Nanosymposium session II

Games of Audio Watermarking: 2002 vs 2022

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Abstract

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

Selected recent publications:

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

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

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

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

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

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

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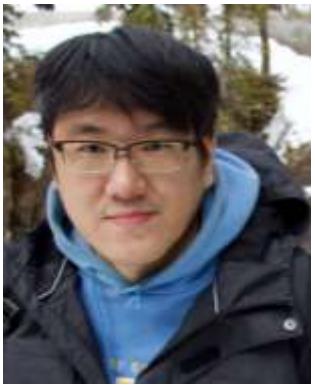

Abstract

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

Selected recent publications:

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

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

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

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

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

Mapping Spectral and Temporal Information to Complex Pitch Perception

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Ph.D.in Cognitive Sciences, University of California-Irvine, USA

Abstract

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

Selected recent publications:

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

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

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

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

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

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

Auditory Processing, Phonology and Reading Difficulties in Chinese

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

Abstract

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

Selected recent publications:

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

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

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

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

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

Nanosymposium session II

Circadian clock and the mood rhythm

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Joint-Appointment Associate Professor, Graduate Institute of Medical Sciences

Joint-Appointment Associate Professor, Ph.D. Program in Neuroscience of Cognition and Consciousness

Taipei Medical University

Ph.D. Kyoto University

Abstract

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

Selected recent publications:

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

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

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

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

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

A working model of the pathophysiology of bipolar disorder

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

Abstract

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

Selected recent publications:

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

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

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

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

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

A working model of the pathophysiology of bipolar disorder

Matteo Martino

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

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

Abstract

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

Selected recent publications:

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

Reward valuation in chronic migraine patients with medication overuse

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Ph.D., Aalborg University (Denmark)

Abstract

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

Selected recent publications:

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

Nanosymposium session II

Zebrafish Model for Research in Neuroscience

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中央研究院 分子生物所

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Abstract

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

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

Selected recent publications:

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

Induced pluripotent stem cells in neurodegenerative disease modelling

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Research Fellow & Deputy Director, Institute of Cellular and organismic Biology, Academia Sinica

Ph.D.King's College London

Abstract

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

Selected recent publications:

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

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

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

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

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

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

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Ph.D., National Yang-Ming University

Abstract

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

Selected recent publications:

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

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

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

Diagnosing nature of disease-associated gene variants in fruit flies

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Associate research fellow

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

Ph.D. National Yang-Ming University, Taiwan

Abstract

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

Selected recent publications:

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

Nanosymposium session II

Stereo-EEG the Route to the Field of Neuroscience

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

國立陽明交通大學醫學系 助理教授, Aug 2018 - present

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

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

台灣疼痛醫學會監事, May 2021 - present

台灣中青年神經外科學會理事, Nov 2021 - present

Abstract

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

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

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

Selected recent publications:

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

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

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

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

Using SEEG to investigate language processing

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Abstract

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

Selected recent publications:

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

The human orbitofrontal cortex and subjective value

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Abstract

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

Selected recent publications:

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

Functional mapping by direct electrical stimulation in SEEG

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Abstract

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

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

Selected recent publications:

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

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

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

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

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

Focused Ultrasound and Its CNS Application

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Professor

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Abstract

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

Selected recent publications:

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

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

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

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

5. IC Lee, S Faderaa, **HL Liu***, "Strategy of differentiation therapy: effect of dual-frequency ultrasound on the induction of liver cancer stem-like cells on a HA-based multilayer film system," Journal of Materials Chemistry B, Vol. 7, No. 35, pp. 5401-5411, 2019.

Nanosymposium session II

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

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Abstract

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

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

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

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

Selected recent publications:

1. KT Chen, TY Ho, TY Siow, YC Yeh, SY Huang, *Individual cerebrocerebellar functional network analysis decoding symptomatologic dynamics of postoperative cerebellar mutism syndrome.* Cerebral Cortex Communications, (2022), 3, 1-11

2. KT Chen, KC Wei, HL Liu, *Focused ultrasound combined with microbubbles in central nervous system applications.* Pharmaceutics, (2021), 13(7),1084 (2020 IF=6.321)

3. KT Chen, WY Chai, YJ Lin, CJ Lin, PY Chen, HC Tsai, CY Huang, J Kuo, HL Liu*, KC Wei*, *Neuronavigation-Guided Focused Ultrasound for Transcranial Blood-Brain-Barrier Opening and Immunostimulation in Brain Tumors.* Science Advances. (2020) Accepted (IF = 13.116, 5/69 in "Multidisciplinary Science")

4. Po-An Chen, Yi-Chun Chen, Kuo-Chen Wei, Ko-Ting Chen*. *Awake craniotomy for a left pan-hippocampal diffuse low grade glioma in a deaf-mute patient using sign language.* World Neurosurgery. (2020),134:629-634.e1 (2019 IF=1.829)

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

Synergic effect of Focused ultrasound and radiation therapy in glioma: a preclinical and upcoming clinical study

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Abstract

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

Selected recent publications:

1. **Lin YJ**, Wei KC, Chen PY, Lim M, Hwang TL. Roles of Neutrophils in Glioma and Brain Metastases. Front Immunol. 2021 Aug 13;12:701383.
2. Chen KT, Chai WY, **Lin YJ**, Lin CJ, Chen PY, Tsai HC, Huang CY, Kuo JS, Liu HL, Wei KC. Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors. Sci Adv. 2021 Feb 5;7(6):eabd0772.
3. **Lin YJ**, Mashouf LA, Lim M. CAR T Cell Therapy in Primary Brain Tumors: Current Investigations and the Future. Front Immunol. 2022 Feb 21;13:817296.
4. **Lin YJ**, Huang CY, Shen YC, Wei KC, Chuang CC, Hsu PW, Huang YC, Hwang TL, Chen PY. A manzamine-derived compound as a potential therapeutic agent for glioma by inducing apoptosis and cell cycle arrest. Am J Cancer Res. 2022 Apr 15;12(4):1740-1751.
5. Chen CH, **Lin YJ**, Lin YY, Lin CH, Feng LY, Chang IY, Wei KC, Huang CY. Glioblastoma Primary Cells Retain the Most Copy Number Alterations That Predict Poor Survival in Glioma Patients. Front Oncol. 2021 Apr 26;11:621432.

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

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Abstract

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

Selected recent publications:

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

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

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

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

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