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# BBMI Quarterly

## First Half 2022

# Director Message

## Hailan Hu

*Director of the BBMI Center*

Mental illnesses and neurological diseases have always been two major problems in the field of medicine. While we may be enjoying life, depression patients are trying their best to escape the shadows. When we may be hiking in nature, epilepsy patients are still struggling with their inappropriate body movements. However, with the recent rapid developments in neuroscience, new hopes are emerging for effective clinical treatments for many intractable human diseases.

President Xi has emphasized that the focus for scientific and technological innovation must be "to satisfy the people's expectations for a better life". Over 2022, the BBMI center has been gathering a steady stream of original results that occupy the important intersection between basic neuroscientific research and clinical translation. Liu Chong's research group, for example, has demonstrated the long -anticipated mechanistic link between sensory stimuli and brain tumors, showing how olfactory function can trigger and regulate the occurrence of gliomas and providing new opportunities for glioma treatment. Similarly, Zhang Jianmin's research group has made progress in applying their novel "chemodynamic therapy", for brain glioblastomas, significantly increasing survival time in animal models. His team also promoted the clinical translation of domestic neurostimulators, greatly improving the quality of life for patients with epilepsy and other movement disorders. Cui Yihui's group has also made great progress towards the understanding of chronic stress in depression. Hu Shaohua's research team has revealed the mechanism of the brain-gut axis in bipolar disorder. Xu Zhenzhong's team revealed the molecular and cellular mechanisms of diabetic neuralgia regulation by GPR177. Wang Hao's group produced a new type of multimodal NMR-compatible hydrogel cortical electrode, increasing options for the treatment of a number of neurological diseases.

The BBMI also continues to have strong links to the Brain Project China Initiative, which has been launched as a 2030 major scientific and technological targeted project for scientific and technological innovation. Focused areas for its research platforms include research on the neural circuit mechanisms of fear, new treatment strategies for affective disorders, and other research from the Chinese Brain Project. Many BBMI research groups have already begun to participate in this initiative.

Translational research in brain science requires continuous efforts and sustained development and there is still a long way to go. However, we believe that under the landscape of the Chinese Brain Project, with its "one body and two wings" commitment, and with the BBMI center's own strong platform of academic freedom and rich community of scientists from diverse fields, the future looks bright. Many new innovations should be forthcoming that will serve the country's major strategic needs for scientific and technological development, lift existing research to higher levels, and bring new perspectives.

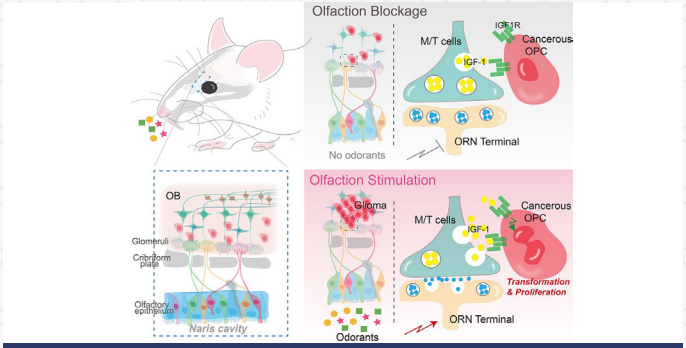
# Can smelling trigger brain cancer?

## Olfaction is demonstrated to regulate gliomagenesis

**Animals constantly receive various sensory stimuli, such as odor, sound, light, and touch, from the surrounding environment.** Whilst these sensory inputs clearly facilitate the animal's external behavior, as in the search for food, a mate, or in the avoidance of predators,such stimuli are now becoming recognized to also be able to affect an animal's internal and physiological status and development. These sensory factors are even beginning to be recognized for their roles in diseases such as cancer. One major type of brain cancer is the glioma. This represents a tumor that originates in the glial (non-neuronal) cells of the brain or spinal cord. Even though the glioma originates in non-neuronal cells, the importance of the role of neurons as is the functional unit of the brain in glioma progression is also being gradually uncovered. However, to what extent neuronal activity regulates the origin of gliomas (gliomagenesis) has remained uncertain. More specifically the question, "Can normal physiological functions of the brain, such as its various sense perceptions or corresponding emotions, directly regulate gliomagenesis?", remained largely unanswered.

Recently, a study addressing these important questions from Dr. **Chong Liu**'s group at the BBMI has been published in ***Nature***. Firstly, Dr. Liu and his colleagues were able to develop a suitable spontaneous glioma model. In this model, most tumors are spontaneously generated in the glomerulus layer of the olfactory bulb, being the brain area where the first-order neurons (olfactory receptor neurons, or ORNs) communicate with the second-order neurons (mitral/tufted cells) of the olfactory circuit. This suggests that the neuronal activity of the olfactory circuit plays a critical role in tumorigenesis.

To precisely manipulate the activity of the ORNs, Liu and his colleagues leveraged cutting-edge chemicogenetic technology to specifically and precisely control ORN activity and its downstream connected neural circuits. Surprisingly, they found that tumor volume correlated with the level of ORN stimulation in both directions. Tumor volume in the olfactory bulb was markedly decreased where there was also inhibition of the activity of ORNs, but conversely increased upon stimulation of ORN activity. To take this further, and in order to facilitate more direct deprivation of olfactory stimulation, the researchers designed an elegant experiment using a small silicon plug to insert into the nasal cavity of the tumor mice, therefore blocking almost all the olfactory sensory input from the external environment. Consistent with the above chemicogenetics data, they observed the deprivation olfaction resulted in smaller tumors in the ipsilateral olfactory bulb upon olfaction deprivation. This clearly demonstrates that olfaction can regulate gliomagenesis.




Olfactory sensory experience can regulate gliomagenesis by IGF–1 in mitral/tufted cells

Next, Liu and his colleagues explored the underlying mechanism by analyzing RNA-seq data of the bilateral olfactory bulbs from the unilateral olfaction deprivation mouse group. In this they specifically screened for the potential effector Insulin-like growth factor (IGF-1), the receptor of which, IGF1R, which had previously reported by Dr Liu's team to be essential for the initiation and progression of gliomas.

After confirming that Igf1 is mainly expressed in the mitral/tufted cells of the olfactory bulb, they established an elegant mouse genetic model to mimic tumorigenesis and simultaneously and precisely manipulate the tumor microenvironment in the OB. After knocking out mitral/tufted cell-specific Igf1, the tumor volume in the olfactory bulb was found to be significantly decreased. Finally, the team simultaneously manipulated ORN activity and IGF-1 signaling, and demonstrated that olfaction regulates tumorigenesis primarily through the IGF-1 signaling pathway.

By applying a series of state-of-arts mouse genetic models, together with other cutting-edging neuroscience and cancer biology methods, Liu and his colleagues have established a unique and direct link between olfactory sensory experience and gliomagenesis. This finding provokes intriguing studies to explore the potential roles of different sensory experiences, consciousness, emotion, or psychological disturbance, on tumorigenesis.

## Chong Liu's Research Group

Through developing a series of high temporal-spatial resolution genetic engineering mouse models, the Liu's group has been able to visualize and track the whole process of glioma genesis and development. Combining interdisciplinary advantages with developmental biology research concepts, this group then drives this study of the biological basis of gliomas through into clinical and translational applications on a number of levels and perspectives.

**Does olfaction deprivation lead to compensatory enhancement of other sensory signals, thereby increasing the incidence of gliomas in other brain regions?**

**Liu:** When analyzing tumor locations in olfaction deprivation mice, we found a very interesting phenomenon. After blocking the left naris, the tumor incidence decreased in the primary olfactory circuit (olfactory bulb), but slightly increased in the higher olfactory circuit, as well as in other functional brain regions such as the habenula. This suggested that after suppressing olfaction, these regions beyond the olfactory bulb may gain compensatory activities to promote tumorigenesis. However the underlying mechanism for this requires further exploration.

**Is the predisposition of gliomas in the olfactory bulb mainly due to the specificity of olfactory input or the specificity of glioma precursor cells in the olfactory bulb?**

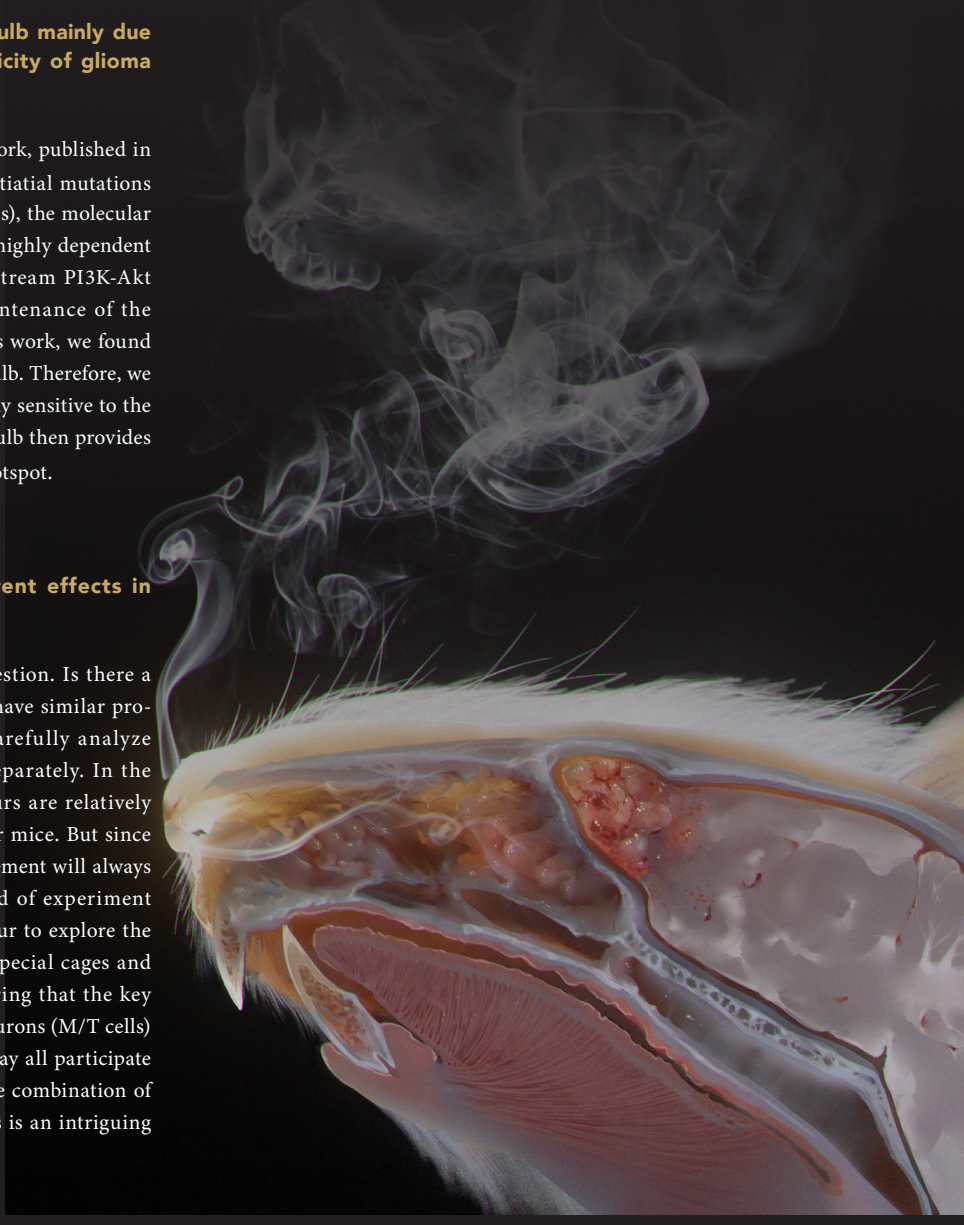
**Liu:** We think both mechanisms count. In our previous work, published in ***Advanced Science***, we found that after introducing initiatial mutations of p53 and NF1 into oligodendrocyte precursor cells (OPCs), the molecular signaling network of OPCs is re-programed and becomes highly dependent on the IGF1R signaling for the activation of the downstream PI3K-Akt signals. Such latter signalling is essential for the maintenance of the stemness of pre-malignant and transformed OPCs. In this work, we found that IGF1 molecules are highly enriched in the olfactory bulb. Therefore, we believe that precursor cells with driver mutations are highly sensitive to the IGF1R signaling pathway. IGF1 enriched in the olfactory bulb then provides the essential nutrient, making the olfactory bulb a tumor hotspot.

**Do different olfactory signal inputs have different effects in gliomagenesis?**

**Liu:** We are also very curious about this interesting question. Is there a specific odour that plays the key role? Or do all odours have similar pro-tumor effects? To answer this question, we need to carefully analyze the specific odour in the mice's living environment separately. In the environment of experimental mice, the sources of odours are relatively simple, mainly from food, excrement, bedding, and other mice. But since mouse excrement is constantly produced, odors from excrement will always be present in the conventional cages, making this kind of experiment very challenging. To precisely control the individual odour to explore the impact on tumorigenesis, we are currently redesigning special cages and a corresponding ventilation system. Of course, considering that the key effector IGF1 is uniformly expressed in all second-order neurons (M/T cells) of the olfactory circuit, different olfactory signal inputs may all participate in tumorigenesis. However, whether a specific odor or the combination of a panel of odors take account for the triggering of tumors is an intriguing question deserving further exploration.

**Does a similar neuromodulatory mechanism exist in peripheral organ tumors, and does this provide the potential for therapy by neural stimulation?**

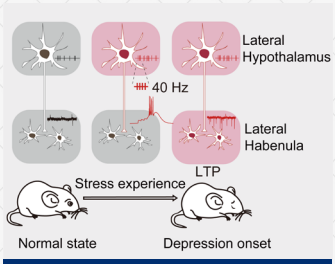
**Liu:** In the peripheral nervous system, nerves can directly regulate various tumors such as prostate cancer, gastric cancer, breast cancer, skin cance, r and pancreatic cancer through neurotransmitters or growth factors. Many studies have emphasized the effect of neural activity on tumor progression. Therefore, it is completely feasible to treat tumors by regulating neural activity. Of course, there are still many problems to be addressed. For example, different types of neurons in a specific region may have different or even opposite effects on tumorigenesis, so the specificity of stimulated neuronal cell type should be carefully defined for the best therapeutic outcome.



# Identifying the pathway from stress to depression

## The Hypothalamus-habenula synapse unpacked as a potential therapeutic target for chronic stress-induced depression

**Whilst stress relates to the sense of tension that the circumstances of daily life can so often bring, depression is a deeper concept.** It describes a more fundamental change in mood, often characterized as a persistent sadness, linked to biochemical imbalance, and is globally recognized as a leading cause of disability and a top contributor to the overall burden of disease. However, stress and depression are clearly linked. Chronic stress has been identified as a major risk factor for the onset of depression. Decades of dedicated investigations have been devoted to depression. However, whilst numerous studies have focused on the neural dysfunctions under the depression state, far fewer have paid attention to the potentially linked or even causative dynamic changes that occur in neural circuits prior to the onset of depression. In particular, there is a great need to focus upon how repeated stress can sculpt neural circuits into the eventual elicitation of depression.




Hypothalamus-habenula potentiation encodes chronic stress experience and drives depression onset

The team of **Yihui Cui** has been committed to deciphering the spatiotemporal dynamics related to chronic stress and the mechanisms underlying depression onset at the molecular and circuitry levels. Their studies have led them to a focus upon a particular key brain region, the lateral habenula (LHb), which acts as a convergent hub integrating value-, sensory- and experience-dependent information to mediate various motivational processes. This subcortical brain region is notably active in the pathophysiology of depression where enhanced bursting can be observed for the firing of LHb neurons under such a depression state. This brain region also receives inputs from various limbic and cortical areas. Interestingly, previous studies have revealed that negative emotions can be induced instantly via optogenetic activation of LHb afferents. However, most of the studies used artificially stimulating patterns and neglected to investigate whether these afferents were physiologically involved in processing the experience and/or to what extent they represent real activity patterns in response to stress.

After thorough investigation, Yihui Cui and her team may have come to the bottom of this question and have now definitively demonstrated a causal role for lateral hypothalamus (LH)-LHb activity in driving depression-related behavior during chronic stress. Their latest research has just been published in ***Neuron*** (February, 2022).

Using an unbiased whole-brain scale, their studies first combined viral tracing techniques, immediate early gene expression analysis, calcium imaging, and electrophysiology, to explore the source of stress signals that are processed onto the LHb. By comparing the degree of neuronal/synaptic activation from different afferents onto the LHb under stress, they were finally able to provide a comprehensive LHb-centric brain atlas for the processing of stress information. They identified the LH as a key node for the processing of stress onto the LHb. Then, with the help of both in vivo and in vitro electrophysiology (a particular expertise of Yihui CUI's lab), they found that the LH exhibits a unique firing pattern (40 Hz clusters, 4-5 spikes/cluster) that efficiently drives temporally coincident LHb bursting. The repeated excitatory postsynaptic potentials (EPSPs) burst pairings during chronic stress thus evoked a "Hebbian[1]" potentiation at LH-LHb synapses. Notably, such "Hebbian potentiation" is necessarily required for depression onset. Furthermore, applying optogenetic stimulation, the team conducted the first demonstration of the application of a transplantation of a stress experience that never actually took place through the inception of extracted "stress coding" at the LH-LHb synapse. This confirmed such activations to be determinants of stress-induced depression where, by merely potentiating this pathway, the research team were able to successfully induce a depressive state onto naïve mice.

Collectively, this data delineates the spatiotemporal dynamics of chronic stress processing at the LH-LHb synapses. This bypasses the actual learning from stress experiences and embeds memories that guide such an internal state transition from normal to depression status.

As a team spokesperson commented, "We were impressed by the striking fact that we had created an 'emotional status' via the deliberate implantation of an artificially extracted 'stress code'. We believe this provides a plausible biophysical implementation of the physiological basis for many types of 'memory' which explicitly conform to Hebb's postulate[2], and largely expands the 'memory hypothesis' previously raised by Morris." They concluded, "Stress leads to synaptic dysfunction. This dysfunction can therefore be a potential therapeutic target for stress-related mood disorders. We believe our study takes a significant stride towards the elucidation of the mechanisms of neural circuitry underlying the onset of chronic stress induced depression, and sheds light on early interventions that may be achievable prior to the onset of depression. "

1. Hebbian theory is the concept that "neurons that fire together, wire together,"

2. Hebb's postulate envisages that the "activation or inactivation of extant synaptic contacts in plastic neural networks depends on the synchronous impulse activity of pre- and postsynaptic nerve cells".

### YIHUI CUI'S RESEARCH GROUP

The team has its focus upon chronic stress, a major risk factor for depression onset. The team of Yihui Cui has been using multiple animal models to analyze stress-related neural circuits and their underlying mechanisms. Multi-disciplinary methodologies have been applied throughout their studies, including in vivo and in vitro electrophysiology, fiber photometry, optogenetics, chemogenetics, pharmacological and behavioural interactions, molecular biology, and other cutting-edge techniques. Their goal is to decipher the dynamic code of stress and clarify the key nodes of stress-induced depression onset at the molecular, cellular and circuitry level. To translate their research findings, they have also been in collaboration with clinicians. Based on their decoding data, they hope to find novel neuromodulation strategies that could be utilized to prevent stress-induced depression.

# Diabetic neuropathic pain relief

## Identifying the molecular and cellular mechanisms underlying diabetic neuropathic pain

**Diabetic neuropathic pain (DNP), caused by diabetic neuropathy, is a common and devastating complication of diabetes mellitus.** People with DNP often suffer from tingling, burning, sharp, shooting sensations, or even the sense of electric shocks. This occurs especially at night often making sleep extremely difficult. DNP occurs in about 30% of diabetic patients and severely affects their physical and mental health and life quality. Since effective treatments are lacking due to the mechanisms of DNP remaining unclear, it is urgent to clarify the pathogenesis of DNP and explore new therapeutic targets.

G protein-coupled receptors (GPCRs) represent a seven-transmembrane protein superfamily. They play important roles in cellular signal transduction and are widely involved in physiological and pathological processes including those related to pain sensations. One-third of FDA-approved drugs target GPCRs, thus highlighting the GPCRs as a fertile area in the search for new potential therapeutic targets. In April 2022, **Zhen-Zhong Xu**'s team from the Brain and Brain-Computer Interface Frontier Science Center published their latest research in the journal ***Science Translational Medicine***. They revealed that the orphan G protein-coupled receptor GPR177 in primary sensory neurons, drives DNP pathogenesis via WNT5a-mediated activation of the TRPV1 ion channel. Potential mechanisms to suppress and treat the condition were then revealed.

Orphan GPCRs are GPCR receptors whose functions and endogenous ligands have not yet been clearly identified. Xu's group discovered GPR177 to be mainly expressed in large-diameter A-fiber dorsal root ganglion (DRG) neurons and realized their actions were integrally linked to the development of DNP. This led the team to consider how GPR177 participates in DNP regulation. The team found that GPR177 mediated the secretion of WNT5a from A-fiber DRG neurons into the cerebrospinal fluid (CSF) and that this process was necessary for the maintenance of DNP. Knockout of Gpr177 from DRG neurons was then demonstrated to block the secretion of WNT5a and prevent DNP. Knockout of Wnt5a, or antagonizing the secreted WNT5a with neutralizing antibody, could also mitigate DNP. The research team were able to show that WNT5a can directly activate the TRPV1 ion channel and induce rapid inward currents and single channel activity in TRPV1-expressing heterologous cells. WNT5a is also able to selectively activate small-diameter C-fiber nociceptive DRG neurons in a TRPV1-dependent manner, resulting in neuropathic pain symptoms. These results reveal the role for WNT5a as an endogenous TRPV1 agonist, and the GPR177-WNT5a-TRPV1 axis as a driver of DNP pathogenesis (Fig. 1).

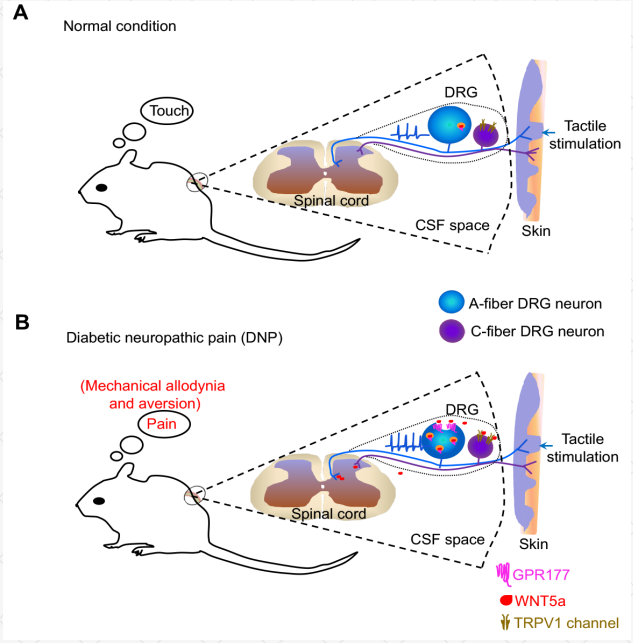



Figure1. Proposed model for GPR177-WNT5a-TRPV1 axis driving DNP pathogenesis

The team further considered whether DNP could be alleviated by disrupting the WNT5a/TRPV1 interaction. Through interdisciplinary cooperation, and based on the three-dimensional structure of the TRPV1 channel, the team used computer simulations and protein docking experiments to discover the potential of multiple binding sites between WNT5a and its residues at the extracellular S5-S6 loop of TRPV1. The team further designed blocking peptides for their predicted interaction sites to block the binding and activation of TRPV1 by WNT5a. Such results showed that a blocking peptide could effectively suppress DNP- and WNT5a-induced neuropathic pain. Finally, the team also confirmed the co-expression of GPR177/WNT5A in human DRG neurons and showed WNT5A secretion levels in the CSF from diabetic patients were positively correlated with pain intensity. This strongly suggested that the GPR177-WNT5A-TRPV1 axis could be a new therapeutical target for treating clinical DNP.

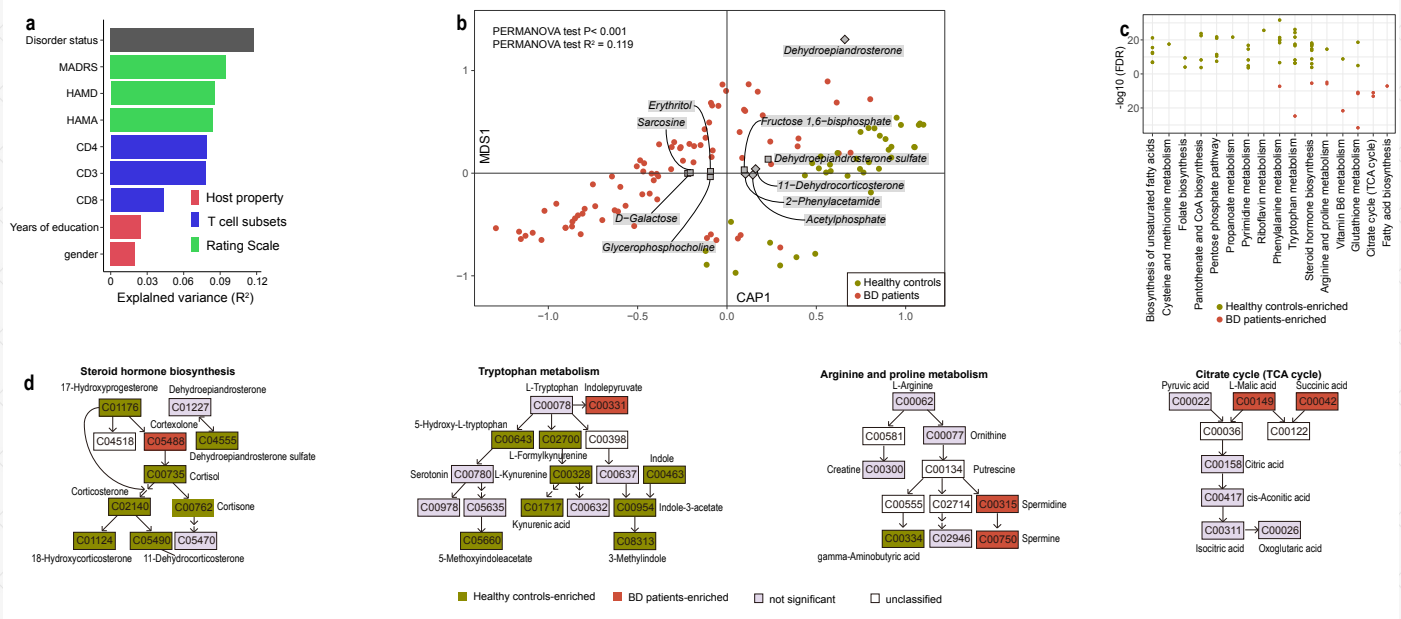
As spokesperson from the team explained, "The GPR177-WNT5A-TRPV1 axis identified in this study is not only the key molecular mechanism driving the pathogenesis of DNP, but also represents a new mechanism for crosstalk between A-fiber and C-fiber primary sensory neurons. Related studies can therefore provide new insight into the study of chronic pain which may lead to potential strategies for many kinds of chronic pain treatment."

### ZHEN-ZHONG XU'S RESEARCH GROUP

Zhen-Zhong's group studies the molecular, cellular, and circuitry mechanisms underlying sensory signaling and their plasticity, including pain and itch. They also focus on the molecular mechanisms and circuits related to negative emotions induced by chronic pain. They are committed to exploring new drug targets and discovering interventional strategies for chronic pain.

# Gut Microbes could mediate depression

## The microbiota-gut-brain axis for bipolar disorder




Comparison of serum metabolites between depressive episode patients with bipolar disorder (BD) and healthy controls (HC)

**Bipolar disorder (BD) is a common and severe mental disorder characterized by alternating depressive and/or (mild) manic symptoms.** It affects 2-3% of the global population. Clinical diagnosis and treatment of BD are challenging due to its complex etiology. Over recent years, the microbiota-gut-brain (MGB) axis, the bidirectional regulation mechanism between the brain and gut microbes, has gained increasing attention in neuroscientific research. Alongside many other findings that have elevated the importance of the MGB axis has come evidence that strongly implicates the involvement of the MGB axis in BD. However, the specific mechanisms by which this may occur have remained unclear.

In April 2022, the team of **Shaohua Hu** (the First Affiliated Hospital of Zhejiang University School of Medicine) with Xueqin Song (the First Affiliated Hospital of Zhengzhou University) and Chao Nie (Shenzhen BGI) co-published research that strongly clarifies this issue in the journal ***Molecular Psychiatry***. This study was the first one to show the specific relationship between the gut microbiota and BD through the combined analysis of serum untargeted metabolomics, fecal metagenomics sequencing, and resting brain functional magnetic resonance (rest-f-MRI).

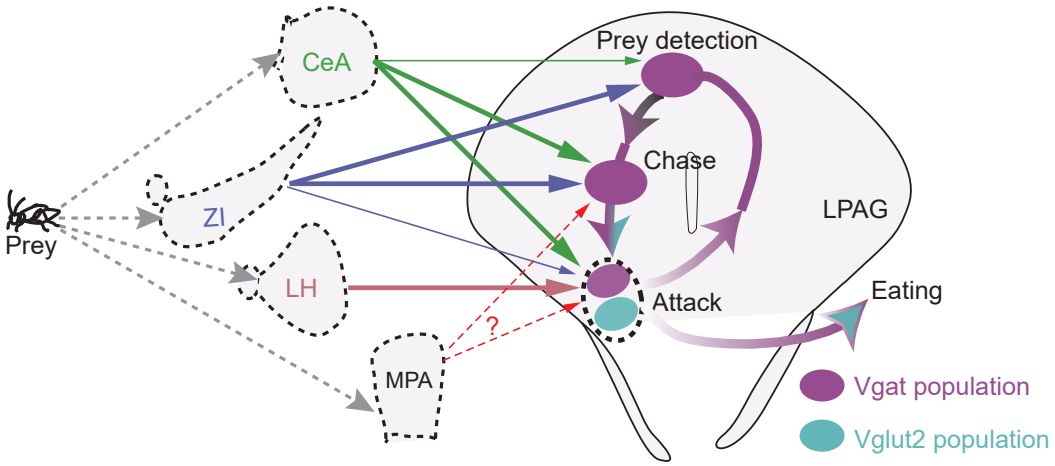
This study found that the levels of serum metabolites such as short chain fatty acid (SCFA) derivatives, kynurenine (KYN), gamma-aminobutyric acid (GABA), riboflavin and folic acid were decreased in BD patients, while gamma-glutamylcysteine, succinic acid, malic acid and indole-pyruvate were all increased. Such metabolites, being active participants in the fundamental tryptophan, citric acid cycle, glutathione metabolism and SCFAs metabolic pathways, show that that the serum metabolic levels of BD patients are significantly altered (Figure 1). Correspondingly, the fecal abundance of microbes such as *Streptococcaceae* and *Bacteroidaceae* increased while *Akkermansia muciniphila* and *Faecalibacterium prausnitzII* were decreased in BD patients, suggesting dysfunctions of gut microbiota relating to BD. More specifically, gut microbes were significantly correlated with serum metabolites. For example, the *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* were closely related to the "Neuromodulator" metabolic pathway including its folic acid and riboflavin, SCFAs, KYN, and GABA components. Furthermore, the influence of serum metabolites on brain functions in BD patients was even greater than upon the gut microbes, indicating that serum metabolites may mediate the regulation of gut microbiota to the brain. In other words, gut microbiota and their metabolites may transmit signals to the central nervous system through the circulatory system, thus regulating the functional activities of the brain and participating in the pathogenesis of BD depression.

### SHAOHUA HU'S RESEARCH GROUP

Within the scientific field of biological psychiatry and clinical psychiatry, Shaohua Hu's group is dedicated to study affective disorders which include bipolar disorder and other major depressive disorders. They are particularly focused upon pathogenesis, biological markers, new therapeutic techniques, and clinical transformations from basic research.

# Programming Predators

## Unmasking the sequential coding mechanism of predatory hunting




LPAG neurons encode the movement sequences of predatory behavior

**Many extraordinary instinctive behaviors that are fundamental for survival, such as foraging, avoiding danger, mating, and parenting, seem to have been pre-programmed into many animal species during their developmental history.** How such behaviors are hardwired into neural circuits for each individual during their early development and experiences, which then enabling them to quickly and robustly respond to specific stimuli, has remained a key question. In addition, as the complexity of such requirements increases, the related neural responses must incorporate increased flexibility to account for the often swift modifications required due to changes in the environment.

The sequential encoding of motor programs is an essential process required for such behavior generation. Sequential neuronal activity is established in the hippocampus and motor cortex during memory and decision-making tasks. This then becomes incorporated into subsequent navigation, planning, and motor generation. However, the neural substrate underlying instinctive behavioral sequences, such as those specifically related to hunting for example, remain mostly unknown.

In November 2021, the team of Professor **Li Haohong** (Zhejiang University) and Professor Wei Shen (ShanghaiTech University) co-published their latest research results in ***Nature Communication***. In this, they clarified for the first time the basic rules of predation behavior as encoded by lateral periaqueductal gray (LPAG) neurons.

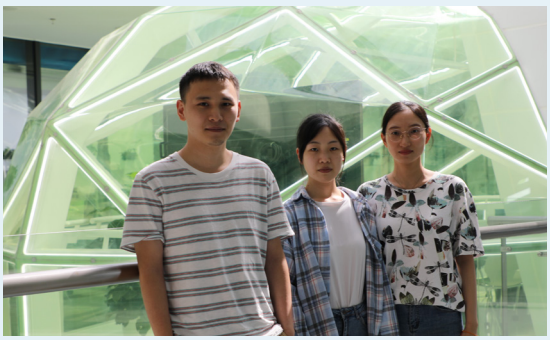
This study demonstrated that distinct subpopulations of LPAG neurons are sequentially recruited for the prey detection, chase, and attack phases of hunting. When such behavior is generated, a series of neuronal ensembles are activated sequentially. These chain various actions into sequences. In this manner, the behavior is robustly performed and is primed for both consistency and quick response, whilst also retaining flexibility.

Meanwhile, the team also found that the central amygdala, lateral hypothalamus, and zona incerta provided key GABAergic inputs to regulate this LPAG neuronal activity during the different hunting phases. Selective ablation of any of these inputs interrupted the sequential activity pattern in the LPAG and impaired almost all the hunting motor actions, with the exception of eating.

"Here, we provide a framework of neuronal ensemble sequences that may occur across predatory hunting species. This may also shed light on other instinctive behaviors", the team spokesperson explained. "Due to the limitations for precision measurement of behavioral analysis, we cannot yet link predation actions into the sequence coding theory based on stimulus-response theory. In the future, we will study how neuronal ensembles code actions with built-in flexibility by combining motion capture technology with in vivo electrophysiological techniques and at higher temporal-spatial resolutions."

### HAOHONG LI'S RESEARCH GROUP

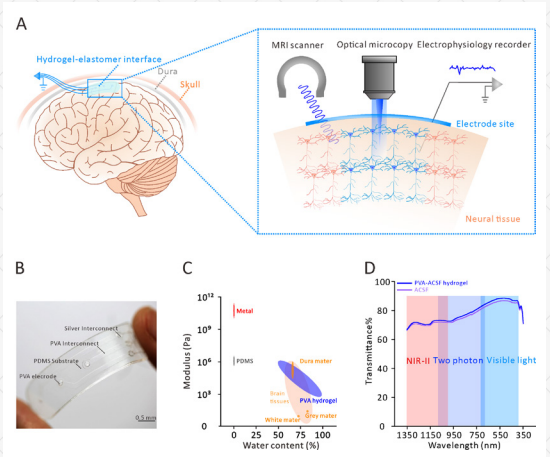
Li's group is dedicated to the study of the neural circuit of sleep-wake control and the mechanism of oscillation in related neural networks. Their research has resulted in the discovery of the paraventricular nucleus of the thalamus as an important center for sleep-wake control; verified the principle of how modulated wakefulness affects learning and memory; and analyzed the neural mechanism behind slow-wave oscillation induced by high-level wakefulness stimulation. Related works have been published in ***Nature Neuroscience, Neuron, Nature Communication, Current Biology, Cell Reports,*** and others.



# The Hubble Telescope of Neuroscience!

## Multimodal soft brain-machine-interfaces

**The term the "three-pound universe" describes the brain perfectly.** Its 86 billion neurons represent a larger number of connections than there are galaxies in the universe, but these are all encompassed in the weight of a small bag of potatoes! Just as the development of the "Hubble Telescope" opened up the secrets of the heavens, so some scientists are beginning to think that the development of multimodal brain-machine-interfaces (BMIs) might represent comparable tools to unlock the inner secrets of the brain. Various types of BMIs have been developed at different scales to collect and transmit electrical or optical signals of neuronal activity to produce and visualize data. Since 2017, **Hao Wang** and his team have concentrated on developing a new hydrogel-based BMI in cooperation with the team of Zhigang Suo from Harvard University, and the team of Wang Xi from the Institute of Systems Neurology (Zhejiang University). Their research team has just published their latest work in ***Biomaterials***, representing a second phase following the initial work published in ***Extreme Mechanics Letters*** in 2019. In this, they outline their development of a new subdural cortical electrode called the hydrogel-elastomer neural interface (HENI). The HENI consists of PVA-ACSF hydrogel, functioning as an ionic conductor, and with a Polydimethylsiloxane (PDMS) elastomer as an insulating layer. Compared with traditional metal electrodes, HENI electrodes have both a high bio and nuclear magnetic compatibilities, as well as having broad multimodality characteristics with the capacity for utilization in conjunction with many existing optical imaging techniques.




A novel multimodal neural interface with MRI compatibility and biocompatibility

Subdural cortical electrodes (ECoG electrodes) are partially invasive electrodes embedded above the cortex. ECoG electrodes have a pivotal role in both clinical diagnosis (e.g., localization of epileptic sites) and basic brain research, as they can capture high-quality cortical signals. Traditional ECoG electrodes have often used metal as the conductive material. However, the use of metals impairs long-term high-quality recording, not only because its hardness easily damages the brain surface, but also due to the poor biocompatibility caused by excessive activation of glial cells and proliferation of glial scars. By contrast, soft hydrogel is considered an ideal succedaneum, not just that it solves or avoids such issues of abrasion, excessive activation and scaring, but also because of its high ionic conductivity derived from the high level of ionic solution that it contains.

The specific HENI ECoG electrode that the team have developed relies on PVA gel with artificial cerebrospinal fluid (ACSF) as the solvent to collect electrical signaling. The mechanical and chemical properties of HENI are highly similar to that of neural tissues, thus providing outstanding biocompatibility. After prolonged embedding, the HENI electrode caused significantly less vascular proliferation, deformation, and glial cell proliferation than commercial metal electrodes. In addition, the PVA-ACSF hydrogel material has an average transmittance of 86% for wavelengths commonly used in optical microscopy, allowing simultaneous optical observation above the electrode recording site.

With the help of two-photon microscopy, the team simultaneously collected calcium and vascular signals from neurons below the electrode site and recorded electrical signals from the cortex. This enabled concurrent multi-method and multi-dimensional observation to resolve the physiological state of neurons and the surrounding blood vessels of the same region. Finally, the team evaluated the MRI compatibility of the HENI electrodes. The MRI images showed clear imaging on the buried side of the gel electrode, indicating that, in contrast to metal electrodes, the PVA-ACSF hydrogel electrode did not adversely affect MRI imaging.

Overall, it is the construction of the conductive material part of the HENI electrode (PVA-ACSF hydrogel), deliberately engineered to be highly similar to natural neural tissue in terms of chemical composition, conductivity and its elastic modulus value, which is its most notable and highly attractive feature of this newly developed electrode. The PDMS silicone used in the insulating layer has also been specifically engineered to be similar to the dura mater in terms of its elastic modulus value, making the HENI electrode a biofilm-like electrode. Through a series of evaluation experiments, the safety of the long-term clinical implantation of HENI electrodes is expected to be soon confirmed. If so, it can then be used to replace the existing metal electrodes. Such a replacement should not only represent improvements in increased use potential and longevity for such probes, but also to considerably improve patient comfort and decrease adverse effects. Regarding specific applications, with the help of these new HENI electrodes the research team now hopes to focus on neuro-vascular interactions and signal recording from the cortical sulcus gyrus.

### HAO WANG'S RESEARCH GROUP

Hao's group focuses upon innate behaviors as the basic skills animals must possess to survive and reproduce. They consider that revealing the neural circuitry of innate behaviors can help us to understand how the brain works and provide new insights into the pathology of many related brain diseases. In particular, his group employs advanced techniques including optogenetics, in vivo calcium imaging, electrophysiological recordings, and single-cell sequencing, to systematically uncover the neural circuit mechanisms of fear, feeding, social behaviors, and other related areas.

## Scientific and Tecnological Innovation 2030 -"Brain Science and Brain-Inspired Research"

### major projects for answering major scientific questions and developing key technological support

01 **Director** Gang Pan
**Project** Brain-computer fusion research platform

02 **Director** Xiaoming Li
**Project** Research on the mechanism of the neural circuitry of fear

03 **Director** Hailan Hu
**Project** Mechanistic study of new therapeutic strategies for mood disorders

04 **Director** Haiteng Jiang
**Project** Precise diagnosis and treatment for major psychiatric disorders (Young Scientist Program)

05 **Director** Ruiliang Bai
**Project** The glymphatic system in sleep: key measurement techniques and regulation mechanism (Young Scientist Program)

06 **Director** Lixia Gao
**Project** The intrinsic and environmental regulation mechanisms underlying vocal development and vocal communication in different animal models

07 **Director** Lijun Kang
**Project** Molecular, cellular, and neural mechanisms of visceral mechano-sensation

08 **Director** Haohong Li
**Project** Removing potential addiction - a new therapeutic strategy

09 **Director** Zhihua Gao
**Project** Hypothalamic neural circuit mechanisms underlying fear expression

10 **Director** Yanqin Yu
**Project** New targets and methods for the treatment of sleep-wake disorders

11 **Director** Xuhua Wang
**Project** Fusion and application of non-invasive Brain-Computer Interfaces (BCIs)

12 **Director** Aimin Bao
**Project** China's Southeastern Brain-Bank Network Platform Development

13 **Director** Yi Shen
**Project** Standardization of quality control for China's Brain-Bank Network

**Professor Hu Hailan, director of the BBMI, wins the prestigious 2022 L'Oréal-UNESCO for Women in Science International Award.**

Hu Hailan is a professor at the Zhejiang University School of Brain Science and Brain Medicine and the director of the MOE Frontier Center of Brain Science and Brain-machine Integration (BBMI). She has just been honored with the 2022 L'Oréal-UNESCO for Women in Science International Award on June 23rd 2022. UNESCO highlighted her award for her "pioneering discoveries in neurobiology that have revolutionized our understanding of social and emotional behavior and mental disorders."

Founded in 1998, the award annually celebrates the scientific excellence of five eminent women scientists, each from a major region of the world. Prof. Hu is the 2022 laureate for Asia and the Pacific.

The permanent Mission of China to UNESCO held a reception to congratulate Professor Hu Hailan on winning the 2022 L'Oréal-UNESCO for Women in Science International Award on June 21st. Yang Jin, the permanent representative of China at UNESCO, delivered his congratulations to Hu Hailan, hoping that her success story would encourage more women to devote themselves to scientific careers, and looking forward to the progress in drug research and development that has been brought about by her scientific research achievements to provide pain relief to countless patients with clinical depression.

Professor Hu Hailan thanked the permanent mission of China to UNESCO for its arrangements, and L'Oréal and UNESCO for their outstanding efforts in supporting women scientists and promoting gender equality. She expressed that the L'Oréal-UNESCO for Women in Science International Award conveys UNESCO's conviction, and her own personal hope, that more young women will learn about science, come to love science, and rise to become one of the top women of science, as inspired and motivated by such awards. She accepted the award not just for herself but felt that it also represented an honor for all Chinese women scientists. Six previous Chinese women scientists have won the award including Professor Nancy Yuk-Yu IP, Professor Chen Hualan, and Professor Zhang Miman in the field of life sciences. She expressed great honor to join such a prestigious group. She strongly believes that more prestigious Chinese women scientists will be so awarded in the near future.

Prof. Hu hailan (middle) wins 2022 L'Oréal-UNESCO For Women in Science Award


Prof. Hu hailan (Fourth from the right) wins 2022 L'Oréal-UNESCO For Women in Science Awards


Yang Jin (fourth from right), Permanent Representative of China to UNESCO, with Prof. Hu Hailan (fifth from right) and others.

# The BBMI Academic Reports

## 2022 First Half

### Guojie Zhang

Professor, School of Medicine, Zhejiang University
Distinguished Lecture Fellow, Kunming Institute of Zoology, Chinese Academy of Science

18-03-2022

**What Does Wild Animals Teach Us About the Genetic Basis of Morphology, Physiology and Behavior**

After billions of years of evolution, life on earth has created a variety of strange species in the world today, with a plethora of morphological, physiological, and behavioral characteristics. These colorful biological functions are derived from the unique genetic composition of each species. The comparison of the genomes of different species provides an important research method for us to carry out the association analysis of genotype and phenotype. Professor Zhang's team uses comparative genomics to study the evolutionary dynamics of species and the path of human evolution, as well as to understand the evolution and developmental regulation mechanism of the division of labor and behavior in of social insects through their study of ants.

### Edward M. Callaway

Professor, Member of the National Academy of Sciences,
The Salk Institute for Biological Studies

18-05-2022

**Cell Type-specific Neural Circuit Tracing with G-deleted Rabies Viruses**

Monosynaptic circuit tracing with glycoprotein-deleted rabies virus allows the direct inputs to selected cell types, or even single neurons, to be revealed across the entire brain. Professor Callaway reviewed such methods and reagents used to implement this approach and discussed both their advantages and limitations. In particular, he presented evidence that monosynaptic rabies tracing is synapse specific – inputs are only labelled if there are synaptic contacts between pre- and postsynaptic neurons. While there are hundreds of published manuscripts using this approach, there are no examples in which cells have been labelled but are known not to be synaptically connected. However, there are numerous examples of differential labelling of inputs to intermingled cells of different types and many examples of "newly discovered" connections that have been functionally validated. Some such connections have not yet been labelled, or have been labelled inefficiently, but their mechanisms still remain understood and predictable. Despite this, connections mediated by "volume transmission" (non-synaptic), gap junctions, or axo- axonic contacts are not detected. Professor Callaway presented new data showing that inputs to distal versus proximal dendrites are labelled with nearly equal efficiency.

## Xiaokun Li

Professor, Member of the Chinese Academy of Engineering,
Chancellor of Wenzhou Medical University

24-05-2022

### Translational medicine research on growth factor drugs

Growth factors are a class of highly evolutionarily conserved functional proteins that play crucial roles in organ formation, tissue regeneration, and metabolic regulation. However, how to transform these into drugs with clinical applications remains a gobal problem. Aiming at the problems of poor stability and difficult druggability of recombinant proteins, Prof. Li's team has successfully developed three new drugs made up of of fibroblast growth factors (FGFs) through protein structure-activity theory and engineering technological innovation. They have been the first in the world to achieve FGFs drug industrialization, build a new system for the research and development of original cell growth factor drugs, and promoted the development of protein drug engineering technology in China. In response to major clinical needs such as the healing of complex wounds and refractory ulcers, the FGF series of new drugs have been applied in more than 5,500 hospitals and to the treatment of 65 million people.

## Anna Wang Roe

Professor, School of Medicine, Zhejiang University,
Director of the Interdisciplinary Institute of Neuroscience and Technology

16-06-2022

### Intelligent Primate Systems

The cerebral cortex of human and nonhuman primate brains is characterized by submillimeter functional domains. However, little is known about networks based on such functional nodes. Professor Roe has developed new methods to stimulate single submillimeter nodes in macaque monkey cortical and subcortical sites, and to map at local and whole brain scale the mesoscale networks activated by single node stimulation. Her team's findings show that resulting networks are highly organized, specific and sparse. Their data suggest the presence of intra-areal and inter-areal micro-networks that form basis functions for common domain-based convergence, divergence, and binding strategies. Professor Roe's findings establish a framework for domain-based connectional architecture in the primate brain, and present new constraints for building whole brain networks. She is now working towards developing a brain theory that will impact neuroscience, medicine, AI, and neuromorphics.

## Hongwei Tan

Professor, Academician of the Chinese Academy of Sciences,
Member of the World Academy of Sciences for the Advancement of Science in Developing Countries

06-29-2022

### Functional Nucleic Acid

Modern medicine requires understanding, diagnosis, treatment, and prevention at the molecular level. The discovery and verification of disease markers and the development of molecular probes will greatly improve the level of clinical diagnosis and treatment and promote the study of molecular mechanisms of diseases. However, such molecular tools have remained highly scarce. Functional nucleic acids have broad application prospects in the field of diagnosis and treatment of major diseases and can specifically identify proteins and small molecules. Based on this, the team of Academician Tan pioneered a new method for aptamer cell screening (Cell-SELEX) using intact cells as the screening target. This method is simple, fast and reproducible. Through this screening method, the team obtained nucleic acid aptamers for a variety of diseases and used them in cutting-edge research and clinical applications in biomedicine, including ultrasensitive detection of cancer, molecular imaging, targeted drug delivery, etc. These new molecular tools have established a revolutionary scientific and technological platform for the further development of molecular medicine.

# Interviewing the Department of Neurosurgery

**In the film Doctor Strange, Stephen Strange, as played by Benedict Cumberbatch, miraculously saves a patient's life by removing a bullet near his brain stem.** Such people exit in real life – neurosurgeons, whose daily job is to deal directly with such issues within human's most important "headquarters" – the brain. Scalpels are their sharpest weapon to fight against various diseases, and their profound knowledge and exquisite medical skills can often bring patients the hope of life. In China, neurosurgery mainly covers the areas of brain tumors, craniocerebral trauma, cerebrovascular diseases, brain function diseases, and some other fields. Together with the speed of development of modern neurotechnology, with their attention to brain science, neurosurgeons are no longer just "dancers on tightrope", but also "innovators" who have made great progress in cross-field research. Professor Jianmin Zhang, director of the Brain Center of the Second Affiliated Hospital of Zhejiang University School of Medicine, is exactly such an "innovator" in neurosurgery. With his notable strength and charm and his reputation as a gentle and kind mentor, he persists in exploring and innovating within his chosen professional field. For example, he has made a number of important breakthroughs in new methods for glioma treatment, closed-loop neuromodulation therapy for epilepsy, and in other fields. These results now have brought a new insight for the treatment of brain diseases. It is our honor to have this chance to interview Professor Zhang online. Let's get to know this popular and well-respected neurosurgeon together.

Jianmin Zhang is the director of the Brain Center of the Second Affiliated Hospital Zhejiang University School of Medicine, the director of the ZJU Institute of Brain Science, the director of Zhejiang Provincial Clinical Research Center for Neurological Diseases, and a chief scientist of the National Key Research and Development Program of China. His research mainly focuses on the cerebrovascular surgery, the treatment of nerve tumor and traumatic brain injury, and the translational application of brain-computer interfaces.

# "An innovator" in Neurosurgery

## Interview with Professor Zhang Jianmin of the Second Affiliated Hospital of Zhejiang University

**Hello Professor Zhang! We have learned that one of your research areas is the treatment of gliomas and you have recently published related original research works in Nano Today. Could you please briefly introduce the challenges in the current glioblastoma area? What can chemodynamic therapy provide for its treatment?**

**Zhang:** Gliomas are one of the most common neurological tumor types. More than half of them are glioblastomas. A glioblastoma is highly malignant and lacks effective treatments, so after routine treatment the median survival time is traditionally only about 16 months. However, new treatments are under exploration. Although tumor resection has become more accurate because of the improvement of surgical techniques, equipment, and monitoring technology, it is still impossible to remove the tumor completely due to its borderless growth and the entanglement of tumor tissue with surrounding healthy brain tissue. More recently the median survival time for patients' with glioblastomas has increased to about 21 months, thanks to the development of electric field therapy. However, the treatment effects are still not satisfying. Therefore, targeted- and immuno-therapies are also being explored. It is not easy to seek breakthroughs in the research and development of new chemotherapy drugs. Therefore, we hope to start with aspects of nanotechnology which can make chemotherapy drugs more specifically targeted into tumor cells and change the tumor micro-environment through light reaction. In this way, chemicals targeting only the tumor tissues can be induced, resulting in higher efficacy, improvement of the existing drugs, and with less off-target damage to the healthy brain. This approach, combined with newly developing nanotechnologies, opens up a whole new direction for glioma chemotherapy research.

**In addition to gliomas, your another research is about brain-computer interface technology. As a neurosurgeon, how did you come up with the idea of developing brain-computer interface technology?**

**Zhang:** My research in this area is centers around cerebrovascular disease. Although a large number of our patients with cerebrovascular disease survive after rescue and treatment, many are still troubled by sequelae like hemiplegia. Therefore, brain-computer interface technology has become linked to my hope to improve patients' life quality through intelligent rehabilitation and motor function reconstruction. All these demands are closely related to clinical practice. In addition, the brain-computer interface represents a technology that can directly control an external machine by EEG signals. Therefore, the first step is to extract EEG signals for decoding. At present, owing to the low spatial resolution of EEG signals, we directly implant electrodes into the brain to extract better signals. This involves invasive neurosurgery to implant such technology. Only neurosurgeons are in a unique position to be able to touch and gaze at the brain directly. With a strong sense of respect for this privilege and responsibility, we are aware that this unique advantage allows us to carry out research on implantable brain-computer interfaces. To do this, strong alliances are formed combining our professional advantages and those of the brain-computer interface team of Zhejiang University. On the one hand, we can help patients recover and improve the recovery effect through intelligent brain-computer interface technology; on the other hand, for completely paralyzed patients, we want to help them control external robot arms or other mechanical devices, or even control their own paralyzed limbs to complete daily activities through brain-computer interface technology. This has the capacity to greatly improve patients' life quality.

**We also learned from the media that you and the team of Professor Xiaoxiang Zheng and Professor Yueming Wang rebuild the motor function of high paraplegic patients through brain-computer interface implantation. What is the latest progress of this project?**

**Zhang:** Three years ago, we implanted invasive brain-computer interface electrodes for our volunteer Mr. Zhang. He was a high-degree paraplegic patient with complete brain function but non-functional limbs. We implanted two array electrodes including 200 electrode points into his primary cerebral cortex, and connected the electrode signal wires through fixed posts on his scalp and skull. Thorough these we were able to realize the control of a robot arm by the electronic signals of the motor control area in the precentral gyrus. This is the only case in Asia that uses a mind-controlling external robot arm to complete complex three-dimension movements. Mr. Zhang now can bring water to his mouth to drink and shake hands with President Wu of ZJU through the mechanical hand. However, even these simple actions are still technically difficult for mechanical controls. Three years later, the quality of the collected EEG signals for Mr Zhang remains very good. Since Mr. Zhang is the only volunteer in China who has an implanted array of electrodes in the brain, we are also racing against time to carry out further research. For example, recently we are working on the technology of writing and speaking Chinese through brain-computer interfaces. The brain's electronic signals will be decoded into what to write and to ascribe meaning. Although there are similar studies abroad, only Chinese people are in the situation to conduct such research based upon the Chinese language. Therefore, if the invasive brain-computer interface technology can be used to enable paralyzed patients to write Chinese, this will be another big breakthrough.

**Your team has also successfully developed a domestic closed-loop neuroregulator (Epilcure) recently. What's the mechanism and what's its significance for brain diseases treatment?**

**Zhang:** Actually, this is the second research focus of our brain-computer interface translation research. It is well-known that the ideal brain-computer interface should be a two-way communication, which means human brain can not only control external devices or transmit information to external devices directly, but that the external devices can also generate signals or give feedback through brain signals. That enables the brain to adjust its functions appropriately. We call this two-way communication, 'closed-loop modulation'. For example, although epileptic seizures can occur at any time, there are abnormal tell-tale EEG signals before such seizures occur, much like when seismologists detect abnormal seismic waves as an early warning before an earthquake. When the device captures these abnormal signals, it can automatically and responsively send out an electrical stimulus to balance out the abnormal signals, thus preventing the seizure from occurring. Thus, the function of our own neuromodulator involves not only early warning, but also sending responsive electrical stimulation for treatment in a closed-loop pattern. This is why I call it the "anti-missile system" of the brain. Other clinical solutions currently in application include deep brain stimulation (DBS) and vagus nerve stimulation (VNS). However, these are one-way regulation systems and are clearly insufficient for epilepsy treatment. We had previously noticed that Neuropace (a company in USA) was conducting clinical trials about closed-loop control devices in a project that began about ten years ago. We followed up and started our own research immediately. We have now completed the implantation for the initial, and then another subsequent two, refractory epilepsy patients last March and are currently conducting a national multi-center clinical study. This is our first product of brain-computer interface clinical research so far, and it has played a positive role in the localization and refinement of this new advanced technology.

**Nowadays, brain-computer interfaces have become a worldwide hot topic in scientific research. Many large companies have invested in the related research and development of brain-computer interface technology. Compared with international products of similar functions, what are the advantages and disadvantages of ours? What's your expectation for the future development of brain-computer interface technology?**

**Zhang:** Compared with the research on brain-computer interface in the world, our technology is still developing and the electrodes we use still need to be imported from abroad. However, our previously mentioned closed-loop epilepsy neuromodulation product seems to be better than similar foreign products. I have great confidence that our products have made great improvements compared to foreign products in their algorithms, size, and charging capabilities. Our product is mainly used for epilepsy now, but it actually has wider prospects in terms of neuromodulation such as in the treatment of depression, mania, addiction or other mental diseases. As for patients in unconsciousness or vegetative states with micro-consciousness, such as which might be caused by as cerebral hemorrhage or brain injury, we also hope that neuromodulation technology can help them recover. These new areas have become the emphasis of our research now, and we are constantly exploring it from many aspects. Of course, these studies require the basic research team to figure out the pathogenesis and find the corresponding biomarkers and associated neural circuits. It also requires technical and industrial collaboration with engineering teams and manufacturers. Zhejiang University has many such good platforms, including the artificial intelligence brain-like research team led by President Wu Zhaohui, and our own neuroscience, basic medical, and clinical research teams. Based on such a strong cooperation, I am sure that our research on brain-computer interface and brain science will make more and more progress.

**What's your opinion on the recently started Chinese "Brain project"?**

**Zhang:** Medical development represents constant progress in humanity's attempt to understand itself. The most difficult part of this is the human brain. It is important to study human brain, not only from the perspective of illness and health, but also in other related fields. However, our understanding of human brain is on the same level as that of the universe - it is progressing fast but the prospects are almost immeasurable and unlimited. Therefore, I believe that Chinese brain project has great strategic meaning. In this context, Zhejiang University has built a science research center for brain science and brain-machines and the clinical transformation of brain-computer modulation. This is a very wise choice that can keep pace with the global trend.

**Professor Zhang, your introduction teaches us a lot. How do you balance your scientific research and clinical practice since you have been already busy with your work as a clinical doctor?**

**Zhang:** Interest is the first and foremost thing. If you are interested, you will be persistent and willing to do your work, just like playing games. It is your interest that will make you feel all the efforts are worth while and that leads to progress. The second thing is having a united team, with all members sharing the same goals. Clinical work is my basic job and the foundation of my career. Scientific research and development therefore has to be done in my spare time. Our weekly group meeting will help us to summarize the research results, find deficiencies that need improvement, and make plans for next week, all of which is positive reinforcement. The final thing is persistence. It is remarkable that some breakthroughs can come out quite fast, but scientific research is an on-going process and it can only be achieved by persevering.

**What's your advice for us students focusing on basic research?**

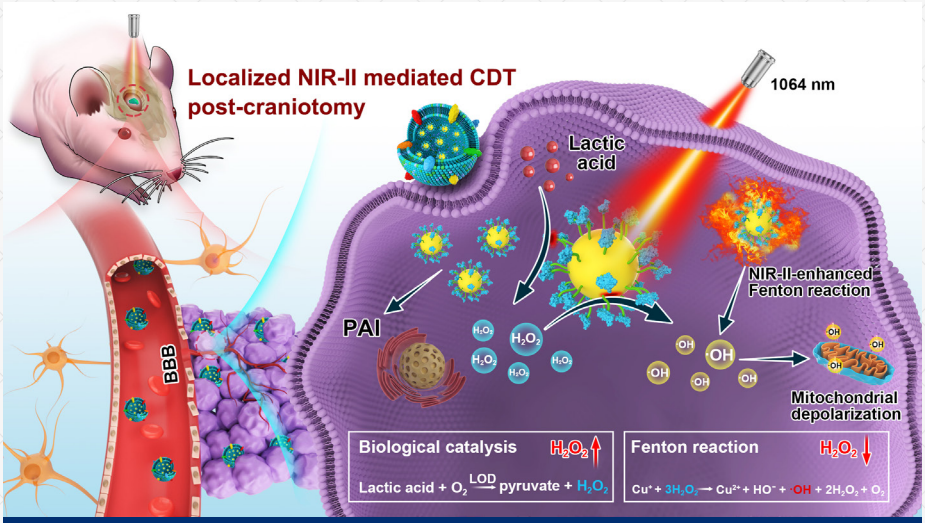
**Zhang:** Basic medical research and clinical practice are closely connected. First of all, you should do your own job well. Make good use of the resources of Zhejiang University, and concentrate on research. It is through accumulation of every tiny breakthrough in basic research that lays a good foundation for us clinical doctors to diagnose and treat patients. Researchers and clinical doctors have different roles. It will be quite perfect that if they can do a good job and make breakthroughs in their own fields. In fact, basic research and clinical practice are on a same pipeline. Each part can only do a little bit, and each product in the pipeline needs everyone's contribution from every separate part. There will be no high-tech development without basic research. Therefore, people working in basic research should have support from the country, society, and also their own peers.

**Professor Jianmin Zhang specializes in neurosurgery. His "magic hands" have brought life and hope to many patients suffering from diseases and made a great contribution on their life quality. Moreover, he is obsessed with finding new treatments methods and advancing technology with "creative minds". He participates in the "one body and two wings" framework of Chinese brain project actively and brings unlimited innovation and infinite vitality to the interdisciplinary sectors of neurosurgery, brain science and computer science.**

**The glioblastoma multiform (GBM) is an extremely aggressive and serious grade 4 giloma brain tumor.** Twinned with its exceptionally serious nature, it is unfortunately also the most common primary malignant brain tumor in adults. The median survival of optimally treated GBM patients remains at about only 16 months. Currently, the primary treatment for GBM involves maximal surgical resection, followed by radiotherapy and alkylating chemotherapy with temozolomide. However, a number of major hurdles remain towards further improving such treatment regimens. Most significantly, GBM diffusely infiltrates normal brain tissues, making it impossible to totally resect. In addition, the blood-brain barrier (BBB) prevents most drugs and nanoparticles from entering the brain, despite the BBB of GBM patients being partially disrupted. Moreover, most cancer therapeutics cannot actively restrict their targeting to tumor cells, even if they cross the BBB. Such treatments therefore cause serious toxicity side effects to off-target healthy brain cells. With such barriers in mind, any construction and localized delivery option that combines BBB-crossing nanoparticles with minimal brain toxicity could represent great significance for achieving a far more ideal therapeutic outcome for GBM treatment.

Over recent years, Fenton reaction-based chemodynamic therapy (CDT) has begun to represent an emerging hotspot as a nanocatalytic tumor therapy. It uses an iron-mediated Fenton reaction to convert the less active $H_2O_2$ into •OH, the most toxic reactive oxygen species (ROS), to induce oxidative stress in cancer cells.

A key question for CDT is "How to improve *in vivo* CDT efficiency?" Although CDT-based nanotechnology provides a promising method for tumor treatment, there are still challenges to be solved to improve its therapeutic effect. The efficacy of Fenton reaction-based CDT is dependent on the intracellular $H_2O_2$ concentration, which can be consumed so rapidly that the reaction cannot produce enough •OH radicals to effectively kill tumor cells. One previous study proposed the delivery of exogenous $H_2O_2$ to the tumor site through polymersomes. However, such an $H_2O_2$ exogenous delivery could be problematic in that it might leak and damage normal tissues. For this the *in situ* production of $H_2O_2$ at the tumor site would be much preferred where, if overproduced in cancer cells rather than normal cells, it could then act as an endogenous prodrug of CDT.



Localized NIR-II laser mediated chemodynamic therapy of glioblastomas

# Chemodynamic therapy may lead to a long-awaited breakthrough for the most dreaded of brain tumors (GBM)

## Localized NIR-II laser mediated chemodynamic therapy for glioblastomas

In 2022, the team of **Jianmin Zhang** published their research related to this finding in ***Nano Today***. They proposed an *in situ* strategy to elicit chemodynamic therapy (CDT) for orthotopic GBM using biomimetic $CuFeSe_2$-LOD@Lipo-CM (CLLC) nanocatalysts. These nanocatalysts are composed of ultrasmall $CuFeSe_2$ nanocrystals (CFS), lactate oxidase (LOD), and liposome containing GBM cell membrane proteins (Lipo-CM). The principle by which they operate links to lactic acid, which is continuously generated by the aerobic glycolysis of tumor cells for energy generation and is abundant at the tumor site. The level of lactic acid in the tumor region ranges from 10 to 40 mM, which is suitable for LOD-mediated catalysis. Lactate oxidase (LOD) and the 80-KD enzyme can then catalyze the oxidation of lactic acid to produce pyruvate and $H_2O_2$, which may be used to enhance the Fenton-like reaction *in situ*.

In addition, the CLLC nanocatalysts, with their high photothermal conversion efficiencies, are able to easily achieve localized NIR-II (1000-1350 nm) light mediated mild hyperthermia, which could further enhance CDT in the murine orthotopic GBM model. For this, since the mouse brain is protected by the skull which significantly affects the penetration of the laser, the skull section above the GBM would require removal to enable this photothermal therapy (PTT).

In this study, an *in situ* NIR-II mediated CDT strategy for targeted orthotopic GBM therapy was proposed. The ultrasmall CFS nanocrystals were conjugated with LOD and then coated with GBM cell membrane-based biomimetic membrane (Lipo-CM) to form the biomimetic CLLC nanocatalysts. The CLLC nanocatalysts could then penetrate the partially disrupted BBB and precisely target the orthotopic GBM due to the GBM cell membrane proteins in the nanocatalysts. LOD could therefore improve the

intratumoral $H_2O_2$ content via *in situ* oxidization of lactic acid at the tumor site, which could then enhance Fenton-like $Cu^+$ based CDT activity. As mentioned, the skull above the orthotopic GBM was therefore removed to reduce the loss of NIR-II laser energy. Then, the nanocatalysts with high photothermal conversion efficiency could easily achieve localized NIR-II light mediated mild hyperthermia. The accumulation of nanocatalysts in the GBM could also be characterized by photoacoustic (PA) imaging. Due to the precise targeting of nanocatalysts to the GBM, PA image-guided NIR-II laser irradiation of mouse brain post-craniectomy could induce *in situ* mild hyperthermia with minimal side effects for normal brain function, and further accelerate localized catalytic Fenton-like reactivity, enabling synergetic PTT/CDT. This work demonstrated that localized CDT enhanced by the LOD and the NIR-II laser is an alternative treatment for GBM.

## Cross-talk

## Yuanbo Pan

**You recently published your neurobiology and nanomaterials research results in Nano Today as the first author. How did you decide to study this interdisciplinary topic?**

**Pan:** During my PhD studying, under the supervision of Professor Jianmin Zhang at Zhejiang University, I had my main focus upon the mechanisms and clinical features of cerebrovascular diseases and brain tumors. I then joined the research team of Dr Aiguo Wu at the Ningbo Institute of Materials Science, Chinese Academy of Sciences in December 2019 to carry out research in nanomedicine. Last year, I joined the research group of Professor Xiaoyuan Chen in the School of Medicine at the National University of Singapore to carry out nanomedicine research.

**As you had rich research experience in both basic medicine and clinical fields, what are the similarities and differences between nanomedicine and your past research areas?**

**Pan:** During my Master's study, I mainly focused on a number of basic mechanisms in my research. These included mechanisms of neuronal axonal injury; the regeneration potential beyond diffuse axonal injury or optic nerve injury; and the occurrence and development mechanisms of gliomas. Such research often began with the discovery of a phenomena, which then naturally led into digging into the pathways and molecular mechanisms behind it. However, the research on nanomedicine did not progress in this way at all. Nanomedicine is the application of nanotechnology to the medical field, based on specific clinical needs. Using nanoscale materials such as inorganic/organic/biomimetic nanoparticles, nanorobots, etc., it has a focus upon specific prevention, diagnosis, and treatment of those diseases. Therefore, compared with my previous research areas, nanomedicine was far more focused upon clinical applications.

**The School of Brain Science and Brain Medicine at Zhejiang University is committed to developing brain science research by promoting cooperation between different disciplines. As someone involved in the interdisciplinary exploration in the field of nanomedicine, could you please share your personal experience about the best way to break down disciplinary barriers and promote interdisciplinary cooperation?**

**Pan:** I think the most important thing is communication. From my own experience, the members of the nanomedicine team are excellent. They have accumulated rich experience in the fields of chemistry, materials, pharmacy, and physics, and can therefore collaborate to design novel and high-performance nanoparticles. However, due to a general lack of clinical background, it is difficult for such a team to accurately meet clinical needs. For example, in the mouse models of gliomas, mice with subcutaneous tumours and orthotopic tumours have different survival times, treatment methods, and tumour microenvironments. Another example would be the orthotopic injections of different glioma cell lines. The post-occupancy and invasive effects are also different, and orthotopic glioma models are located in different brain regions and result in different prognoses. Therefore, this requires pragmatic exchanges and cooperation between researchers from different backgrounds. As a researcher with a medical background, I fully appreciate the advantages of my background towards facilitating clinical translation. Through sharing my past experiences from dealing with actual clinical problems and situations, part of my role is therefore to help smooth the focus of the team from that of a basic research type focus, to that which is more focused upon clinical diagnosis and treatment.

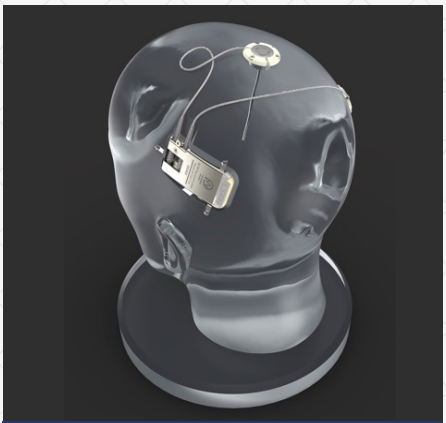
Yuanbo Pan is a PhD student from Zhejiang University School of Medicine (neurosurgery), under the supervision of Professor Jianmin Zhang. His main research area is the design and synthesis of novel nanomedical devices for the diagnosis and treatment of brain diseases such as brain tumors and stroke.

# Ending the ‘closed-loop monopoly’.

## Promoting the clinical transformation potential for a domestically produced closed-loop neuromodulation system

Components of the Closed–Loop RNS System

The Pulse Stimulator and two types of electrodes



The head model of installed RNS system

**In China, the prevalence of epilepsy is about 4.7-8.5, with about 400,000 new cases each year.** Around 30% of these cases are diagnosed as refractory epilepsy due to their unresponsiveness to drug therapy. Although resective surgery, the removal of a small portion of the brain that is triggering epileptic seizures, is often the first choice in such refractory epilepsy cases, there are still some patients who cannot receive resective surgery due to the risk of neurological deficit or the presence of multiple lesions. For these patients, neuromodulation may be a better treatment option. Most previous neuromodulation techniques have been based on open-loop systems (unresponsive and unidirectional stimulation of epileptogenic areas base on fixed parameters). However, over recent years, reactive neurostimulation systems based on the more responsive closed-loop systems have been gradually applied in clinical practice and have been proven to be safe and effective.

The most prominent features of the closed-loop neuromodulation are " precision" and “responsiveness”. The "closed-loop" feature, initially monitors the brain electrophysiological activity of patients in real time. It then automatically identifies the specific EEG signals at the point they begin to occur that, if left unimpeded, would proceed to trigger epilepsy or other diseases. The system then automatically and responsively activates a pulse generator to give precise electrical stimulation to inhibit the abnormal electrical activity it has just detected. In this way it is able to prevent the escalation of such signals to the point of triggering seizures or other disease manifestations. This whole integrated ‘early warning and treatment’ process is completed by the closed-loop neuromodulation system, to achieve a ‘closed-loop’ of diagnosis and treatment based on the "brain-computer-brain" feedback pattern. In broader terms, this concept is also an important embodiment of brain computer interface technology with many other potential clinical translation applications.

Currently, there is only one company in the world (Neuropace) with a fully developed and operational closed-loop neuromodulation system (Responsive Neurostimulation, RNS) approved by the FDA for the treatment of clinically refractory epilepsy. Despite a large number of clinical studies reporting the superiority of closed-loop neural regulation in the field of refractory epilepsy diagnosis and treatment, including those published in the prestigious journal ***Neurology***, no refractory epilepsy patients in China or elsewhere in Asia can have access to the RNS system due to the technological monopoly that this company has upon such technology, and due to political blockades. To break through such barriers, to master core technologies in the field, and to gain independent intellectual property rights remating to such high-end medical products, the "Brain-Computer Interface Clinical Translation" research team, led by Professor Jianmin Zhang, has been exploring the development of domestic systems for clinical transformation using closed-loop neuromodulation. Such systems would exist with completely independent intellectual property rights and have been under development since 2012. The research has been funded by many national and provincial research projects. After more than 8 years, the team, cooperating with Hangzhou Nuowei Medical Technology Co., Ltd., has achieved breakthroughs both from technological trial through to product, and from basic to clinical research for the joint development of a domestic closed-loop neuromodulation system (Epilcure™). For the first time in China, the clinical treatment of 3 refractory epilepsy patients using Epilcure™ has been completed. Postoperative short-term evaluation of epileptic seizures showed that the rate of epileptic seizure was reduced by more than 50% and that the response rate was 100%.

Professor Zhang explained that as a new type of neuromodulation treatment technology, closed-loop neuromodulation has the advantage of minimally invasive craniotomy without large bone flaps, compared with traditional epilepsy foci resection. Moreover, it fills in some clinical gaps for treatment, such as for bilateral hippocampal sclerosis, which cannot be treated using traditional surgery. Compared with other neuromodulation treatment techniques such as VNS and DBS, closed-loop neuromodulation has the advantages of on-demand precise stimulation, closed-loop responsiveness, and automatic early-warning. In addition, closed-loop neurostimulation has far-reaching implications for improving quality of life for patients after surgery. The team will continue to advance this work which has now entered the Randomized Controlled Trial (RCT) stage to evaluate its long-term safety and effectiveness. Upon the successful completion of such trials, such closed-loop neuromodulation can be applied to the clinical diagnosis and treatment of refractory epilepsy and other diseases, bringing new hope for a more advanced, safer, and more effective treatment for the large numbers of patients suffering from such issues here in China and in other Asian countries without access to the US technology.

# Cross-talk

## Hongjie Jiang

**As a neurosurgeon and an important participant in the development team for the responsive neurostimulation (RNS) closed-loop neuromodulation interdisciplinary project, can you describe your prior personal learning experience?**

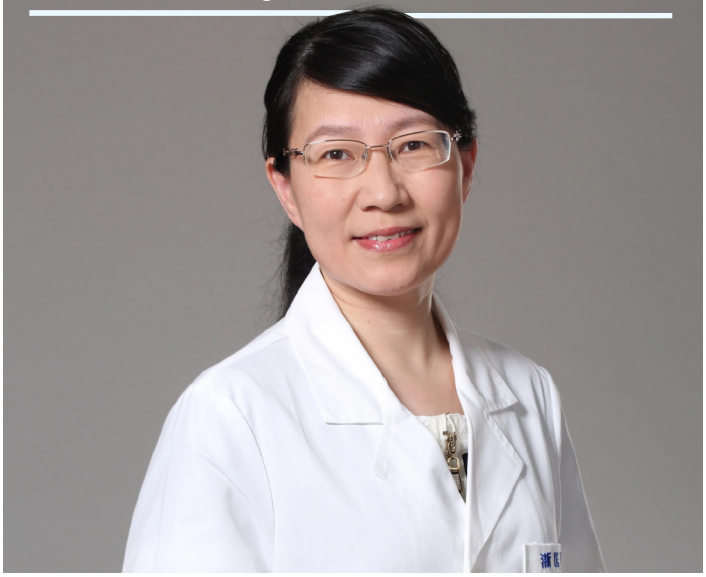
**Jiang:** I was an undergraduate student in the Denian-Ba Program of Zhejiang University, which adopted the "4+4" teaching mode. This meant that before the latter 4 years of medicine-focused studies, we could choose any subject of interest for our first four years of study. At that time, I chose to take applied mathematics and engineering classes, which linked to my interests. Later, I began to study neurosurgery and entered the field of functional neurosurgery, a relatively young subspecialty subject. We focused on various functional neurological diseases, including intractable epilepsy, Parkinson's disease and others, and we also began to explore precision and personalized medicine by applying brain-computer interfaces and other advanced technologies.

**As a surgeon, how did you participate in the development of RNS, an interdisciplinary project combining engineering, basic medicine and the other subjects?**

**Jiang:** The research that a surgeon is involved in is usually not like the doing experiments in the laboratory. We focus on clinical transformation and take a leading role in projects. We introduce new ideas according to actual demands and communicate with collaborators in engineering and basic medicine. We also make specific technical requirements based on clinical experience. For example, in order to help patients to reduce the costs and risks of battery changing surgery, we asked the engineering team to add wireless charging as a necessary feature of the RNS system during the R&D stage. During the verification phase of animal experiments, we also provided guidance to the basic research team to make the animal surgical operation more reflective to the actual medical practice conducted on patients. After the product was finally produced, it was also the surgeon who performed the installation operation for the patient. Of course, interdisciplinary cooperation cannot simply involve different people performing their own duties independently. Our team members from different fields often participate in the areas that they are unfamiliar with to enhance mutual understanding. During the recruitment of patient volunteers, our collaborators from the engineering team would participate in our communication with the patients, and we surgeons would also attend the group meeting of the basic research team on the construction of models such as mouse epilepsy models etc. It is the common goal of serving patients that truly unites all the participants from different fields, leading to the final success.

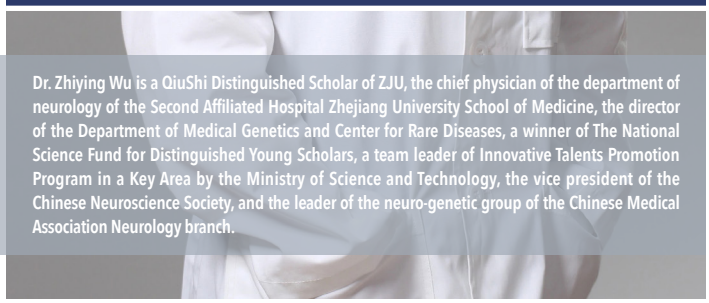
**The author, Hongjie Jiang, is an attending neurosurgeon in the Second Affiliated Hospital of Zhejiang University School of Medicine, under the supervision of Professor Jianmin Zhang. His research focuses on brain-computer interfaces and their clinical translation for neuromodulation diagnosis and the treatment of functional neurological diseases.**

# Simplicity and Professionalism Leads to Huge Success



## A special interview with Professor Zhiying Wu

(Second Affiliated Hospital, School of Medicine, Zhejiang University)



Dr. Zhiying Wu is a QiuShi Distinguished Scholar of ZJU, the chief physician of the department of neurology of the Second Affiliated Hospital Zhejiang University School of Medicine, the director of the Department of Medical Genetics and Center for Rare Diseases, a winner of The National Science Fund for Distinguished Young Scholars, a team leader of Innovative Talents Promotion Program in a Key Area by the Ministry of Science and Technology, the vice president of the Chinese Neuroscience Society, and the leader of the neuro-genetic group of the Chinese Medical Association Neurology branch.

**Have you ever heard about "bronze babies" or "panda babies"?** Behind such nicknames there are many children suffering from rare diseases, many anxious families, and an army of affectionate doctors who deeply care about their patients.

According to the definition from the rare diseases in China 2021 report, rare diseases refer to diseases with a neonatal morbidity or prevalence lower than one in ten thousand, or those where the total number of patients remains fewer than 140,000. Many of these are also classified as orphan diseases. These represent diseases that are largely ignored by the pharmaceutical industry due to their rarity. For these, there remains little financial incentive for a commercial drug-development focus. The 28th February 2022 was International Rare Disease day. Its slogan this year, "Rare is many. Rare is strong. Rare is proud.", was proposed to raise awareness of rare diseases and of the many patients with such conditions that require specialist care.

With the constant development of genetic editing technology, together with efforts from all levels of society, treatment for rare diseases has made a huge progress and attracted increasing public attention. Professor Zhiying Wu is the director of Diagnosis and Treatment of Rare Diseases Center of the Second Affiliated Hospital, School of Medicine, Zhejiang University. In addition to her earlier breakthrough in the discovery of mutations in the proline- rich transmembrane protein 2 (PRRT2) which was associated with the rare involuntary movement disorder Paroxysmal Kinesigenic Dyskinesia (PKD), she has recently discovered a second gene (TMEM151A ) able to induce PKD, which further enables yet more accurate diagnosis and treatment of this important rare condition. We had an opportunity to meet with Professor Wu, and learn the story of her dedication and commitment towards the study of rare diseases, and discuss her opinions about the current progress and future directions regarding rare diseases.

**Dear Prof. Wu, could you briefly introduce the Laboratory of Medical Genetics in the Second Affiliated Hospital, School of Medicine, Zhejiang University, and its advantages?**

**Wu:** It was on November 1st 2021 that we set up the Department of Medical Genetics and the Treatment Center of Rare Diseases in the Second Affiliated Hospital, School of Medicine, Zhejiang University. We proposed a model combining care units, clinics, and laboratories, aiming to accurately diagnose and treat rare diseases. The Laboratory of Medical Genetics in the Second Affiliated Hospital, School of Medicine, Zhejiang University is divided into different departments, each of which is strictly managed. There are professionals in charge of different specific issues such as preserving the samples, or data analysis, and those helping the employees to work with a high efficiency and adhere to strict principles. In addition, we have a large biological sample bank with a strengthened floor. This supports the storage of a large amount of refrigerators, allowing us to repeatedly analyze abundant samples from different rare disease cases.

**Prof. Wu, is there any similarity between the newly discovered pathogenic gene *TMEM151A* and the previously reported *PRRT2*?**

**Wu:** We used whole exome sequencing to select these two genes, and found that both are characterized by incomplete penetrance. This indicates that some people who have these special genes may not develop any apparent symptoms. This phenomenon was consistent with what we had previously observed in mouse models in which the same genes had been induced.

**You have been studying PKD for such a long time. How do you organize your research, and what is the focus of your work?**

**Wu:** For doctors, some may consider it better to simply focus on patients when conducting studies involving diagnosis and treatment. However, most experiments cannot be conducted directly on humans for ethical reasons. I prefer to follow this pattern: Firstly, we need to screen for the relevant pathogenic genes such as *TMEM151A* from patients. Secondly, we then can establish an animal model by direct gene manipulation to see whether knockout induces similar pathological changes. Thirdly, on the basis of these animal studies, we will further study the pathogenic mechanisms including the selection of possible therapeutic targets and corresponding drugs. Then, we will verify the results obtained from mouse models using non-human primates such as monkeys. Once these steps are completed, we can finally move on to human patients to conduct clinical studies. As a clinician, I would prefer to focus on the overall strategy based on my observation of the patients and then propose suggestions for diagnosis and treatment that will directly benefit those patients. However, for more basic research, such as studies involving neural circuitry and molecular mechanisms, we need to cooperate with specialized scientists. In this way, we can achieve a higher efficiency. All aspects can be conducted concurrently enabling more research to be completed with limited resources.

**The combination of clinical and basic research empowers studies related to the mechanisms of rare diseases. What is the relationship between rare diseases and hereditary diseases in your opinion, Prof. Wu?**

**Wu:** Rare diseases and hereditary diseases are defined differently, but there are also some overlaps between the two. Hereditary diseases refer to diseases that have a genetic family history or diseases that have a specific pathogenic gene. Rare diseases are defined specifically related to their prevalence. However, more than 80% of rare diseases are also related to genetic defects. For example, amyotrophic lateral sclerosis (ALS), also called Motor Neuron Diseases (MND), is a typical rare disease, but only about 10% patients have family history, and carry mutated genes. That is why ALS cannot be listed as a hereditary disease. Nevertheless, when trying to discover new drugs for ALS treatment, we need to treat it as if it is a hereditary disease and search for the targets on pathogenic genes or proteins. We can then better cure the disease by looking into therapeutic targets and predicting relevant drugs through gene editing studies. If we look for the drug target using a more traditional approach the options become far more limited and progress is likely to be much slower. In this way, it will not only become difficult to proceed, but also only scratch the surface without reaching the root cause of the disease.

**It was reported that Wei Xu, a young father, learned to produce by himself medicine that was previously inaccessible for his son who has a rare disease, attracting extensive attention from society. Rare diseases are still causing huge difficulties for tiny groups within the population. So, Prof. Wu, what needs to be addressed in the field of rare diseases nowadays in your opinion?**

**Wu:** Because of the large population, rare diseases are actually not so 'rare' in China! Increasing numbers of reports are now emerging concerning rare diseases and the government has been paying increased attention to these diseases. In 2018, the "Rare Diseases Directory" was released by the Chinese authorities listing 121 kinds of disease for inclusion. In 2019, the National Health Commission of the People's Republic of China then established a cooperation network for the diagnosis and treatment of rare diseases on a national level. While some medical personnel and social communities have been managing to help the patients, the investment and publicizing from the government is also providing strong support in calling on the whole of society to pay attention to these patients and conditions. Our doctors, having experience of helping large numbers of patients, an aspect rarely repeated in other countries. This can then often provide better diagnosis and treatment for patients with rare diseases here at home than is available abroad. However, the supply of medicine is still a big issue. Drugs for rare diseases in China are mainly imported from foreign countries or produced based on existing foreign design. This makes them extremely expensive. We sincerely hope that in the future scientists can conduct more innovative studies, the government can invest more on rare diseases, and that the corporations and other social organizations will be willing to donate and support research on therapeutic targets and towards the development of relevant drugs. I believe with enough funding, Chinese scientists can definitely find many effective targets and develop new original drugs to treat numerous rare diseases.

**What's your advice for patients and doctors who are facing rare diseases?**

**Wu:** For patients, they need to seek help from medical personnel at the earliest possible stage. For doctors, they have to learn more about the rare diseases and convey useful information to the public. In addition, the government of different provinces should collect and publicize the information from rare diseases experts so that patients can easily find the doctors who are more specialized to their specific conditions. Different hospitals are also supposed to cultivate multi-discipline groups for the treatment of rare diseases to provide accurate and timely diagnosis and treatment for patients. We should therefore construct a network that connects doctors in different fields. For example, a patient with hepatolenticular degeneration may develop neurological symptoms, so he or she could visit the department of neurology. If there are pathologies involving liver, the department of infectious diseases, the department of gastroesophageal reflux diseases, and the department of hepatobiliary surgery could also be considered. Patients may also end up in the department of orthopedics if there are arthropathies. Doctors in all of these departments require training so that they may have relevant knowledge about symptoms of rare disease and know when and to where they should transfer such patients. This will provide a much more efficient system and highly increased convenience for patients.

**It can be easily seen that you are full of enthusiasm and hope when talking about rare diseases. We have heard that you were studying hepatolenticular degeneration when pursuing your Master's degree. Why did you make such a choice?**

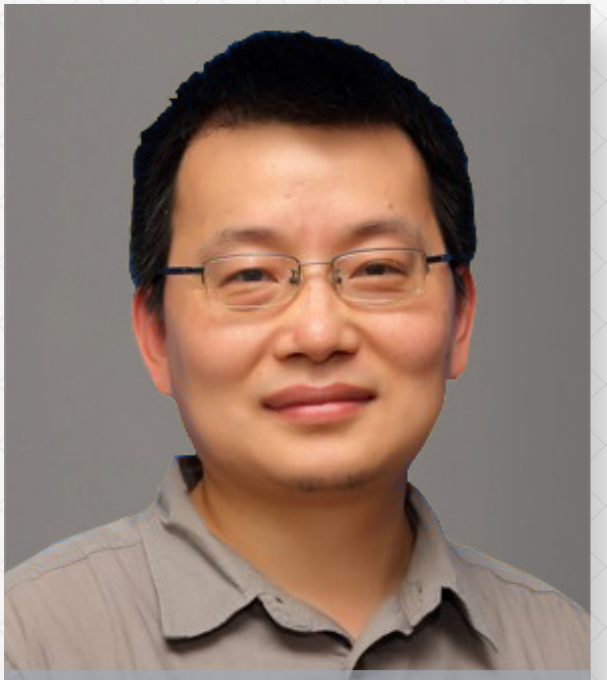
**Wu:** It was mainly out of my personal interest. At that time, I encountered a patient with hepatolenticular degeneration together with a tutor. The patient, who could not talk clearly and seemed to be in extreme pain, was twisting on the wheelchair with a rigid body. My tutor checked the patient with a flashlight, and then immediately concluded that the patient had hepatolenticular degeneration. I was shocked. But my tutor simply explained that there is a brown circle in the patient's eyes. He taught me that "you will easily know what kind of diseases patients have with experience from diagnosing more patients and reading more books." This motivated me to enter into the field of rare diseases. The most straightforward way to study rare diseases was to find the patients and collect their families samples for analysis. In order to proceed with my Master's project, I searched through the medical record rooms in many hospitals in Fujian. As there was no telephone at that time, I had to copy down the addresses of patients with hepatolenticular degeneration, and then visit them one by one on my bike. After acquiring the consent of both patients and their relatives, I would collect blood samples and then bring them to Fudan University for gene analysis. If I showed up without scheduling in advance, I could easily be seen as a swindler. For every visit, I would show my employee card as soon as the door opened, telling people that "I am a doctor and we are look for patients to collect blood samples for a study." I eventually found a just over 20 families with hepatolenticular degeneration across the whole province.

**From your brief narration, we can see that it was extremely hard for you to find patients and collect samples. However, you persisted for many years and never gave up. What motivated you through these years and how could you balance the clinical work and scientific research?**

**Wu:** Interest is the most powerful driving force. I was fond of reading detective novels and enjoyed the progress of investigation since childhood. A doctor exploring the mechanisms of rare diseases is just like a detective trying to gradually uncover truth from complex clues. Every step is progress. Once you manage to make an accurate diagnosis, you will also gain a sense of success and satisfaction. This will motivate you to make constant progress, particularly as what you have done is useful and helpful for patients. Thus, when instructing graduate students, I not only teach them how to do experiments, but, more importantly, also raise their interests by letting them realize their reason and motivation for study. I generally spend a lot of time working. On work days, I often only travel between the hospital and my home. And I will work in the laboratory on weekends. Only in this way can I have enough time to do well in both clinical works and scientific research. Additionally, I often read professional books during my spare time, as I also need to keep up with new knowledge as well. For example, reading ***Principles of Neural Science*** gave me more insight into the mechanisms of neurological diseases and helped me better understand the ideas of scientists focusing on basic research.

**Prof. Wu never forget her original determination and continues her fight in the treatment of rare diseases. She serves as a beacon of light as she, together with her team, is trying her best to diagnose and treat patients and by doing so is bringing hope for cure to many patients. When asked which case had impressed her the most during these years of clinical work, Prof. Wu answered with a smile, "Every patient has left a deep impression on me." It is through her simplicity, compassion, and professionalism that Dr. Wu has witnessed the progress of the diagnosis and treatment of rare diseases in China.**

*"Every patient has left a deep impression on me."*
Prof. Zhiying Wu



Prof. Gang Pan is a Professor of College of Computer Science and Technology of ZJU, a winner of National Science Funds for Distinguished Young Scholars, a Leading Talent in Science and Technology Innovation of the National "Ten Thousand Talents" Program. He is mainly studying artificial intelligence, brain- computer interface, neuromorphic computing and other areas.

Dr. Peng Lin is a member of the ZJU 100 Young Professors and a recipient of the National High-Level Young Talents Introduction Program. His main study involves the development of new neuromorphic computation programs.

# Approaching Brain-like Computing

## An interview with Prof. Pan Gang and Researcher Lin Peng

**In 2016, Google DeepMind's AlphaGo sealed a 4-1 victory over South Korean Go grandmaster Lee Sedol and followed this a year later with a 3:0 triumph against the World No.1 Chinese Go grandmaster Ke Jie.** Mirroring the great chess victory in 1997, when IBM's Deep Blue shockingly beat the Russian chess grandmaster Garry Kasparov, computers had defeated humans in yet another field. Wider applications of intelligent computing technology in areas such as industrial production, safety management, and artistic creation, etc, are also now becoming well-known and increasingly established into many areas of public society. Along with such technological advances, more and more people are discussing the inevitability that artificial intelligence will soon become omnipotent. Fears are being expressed that humans will eventually be completely surpassed by computers running on pure mathematical logic, providing constant optimization for all fields, and rendering the majority of human jobs redundant.

However, many scientists have the opposite view. Although having unique competitive advantages in mathematical operations, computer intelligence is still left far behind in many aspects, such as consciousness, decision-making, ethics, recognition, memory and energy consumption efficiency, as compared to the biological brain. As such, a far more advanced and intelligent computing structure already exists in nature. With this comes the understanding that computer systems will become more intelligent and efficient in the future by learning from and imitating the structure and design of the human brain. That is one of the frontiers of computer science for our world today and it now encompasses the entire powerful sub-field of 'brain-like computing'. Here, the BBMI editorial team are honored to invite Prof. Pan Gang and researcher Lin Peng, two experts in brain-like computing, to introduce this wonderful interdisciplinarity field which combines and integrates aspects of both computing and neurobiology.

**Most of us have been familiar with the concept of traditional computing, but brain-like computing remains largely unknown. Could you please summarize the difference between them?**

**Pan:** Instead of being inspired by the brain-like or brain-imitation, traditional computational techniques (like deep learning) are purpose-oriented and advanced from mathematical optimization. By setting and continuously adjusting parameters and objective functions, traditional computing techniques may perform well but the final optimized model is quite different from the brain connection structure. On the other hand, brain-like computing firstly begins with the determination of the method. According to our knowledge of the neurobiology of brain regions we can see how specific brain regions relate to specific tasks. Brain-like computing, using this as a model, therefore sets up a pre-programmed network structure which is conducted based on brain imitation. Take visual recognition tasks as an example. Traditional computing techniques may build a network with a thousand layers after algorithm optimization, but this has nothing to do with the actual brain. However, brain-like computing can partition the hardware and software into different areas and then function with reference to the anatomical structure of the visual nervous system, before proceeding with arithmetic processing.

**What are the main aspects of the current brain-like computing research?**

**Lin:** There are various aspects based on different technology routes for software and for hardware. For software, we can simulate the macroscopic connection of the brain through algorithm design and by exploring more efficient and intelligent neural network algorithms using inspiration from biology. As for hardware, a neural network system can be constructed on a chip through a circuit design, making the brain-like computing algorithm faster and more efficient. For example, a new research topic has emerged in recent years simulating neuronal and synaptic functions through the unique physical properties of nanoelectronics. One of the typical devices is a memristor, which can change its state via ionic motion. This feature shows similarities to the biological neurons found in biological communication mechanisms, in contrast to traditional CMOS (complementary metal-oxide-semiconductor) components.

**What is the relationship between brain-like computing and traditional artificial intelligence in recent research? Is there any competition between them?**

**Pan:** Brain-like computing and traditional AI computing ought to be mutually reinforcing and complementary. As in the relationship between humans and computers, each has its own advantage. Computers are more proficient in manipulating large-scale data while humans can perform much better in simple daily tasks such as object recognition. Currently, we are comparing traditional artificial intelligence and brain-like computing using some classic tasks such as classification. Traditional algorithms usually separate the training from the testing, but there is no such distinction in the biological brain. The brain keeps adjusting and training at all times. This could be the reason for its better performance in preserving learned memory. Maybe there will eventually be no tasks remaining that only the brain can do that a machine cannot, but the brain will surely be able to finish some tasks more efficiently. Therefore, our research focuses on discovering and applying these advantages through brain imitation.

**Is compatibility between brain-like computing and traditional computer systems a problem?**

**Lin:** There is no unsolvable compatibility problem between them. It is certainly possible to design a computer system with integrations of both brain-like computing and traditional computing functions. For example, whilst brain-like computers can be used to complete the same tasks that traditional computers can, some aspects are unable to be done in an efficient way. For this, a kind of computer that combines and integrates these two computing systems may be a solution. In this, different developers may apply different design ideas. I would imagine the brain-like computing chip can be used as a coprocessor. If so the brain-like computing and traditional computer systems do not have to be entirely compatible with each other. Each can focus on its own computing tasks. For example, the CPU of a traditional computer can schedule and issues orders for the brain-like computing part to then perform those specific tasks. In this way, there is even no need for the two parts to be closely integrated or share a connected circuit.

**In what fields are brain-inspired computing or brain-inspired chip technology currently being applied?**

**Pan:** At present, brain-like computing has been valued by the industry for its high energy efficiency. For example, although the actual usage time of the voice command in many mobile phones is short, the traditional algorithm may run a vocal recognition program 24 hours a day, consuming a significant proportion of battery life. Therefore, it is a practical choice to use a low-power brain-like module for voice recognition, and then use this to activate a more advanced system when needed. In addition, the Smart Internet of Things (Smart IoT) is an emerging research field can be another application in the future.

**How would you describe the current stage of the brain-like computing research?**

**Pan:** I think brain-like computing is still in the midst of a breakthrough. Even though the history of brain-like computing research is relatively short, emerging techniques are already showing high feasibility. Human brains have provided a fantastic demonstration of a highly intelligent mechanism. The thing we need to do is to find a way to translate, simulate, and apply this into computer systems. It is possible that we do not yet understand enough about the brain and brain simulation, or maybe the materials for building related hardware are not yet fully suitable or compatible, but I do believe that there will soon be a huge breakthrough in these areas.

**The development of brain-like computing is based on the understanding of biological brains, so what specific kinds of neurobiological findings can be referred to?**

**Pan:** Two main aspects need to be mentioned. Firstly, we focus on the mesoscopic scale of neurons. The macroscopic description of large brain region is too abstract, while the microscopic molecular mechanism can only represent a tiny part of the whole working system. Therefore, neuroscience research involving the mapping of networks of multiple and multi-scale brain regions would provide a more helpful reference point. Secondly, the abstract cognitive mechanisms in the neural system, such as attention, are also important for recognition and identification tasks. These have already been applied in some deep learning research. All these things can provide further insight that can then be applied into brain-like computing.

# Professor Xiaodong Wang: Touching research.

## New discoveries of how touch modulates cognition and emotion

**The main research of Xiaodong Wang: (1) Mechanism of synaptic cell adhesion molecules in memory and early stress-related psychiatric disorders (2) Cross-modal sensory integration and stress-related psychiatric disorders.**

**Touch is one of the most important human senses.** Positive tactile stimuli can promote cognitive development and relieve repressed emotions. Conversely, some psychiatric patients also show difficulties in the processing and integration of tactile information. Medical staff often recover preterm infants' cognitive function through touching, or with kangaroo care, with its strong emphasis on skin-to-skin contact. More generally hugging, touching, and other tactile behaviors can clearly result in a temporary reduction of anxiety in daily life. However, the biological mechanisms of how tactile experiences modulate cognition and emotion remain unclear. At present, light therapy, focusing on visual intervention, is the main treatment method that utilizes the basic senses. Tactile interventions have been studied to some extent in mice with autism, but so far the mechanism and effects remain unclear. Overall, medical research related to touch remains unsystematic, far from comprehensive, and with many related issues worth exploring. Based on research experiences on stress and mental illness, Professor Xiaodong Wang has raised some creative new issues about how the modulation effect of touch relates to cognition and emotion in mice. In this he has also questioned the reducibility of pathological models. For this, the research team designed a new tactile enrichment model which utilizes increased tactile simulation. They found that concurrent tactile enrichment has a clear effect on releasing the anxiety of mice and promoting cognition. Such results were published in ***Nature Communications***.

Professor Xiaodong Wang explained that as the competitive aspects of research remains so fierce in various biology fields, his primary principle was to propose a research project that utilizes the research focus of the lab to explore this creative and unique topic. At present, invasive approaches are the most common way to manipulate the neuronal activity of mice and non-human primates, using techniques such as optogenetics and electrode implantation surgery. This leaves more natural and less invasive methods far less explored. However, the use of these natural methods as behavioral evaluation indicators requires more creative paradigms. In his way, as we discover new research ideas about touch, it can be something with a high potential to be complementary to animal experiments and to promote their efficiency. To utilize such new principles, a broad imagination, problem-oriented thinking, and constant learning of new technologies that can be applied to the current topic, all remain essential.

Although majoring in clinical medicine when he was an undergraduate student, Professor Xiaodong Wang found himself more interested in basic research. In the process of his studies he began to turn to devote himself more to basic scientific research. During the postgraduate period, he entered the Sixth Affiliated Hospital of Peking University as a clinical research postgraduate, focusing on mental illness. After getting his master's degree, Professor Xiaodong then went to the Max Planck Institute for Psychiatry in Germany to pursue a PH.D. and began to study stress and mental illness. In retrospect, Professor Xiaodong said that his clinical background helped to broaden the perspective of his scientific research and improve his sensitivity to clinical disease-related issues. He told us that when he was a postgraduate student, the clinical research in many domestic universities was still in its infancy. Compared with the present mature training system, the scientific research at that time was more difficult. After joining Zhejiang University, Professor Xiaodong has witnessed the transformation and development of the field of neurobiology. Courses like bioinformatics and computer science have been added that broaden research into multi-disciplinary fields, rather than those limited to pure biology. The result is that these days students can have a more diversified background. The establishment of the BBMI further promotes the intersection of multiple subjects and fields, for example enabling engineering experts to incorporate engineering-linked thought processes into traditional neuroscience for future scientific research cooperation.

Good scientific research work clearly requires a lot of time and energy. For the researchers, Professor Xiaodong also believes that hobbies are good medicine for helping people to remain efficient and relaxed. He loves art and has a guitar in his office. One of his own oil paintings hangs on his wall. He treats such interests as a boost for research, and as a relief from work stress. At present, the national superstructure has provided a lot of support for basic research. Since 2010, the basic research in China has developed rapidly. Professor Xiaodong believes that this trend will cultivate more outstanding talented scientists. Basic research in our country, he predicts, will continue to be improved to higher and higher levels!

# Guided by "Interest", pursue the future with great ambition

## Peichao Li

"Scientific research requires not only interest but also persistence and hard work." said Peichao Li, who is a principal investigator at the MOE Frontier Science Center for Brain and Brain-Computer Integration (BBMI), Zhejiang University.

In 2013, Peichao obtained his Ph.D. from Prof. Haidong Lv's lab at the Institute of Neuroscience, Chinese Academy of Sciences. He then moved to the Salk Institute in the United States to conduct his postdoctoral research in Prof. Edward Callaway's lab, where he focused on the architectures and functions of visual circuits in non-human primates (NHPs). His research on the functions and structures of the visual cortex has been published in ***Science***, ***Neuron***, and the ***Journal of Neuroscience***, etc. In 2022, Dr. Li joined the BBMI where he continues pursuing the truth of his fundamental research on vision.

**Research fields: (1) Study the cell types, connections, and functional mechanisms of the visual circuits in NHPs and cats; (2) Study the retinal origin of orientation selectivity and orientation map in the cat's primary visual cortex.**

### Aim to explore the mysteries of the brain

Back in college, Peichao was attracted to the world of neuroscience by a seminar given by a scientist from the Institute of Biophysics. Since then, his heartfelt desire to explore neural networks began to be established. At that time, neuroscience was not taught in the classroom. Therefore, Peichao spent a lot of time reading neuroscience textbooks in the university library. What he learned in the textbooks stimulated his curiosity towards exploring the mysteries of the brain. He decided to give up the opportunity to be a graduate student at his university. Instead, he applied to the graduate program in the Institute of Neuroscience (ION), due to his determination to devote himself to neuroscience research. After joining the ION, Peichao conducted his rotation in three labs belonging to three main fields of neuroscience, namely molecular, cellular and computational, and system neuroscience. In the end, he chose Prof. Haidong Lv's lab, which belongs to system neuroscience, to do his Ph.D. research. In Prof. Lv's lab, he used intrinsic signal optical imaging and electrophysiological recording to study the functional structure of the macaque's visual cortex. In other words, he studied how the functional cortical structure contributes to visual information processing. Prof. Lv always tries to improve techniques to do better experiments, this work style has been inherited by Peichao.

"Research is not only based on interest, but also persistence and effort." Dr. Peichao Li's earnest gaze expresses his love in scientific research.

### Meet a good teacher and make knowledge into practice

When talked about his post-doc experience in the USA, Peichao expressed his gratitude to his supervisor, Prof. Edward Callaway. Prof. Callaway has rich experiences in using various techniques (such as molecular and cellular techniques, virus tracing, development, brain slice recording, and in vivo electrophysiology, imaging, etc.) in many different animal models (including mouse, rat, ferret, cat, and macaque) to study cell types and their connection in neural circuits. Peichao's knowledge has been widely broadened in Prof. Callaway's lab. Peichao also adopts Prof. Callaway's "open door policy" in his own lab to create an easy and efficient working environment, which he hopes can encourage students to communicate with him freely. Therefore, he can help students in time when they have problems. Peichao is grateful for the opportunity to share the knowledge he learned with students and colleagues in China.

### Inspired by interest and making the practice promotes the study

In terms of his research at Zhejiang University, Peichao has much to say. Using NHPs and cats as animal models, he and his team combine two-photon calcium imaging, extracellular electrophysiological recording, virus tracing, immunohistochemical staining, and other techniques to study the architectures and functions of the visual circuits along the visual pathways from the retina to the visual cortex. Comparing the brain to a "computer", they want to figure out the structure of circuits in this "computer" (the architectures of the neural circuit) and the operating system (the dynamic activities of the neural circuits). Based on the great support of BBMI at Zhejiang University, the 2030 Innovation Project, and other research projects on brain science and brain-like research, Peichao has great enthusiasm and ambition for his future work.

Peichao emphasized his strong desire to study the architectures and functions of the visual circuits more systematically, comprehensively, and in a more detailed manner. At the same time, he is also committed to transforming research into a product. For example, he hopes his discoveries on visual circuits can help design more powerful neuromorphic chips.

Talking about graduate students, Peichao said that there are two important things for a student, which are research interest and a spirit of seeking truth. Research interest is the primary motivation, therefore, a researcher is willing to devote time and energy to pursuit. He thinks that it is the supervisor's responsibility to lead, support, and provide actual help to the student's study. Seeking truth from facts is the base of research. Research should be conducted carefully and seriously like a blind person using his stick. Meanwhile, a student should have an open mind, develop teamworking skills, be willing to learn from others, and to share his/her knowledge. In a lab, students should respect, encourage, and help each other, to work together and push the research forward. Peichao believes that interest is the best teacher, when you keep seeking truth with hard work, it will pay you back.

# Where psychology meets neuroscience

## The work of Dr. Ke Jia

Psychologists have always been eager to find a method to read meaning from the activity of our brains and minds, particularly in the attempts to glean understanding from its unconscious aspects such as dreams. From traditional psychology to cognitive neuroscience, Dr. Ke Jia of the Science Center of Brain and Brain-Machine Integration (BBMI) has always incorporated his interest in psychology into his deep dives into aspects of neuroscience. Clearly, he believes both disciplines converge in their attempts to reveal the secrets of the brain's cognitive process.

Jia Ke graduated from the School of Psychological and Cognitive Sciences at Peking University (formerly the Department of Psychology) in 2011 and received his Ph.D. degree of basic psychology from Professor Sheng Li's research group at Peking University in 2017. From 2017 to 2021, he studied under Professor Zoe Kourtzi, working in postdoctoral research at University of Cambridge. In the February of 2022, Ke joined in the BBMI at Zhejiang University, **focusing on the cognitive mechanism of human learning and memory through psychophysics, ultra-high field functional magnetic resonance imaging, neuromodulation, and computational modeling.**

### Setting out with "Psychology"

The first time Dr. Ke Jia got involved with psychology was at high school. At that time, psychological counseling in China was in its infancy and the Chinese public perception of psychology was minimal. However, his biology teacher had learned some group counseling skills and taught to his students to help them adopt a more relaxed and confident attitude in daily communication or before examinations. From then on, Ke began to develop his interest in psychology, finally choosing Psychology as his major at Peking University.

During his first two years at Peking University, Ke learned psychological counseling skills from Professor Mingyi Qian, who is one of the most famous psychological consultants in China. He noticed that questionnaires were the main method used in counseling research at that time. However, Ke hoped he can use a technique that can measure the brain activity more directly to objectively identify the neural underpinning of mental illness (e.g., social anxiety, depression etc.). Fortunately, many experts and scholars of cognitive neuroscience returning from abroad were bringing back various neurometric technologies which had the capacity to greatly accelerate the transformation of basic psychological research methods. Professor Sheng Li was one of these professors who had previously majored in computer science in the UK. Because of this linked interest, Ke went to Professor Sheng Li's lab to continue his study as a PhD student. Through this collaboration with Professor Li, Ke developed a thorough understanding of psychophysics, fMRI and EEG, and began to use these in a step by step fashion to conduct many kinds of research on the mechanisms of learning and memory.

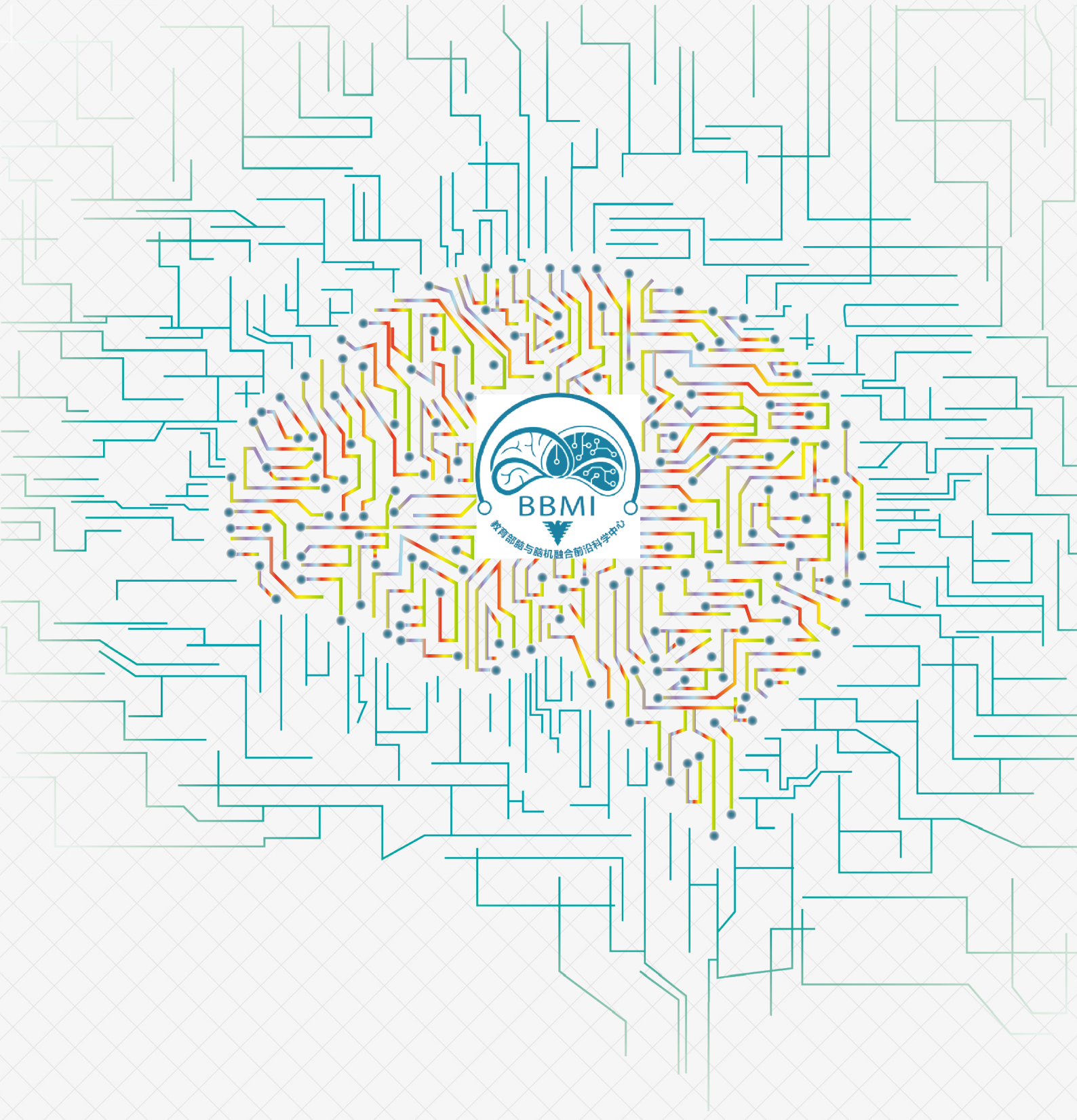
### Based on "Psychology"

When it comes to the connection between psychology and neuroscience, Ke maintained his understanding that these two subjects were quite similar and largely complementary. One of their differences is that psychology focuses on people itself and that its research methods are largely non-invasive. However, compared with animal experiments, temporal/spatial resolution is its inevitable weakness. Therefore, psychology has a macro perspective. In order to improve the preciseness of measurement for human brain activity as much as possible, Ke chose to incorporate ultra-high-field magnetic resonance imaging in the study of human learning and memory processes. Compared with 3T magnetic resonance technology, 7T ultra-high-field magnetic resonance has greatly improved signal-to-noise ratio and a far higher spatial resolution. As Ke explains, "the neocortex of the human brain is divided into six layers to deal with feedforward and feedback information. Therefore, laminar imaging can help us explore the information flow in the human brain during cognitive processing". Furthermore, as many specific neurons in the sensory cortex that represent common functional columns have a width of ~0.2 millimeters, Ke therefore strived to focus his scans into 0.2 × 0.2 × 0.2 cubic millimeters areas. In this way, he could measure the neural activity of specific groups of neurons in the sensory cortex. He explains, "The improvement of spatial accuracy is not just about quantitative changes. If the activities of specific neuronal populations can be recorded, this will greatly promote our understanding of the computational mechanism for cognitive processing invasively." He firmly believes that as the development of science and technology is moving so fast these days that there will soon be more and more sophisticated means, such as micro-robots swimming along blood vessels, to explore the mysteries of cognitive neuroscience.

### Followed with "Psychology"

In terms of scientific research and life, Ke explains about his quarantine experiences abroad due to COVID-19 with smile. After reaching Britain in 2017, Ke often played football with his friends in his spare time and watched football games in Liverpool during weekends. However, the enjoyable time paused after 2020 due to the spread of the coronavirus epidemic. The main thing left for him to do at that time was data analysis. "Scientific research is quite time-consuming" he expounded, "and it is wrong to simply pursue the results blindly. The experiences he learned during the process he considered as also very important." Ke told us that he couldn't agree more about Guowei Wang's (a famous Chinese historian and poet) theory on three levels of study: it is probably perseverance that supports us most to achieve our highest goals. Bad things will surely occur in our lives, but we should respond positively, maintaining hard work, dedication, and an optimistic attitude.

The central philosophy of "one body and two wings" really enhanced Dr. Ke Jia's enthusiasm for the Chinese brain project. Looking back to his original goal of unveiling the neural underpinning of mental illness with the tools of neuroscience, he still firmly believes scientific research should not only be limited to theory. Combining theory with clinical practice ensures that science exists to serve society and people. Nowadays, he feels that he is standing on the edge of an exciting era for cognitive neuroscience. Having started out with psychology, and then incorporating research based on traditional psychological tools, he hopes that he can ride the crest of a wave of vigorous development of Chinese brain science.


BBMI
教育部脑与脑机融合前沿科学中心

## Our Vision

The BBMI center is one of the first six national frontier science centers launched by the Ministry of Education (MOE). The BBMI center capitalizes on the interdisciplinary scientific, medical, and engineering strength of Zhejiang University, and holds the mission to synergize brain science discoveries with brain-inspired intelligence advancement. Ultimately, this synergy shall be reinforced to pioneer new frontiers of fundamental neuroscience investigation, promote the development of novel therapeutics, and implement brain-inspired artificial intelligence.

## "Innovate 2030" Plan

Launched by Zhejiang University, this plan aims to make full use of the comprehensive advantages of the various related disciplines to create a new high-water mark in cross-research innovation, promote the convergence of disciplines and cross-field fusion innovation, and foster a batch of world-leading research results and superior disciplines for the future.

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