wan Zurinah Wan Ngah and Hanafi Ahmad Damanhuri (2019) Tocotrienol Rich Fraction (TRF) Supplementation Modulate Brain Hippocampal Gene Expression In APPswe/PS1dE9 Alzheimer's Disease Mouse Model. Journal of Alzheimer's Disease 70: S239–S254.

Inflammatory Cytokines in and Cognitive Function of Adolescents with First-Episode Schizophrenia, Bipolar Disorder, or Major Depressive Disorder

Mu-Hong Chen
Attending Psychiatrist, Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

Department of Psychiatry, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

M.D., Ph.D., National Yang Ming Chiao Tung University.

Abstract

Background: Few studies have explored the complex relationship of pro- and anti-inflammatory cytokines with cognitive function in adolescents with first-episode schizophrenia, bipolar disorder, or major depressive disorder. **Methods:** In total, 26, 35, and 29 adolescents with first-episode schizophrenia, bipolar disorder, and major depressive disorder, respectively, and 22 age- and sex-matched controls were included in the current study. Cytokines, namely interleukin (IL)-2, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP), were assessed. The Wisconsin Card Sorting Test (WCST) and the working memory task were administered to assess cognitive function. **Results:** Using generalized linear models with adjustment for demographic data and clinical symptoms, patients with bipolar disorder were found to exhibit the highest levels of CRP ($p = 0.023$), IL-6 ($p = 0.022$), and TNF-α ($p = 0.011$) and had the lowest IL-2 levels ($p = 0.034$) among the four groups. According to the results of the WCST and working memory task, adolescents with schizophrenia exhibited the lowest performance in cognitive function. In addition, among the assessed cytokines, only CRP levels ($p = 0.027$) were negatively associated with WCST scores. **Discussion:** Dysregulated pro- and anti-inflammatory cytokines and impaired cognitive functioning were observed in first-episode adolescent-onset schizophrenia, bipolar disorder, and major depressive disorder. The altered cytokine profiles may play important roles in the pathophysiology of schizophrenia, bipolar disorder, and major depressive disorder.

Selected recent publications:

1. **Chen MH**, Chang WC, Lin WC, Tu PC, Li CT, Bai YM, Tsai SJ, Huang WS, Su TP. Functional dysconnectivity of frontal cortex to striatum predicts ketamine infusion response in treatment-resistant depression. Int J Neuropsychopharmacol. 2020 Jul 30:pyaa056.

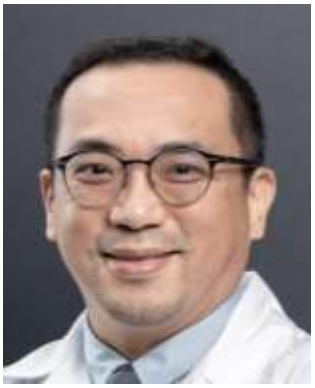
2. **Chen MH**, Lin WC, Wu HJ, Bai YM, Li CT, Tsai SJ, Hong CJ, Tu PC, Cheng CM, Su TP. Happiness During Low-Dose Ketamine Infusion Predicts Treatment Response: Reexploring the Adjunctive Ketamine Study of Taiwanese Patients With Treatment-Resistant Depression. J Clin Psychiatry. 2020 Nov 10;81(6):20m13232.

3. **Chen MH**, Kao CF, Tsai SJ, Li CT, Lin WC, Hong CJ, Bai YM, Tu PC, Su TP. Treatment response to low-dose ketamine infusion for treatment-resistant depression: A gene-based genome-wide association study. Genomics. 2020 Dec 25:S0888-7543(20)32077-2.

4. **Chen MH**, Wu HJ, Li CT, Lin WC, Tsai SJ, Hong CJ, Tu PC, Bai YM, Mao WC, Su TP. Is one or two infusions better in the first week of low-dose ketamine treatment for medication-resistant depression? A post hoc pooled analysis of randomized placebo-controlled and open-label trials. J Psychiatr Res. 2021 Nov 3;144:448-454.

5. **Chen MH**, Cheng CM, Gueorguieva R, Lin WC, Li CT, Hong CJ, Tu PC, Bai YM, Tsai SJ, Krystal JH, Su TP. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. Neuropsychopharmacology. 2019 Aug 17.

HF–Age–Gender (HAG) Index as a Biomarker for Sleep Disorder in mTBI



John Chung-Che Wu(吳忠哲)
Current title and affiliation

Assistant Professor

Division of Neurosurgery, Department of Neurosurgery, Taipei Medical University Hospital,

Division of Neurosurgery, Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University

M.D., Ph.D., Taipei Medical University

Abstract

Biomarkers are emerging as a useful tool for prediction of outcomes in TBI. To identify a screening tool for poor self-reported sleep quality in the first week after mild traumatic brain injury (mTBI) for sleep disorder at 12 weeks, data from 473 mTBI participants were collected and follow-ups were performed at 12 weeks. Patients were then divided into two groups according to the Pittsburgh Sleep Quality Index based on whether or not they experienced poor sleep quality at 12 weeks post-mTBI. The analysis was performed on personal profiles and heart rate variability (HRV) in the 1st week. An analysis of the non-invasive patient data for mTBI patients who did and did not complain of poor sleep quality revealed several factors relevant to the delayed onset of poor sleep quality, including age, gender, and HRV measurements. The HRV–age–gender (HAG) index has a 100% sensitivity (cut-off, 7; specificity, 0.537) to predicting whether the patient will experience poor sleep quality after mTBI at the 12-week follow-up. The HAG index allows identifying the patients with mTBI who have no initial sleep quality complaints but are prone to developing poor self-reported sleep quality at 12 weeks.

Selected recent publications:

1. Wang YJ, Wong HSC, **Wu CC**, Chiang YH, Chiu WT, Chen KY and Chang WC. The functional roles of IGF-1 variants in the susceptibility and clinical outcomes of mild traumatic brain injury. J Biomed Sci. 2019 Dec 2;26(1):94.

2. **Wu CC**, Ekanem TI, Phan NN, Loan DTT, HouSY, Lee KH, Wang CY. Gene signatures and prognostic analyses of the Tob/BTG pituitary tumor-transforming gene (PTTG) family in clinical breast cancer patients.Int. J. Med. Sci. 2020; 17(18): 3112-3124.

3. Tsai YT, **Wu CC**, Ko CY, Hsu TI, Chang WC, Lo WL, Chuang JY. Correlation between the expression of cancer stem cell marker BMI1 and glioma prognosis. Biochem Biophys Res Commun. 2021 Apr 23;550:113-119.

4. Kao TJ, **Wu CC**, Phan NN, Liu YH, TaHDK, Anuraga G, Wu YF, Lee KH, Chuang JY, Wang CY. Prognoses and genomic analyses of proteasome 26S subunit, ATPase (PSMC) family genes in clinical breast cancer. Aging (Albany NY). 2021 Jul 30;13.

5. Ma HP, Ou JC, Chen KY, Liao KH, Kang SJ, Wang JY, Chiang YH, **Wu JCC**. Screening for Poor Self-Reported Sleep Quality at 12 Weeks in Post-Mild Traumatic Brain Injury Patients Using the HF-Age-Gender (HAG) Index. Brain Sci. 2021 Oct 20;11(11):1369.

Visual working memory decline in aging and potential neuromodulatory treatment

Philip Tseng(曾祥非)

Professor and Director, Graduate Institute of Mind, Brain and Consciousness, Taipei Medical University

Vice Dean, College of Humanities and Social Sciences, Taipei Medical University

Ph.D.University of California, Santa Cruz

Abstract

Visual working memory (VWM) is a cognitive faculty that allows us to remember visual information from one fixation to another.However, VWM capacity is far from perfect, and research has demonstrated a high degree of individual difference in VWM performance. Perhaps due to its imperfection and fragility, VWM capacity has been shown to be highly sensitive to one's neurological development and frontoparietal functioning, and can be a sensitive marker to many factors such as aging, and neurodegenerative diseases, etc. In this talk I will explore the possibility of applying VWM to research in traumatic brain injury, as well as some of the brain stimulation techniques such as transcranial electric stimulation and sensory stimulation that have been known to facilitate VWM performance, that may be of interest to clinicians working with TBI patients.

Selected recent publications:

1. Sahu PP &**Tseng P** (2021). Frontoparietal theta tACS nonselectively enhances encoding, maintenance, and retrieval stages in visuospatial working memory. Neuroscience Research, 172, 41-50.

2. **Tseng P**, Iu K-C, & Juan CH (2018). The critical role of phase difference in theta oscillation between bilateral parietal cortices for visuospatial working memory. Scientific Reports, 8:349.

3. Wu YJ, Lin CC, Yeh CM, Chien ME, Tsao MC, **Tseng P**, Huang CW, & Hsu KS (2017). Repeated transcranial direct current stimulation improves cognitive dysfunction and synaptic plasticity deficit in the prefrontal cortex of streptozotocin-induced diabetic rats. Brain Stimulation, 10(6), 1079-1087.

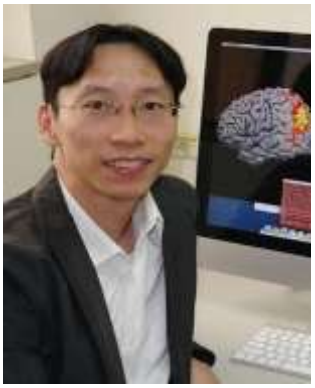
4. Juan CH, **Tseng P**, & Hsu TY (2017). Elucidating and modulating the neural correlates of visuospatial working memory via noninvasive brain stimulation. Current Directions in Psychological Science, 26(2), 165-173.

5. **Tseng P**, Hsu TY, Chang CF, Tzeng OJL, Hung DL, Muggleton NG, Walsh V, Liang WK, Cheng SK, & Juan CH (2012). Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. Journal of Neuroscience, 32, 10554-10561.

Task-related fMRI reveals age-related neuro-functional differences in younger and older adult decision processes

Joshua Goh(吳恩賜)

Associate Professor,Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University



Ph.D.University of Illinois, Urbana-Champaign

Abstract

The ability of the human brain to make appropriate decisions given the context undergoes notable changes with age. This is a puzzling phenomenon since both younger and older adults are faced with the same contextual scenarios, yet differences in decision behaviors reflect age-related influences in the underlying neural processes that culminate in the chosen actions or responses. In a series of studies, our lab has applied the use of psychological value-based decision-making in lottery choices and complex rule contingency decision-making in functional magnetic resonance imaging experiments applied on younger and older adults. Our findings highlight drastic differences in neural network systems engaged by younger and older adults as they process value-based decisions as well as non-linear rule-mappings. Crucially, in these fMRI tasks, we found a shift from rapid, simplifying heuristic-like processing in younger adult striatum and prefrontal operations to slower, more biased processing in older adult medial and lateral frontal systems. These findings delineate how the human brain reorganizes its decision-making neural circuits in the face of neurobiological changes and lifespan experiences with age.

Selected recent publications:

1. Goh, J. O. S.*, Su, Y. S., Tang, Y. J., McCarrey, A. C., Tereschenko, A., Elkins, W., Resnick, S. M. (2016). Frontal, striatal, and medial temporal sensitivity to value distinguishes risk-taking from risk-aversive older adults during decision-making. Journal of Neuroscience, 36(49), 12498-12509.

2. Su, Y. S., Chen, J. T., Tang, Y. J., Yuan, S. Y., McCarrey, A. C., Goh, J. O. S.* (2018). Age-Related Differences in Striatal, Medial Temporal, and Frontal Involvement During Value-Based Decision Processing. Neurobiology of Aging, 69:185-198.

3. Chen, C. C., Su, Y. S., Tu, Y. Z., Goh, J. O. S.* (2019). Default-mode network activation underlies accurate contextual processing of exclusive disjunctions in older but not younger adults, NeuroImage, 201, 116012.

Sleep disturbance and its impacts on cognitive deficits following traumatic brain injury

Hsiao-Yean(Shannon) Chiu(邱曉彥)

Associate Professor and Deputy director of School of Nursing,

College of Nursing, Taipei Medical University

Supervisor, Department of Nursing, Taipei Medical University Hospital

RN, Ph.D.Taipei Medical University

Abstract

Traumatic brain injury (TBI) is one of the most common neurological disorder, which can be classified as mild, moderate or severe types, and may have wide-ranged physical and psychological sign and symptoms. On the other hand, with increasing life expectancy in modernsocieties, the epidemiological pattern of TBI has changed in recent decades,with an increasing proportion of TBI survivors fallinginto the older age group (one-third ofTBI survivors). In general, TBI has becomea major public health concern for young and older adults.Note that some symptoms could appear immediately after brain trauma, while others days or weeks later. Among these symptoms, sleep disturbance is one of the most common complaint in the population. In the lecture, I will review our past study findings regarding the sleep patterns of TBI survivors at acute and chronic stages. During acute stage, sleep duration seems play a critical role in recovering cognitive impairment caused by head trauma; in the chronic stages, psychological factors such as depression may contribute to the development of sleep disturbance following TBI. Furthermore, I will describe the association between post-TBI sleep disturbance and cognitive impairment and illustrate possible nonpharmacological interventions targeting sleep disturbance following TBI.

Selected recent publications:

1. Chen PY, Hsieh SH, Lin CK, Wei L, Su YK, Tsai PS, **Chiu HY.** Mental fatigue mediates the relationship between cognitive functions and return to productive activity following traumatic brain injury. *Brain Injury*. 2022; 31;1-7.

2. Chung JW, Liu D, Wei L, Wen YT, Lin HY, Chen HC, **Chiu HY.** Postconcussion symptoms after an uncomplicated mild traumatic brain injury in older adults: frequency, risk factors, and impact on quality of life. *Journal of Head Trauma Rehabilitation*. 2021; doi: 10.1097/HTR.0000000000000733.

3. Tsai YC, Liu CJ, Huang HC, Lin JH, Chen PY, Su YK, Chen CT, **Chiu HY.** A meta-analysis of dynamic prevalence of cognitive deficits in the acute, subacute, and chronic phases following traumatic brain injury. *Journal of Neuroscience Nursing*. 2021; 53:63-68.

4. Wei L, Wen YT, Thompson HJ, Liu CY, Su YK, Chen PY, Chen CY, Chuang YH, Lin YJ, Chen, CT, Chen CC, Chiu HT, **Chiu HY**. Sleep disturbances following traumatic brain injury in older adults: a comparison study. *Journal of Head Trauma Rehabilitation*. 2020; 35(4):288-295.

5. Chen PY, Tsai PS, Chen NH, Chaung LP, Lee CC, Chen CC, Chiu HT, Lu YJ, Wei KC, **Chiu HY.** Trajectories of sleep and its predictors in the first year following traumatic brain injury. *Journal of Head Trauma Rehabilitation.* 2015, 30(4): E50-55.