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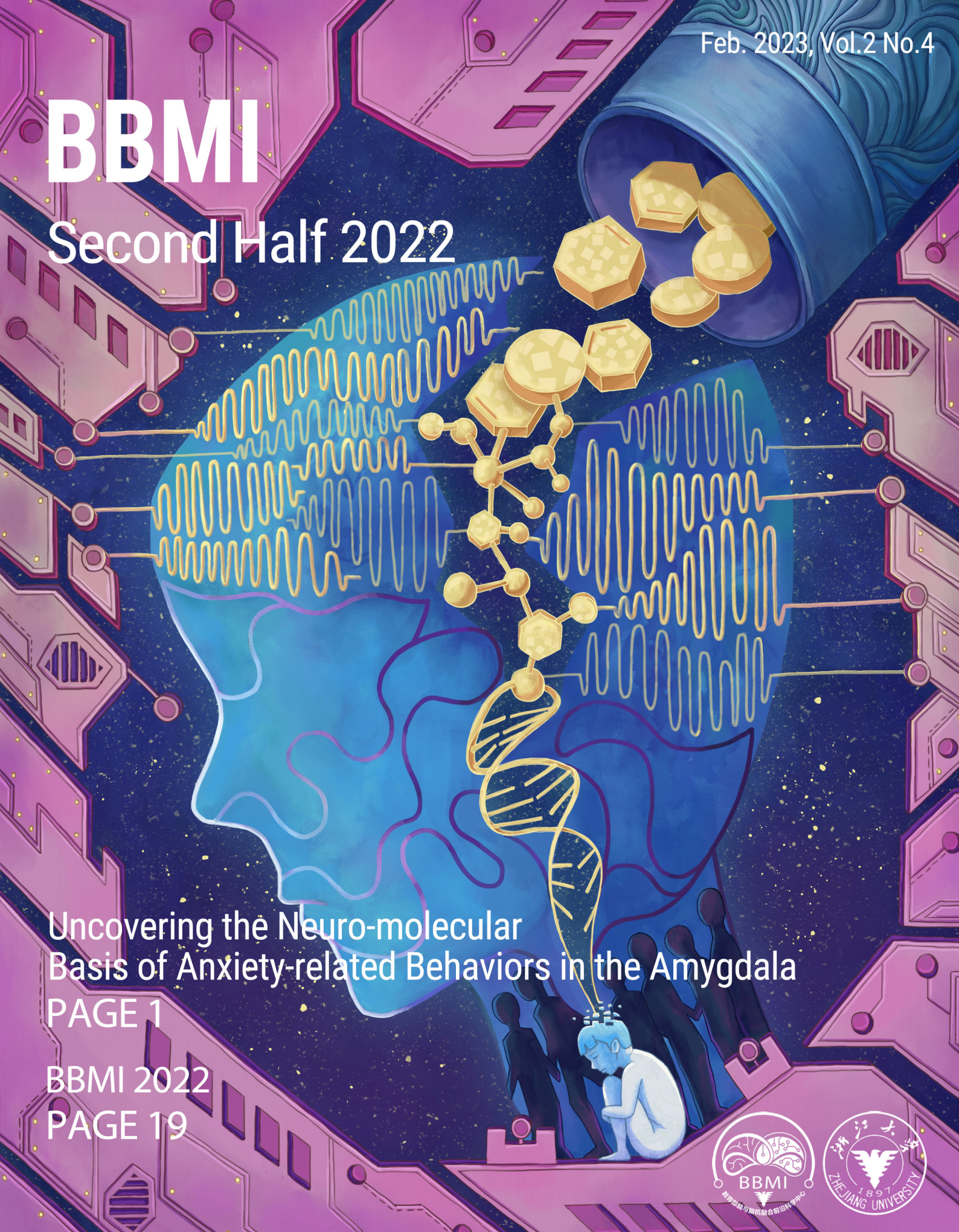

Uncovering the Neuro-molecular Basis of Anxiety-related Behaviors in the Amygdala
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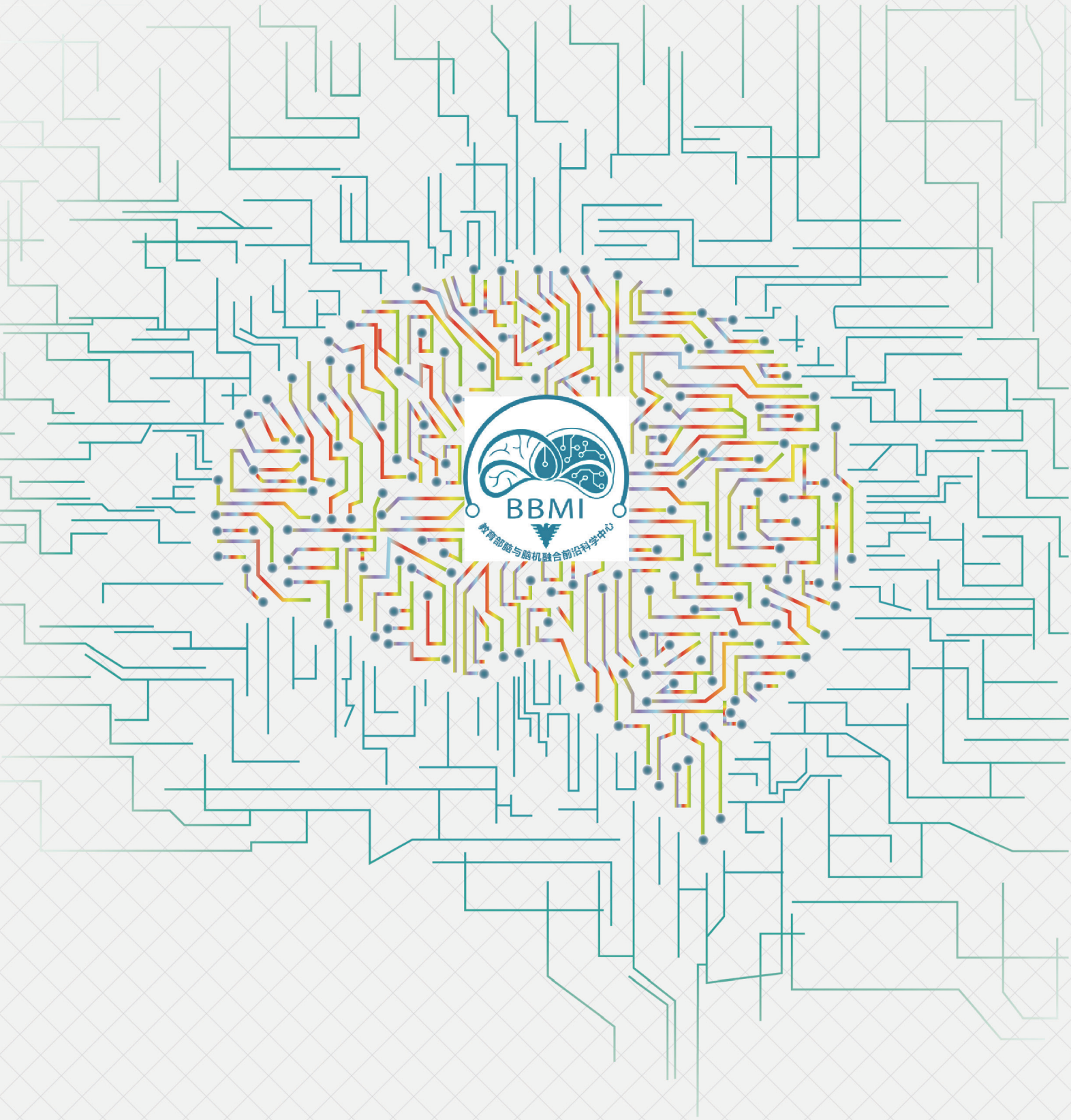

BBMI
教育部脑与脑机融合前沿科学中心

Research Progress

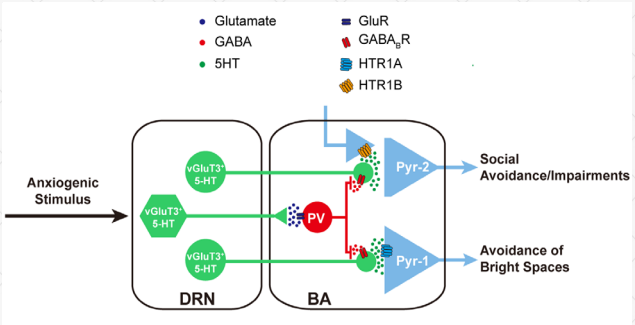
BBMI Scholars

Uncovering the neuro-molecular basis of anxiety-related behaviors in the amygdala

Dissecting Distinct Serotonergic Pathways to the Amygdala Underlie Separable Behavioral Features

Anxiety is a common negative emotion and one of the buzzwords in today's society. However, when we suffer from anxiety, what changes occur in our brains? To answer this question, the research team led by Prof. **Xiaoming Li** conducted an in-depth study. They found that different anxiety-related behaviors are mediated by different neural circuits and molecular mechanisms.

Their research findings were published as a cover article entitled "*Distinct Serotonergic Pathways to the Amygdala Underlie Separable Behavioral Features of Anxiety*" in the journal ***Nature Neuroscience*** on November 29.



Speculative Working Model between DRN$^{vGluT3\cap5\text{-}HT}$ Neurons and Subtypes of BA Neurons underlying Different Behavioral Features of Anxiety

The amygdala, located in the medial temporal lobe, is the brain region primarily associated with emotional processing. The name amygdala is derived from the Greek word amygdale, meaning "almond," owing to the structure's almond-like shape. Previous studies have revealed that the amygdala plays a crucial role in controlling fear, reward, and depression in mice. As a part of the "emotional brain", the amygdala is an evolutionarily conservative organ, enabling studies from the mouse brain to help us gain a better understanding of the human brain. To this end, Xiaoming Li's team has been long committed to researching into the neural circuits of the amygdala and the neural mechanisms for emotions such as fear, anxiety and depression. Their work has yielded many high-level articles, (***Cell Research*** 2016, ***Journal of Neuroscience*** 2017, ***eLife*** 2018, ***Nature Medicine*** 2019, ***Nature Neuroscience*** 2019, ***Neuron*** 2019 and 2020, ***Neuroscience Bulletin*** 2020, and 2022).

As Xiaodan Yu, the first author of the study, explains, "Anxiety is an emotional response to a vague and potential threat and it is manifested by a series of physiological reactions and avoidance behaviors". Chronic exposure to anxiety will deteriorate into anxiety disorders, represented by an extremely anxious state and accompanied social deficits. Mice exposed to anxiogenic stimuli spend more time in 'safe' zones of their behavioral apparatus and spend less time interacting with an unfamiliar conspecifics. However, how the brain processes and integrates anxiogenic (anxiety causing) information and mediates subsequent anxiety-related behaviors remains unclear.

In mice, the midbrain dorsal raphe nucleus (DRN) contains the majority of forebrain-projecting 5-HT neurons. These regulate emotional and motivational processes. DRN$^{5\text{-}HT}$ neurons innervate the basolateral amygdala, especially the basal nucleus, (also known as the basal amygdala (BA)). Previous studies demonstrate that the BA regulates the development of fear to some extent, but whether it induces anxiety and produces a different set of behavioral responses to those of fear, remains unanswered.

To answer, the research team used a genetically encoded GPCR-based sensor for 5-HT ($GRAB_{5\text{-}HT2h}$) to record and compare the dynamics of extracellular 5-HT levels in the BA in either social or anxiogenic conditions. 5-HT in the BA increased in social conditions but decreased in the anxiogenic state. Despite this, in both situations, DRN$^{5\text{-}HT}$ neurons were activated. Given that the activation of DRN5-HT neurons would prompt the release of 5-HT and that the level of 5-HT in the BA displayed opposite dynamics in anxiety and social conditions, this seemingly paradoxical phenomenon and inspired researchers to further investigate its neural mechanisms. They speculated that there would be heterogeneity between DRN$^{5\text{-}HT}$ neurons and the BA, thereby resulting in the decrease of 5-HT in the BA in the anxiogenic state.

In their study, the team found two subpopulations of 5-HT neurons: DRN$^{vGluT3\cap5\text{-}HT}$-BA^{PV} and DRN$^{vGluT3\cap5\text{-}HT}$-BA^{Pyr} neurons, which possess distinct features in electrophysiological intrinsic properties, gene expressions, and responses to anxiogenic and social stimuli. Specifically, DRN$^{vGluT3\cap5\text{-}HT}$-BA^{Pyr} neurons and DRN$^{vGluT3\cap5\text{-}HT}$-BA^{PV} neurons were activated by social and anxiogenic stimuli, respectively. Activation of the DRN$^{vGluT3\cap5\text{-}HT}$→BA^{PV} pathway excited BA^{PV} neurons via glutamate. The robust GABA efflux from BAPV neurons inhibited 5-HT release across the BA via GABAB receptors. The reduction of 5-HT in BA induced avoidance of bright spaces and social avoidance, with avoidance of bright spaces mediated by HTR1A, and social avoidance being mediated by HTR1B. These results revealed a system of DRN$^{vGluT3\cap5\text{-}HT}$-dependent precise control of BA neurons in the regulation of the different behavioral features of anxiety.

This is the first time that scientists have discovered these elaborate neural circuit mechanisms and the specific neuro-molecular basis of different anxiety-related behaviors from the perspective of behavioral phenotypes. This research provides a novel approach and a theoretical foundation concerning the occurrence and pathogenesis of anxiety disorders through symptomatology. In addition, this study reveals the heterogeneity of 5-HT neurons and amygdala glutamatergic neurons from a new perspective, incorporating the understanding of their heterogeneous projections and cell-type specific connectivity. It also further explains the functional diversity of 5-HT and expands the current understanding of the structure and function of 5-HT and the amygdala.

Yu X#, Zhu Yi, Sun Q, Deng F, Wan J, Zheng D, Gong W, Xie S, Shen C, Fu J, Huang H, Lai H, Jin J, Li Y, Li X*. Diverse serotonergic pathways to the amygdala underlying separable behavioral features of anxiety. ***Nature Neuroscience***. 2022

What is the evolutionary significance for the division of social avoidance and bright space avoidance while both are considered behavioral phenotypes of anxiety?

Li's group: Social behaviors help to expand groups and enable them to reproduce, while caution during foraging/exploring in unfamiliar spaces keeps animals alive. In a specific anxious state, animals may not exhibit all anxiety-like behaviors at the same time, but only those necessary to avoid harm in the specific circumstance. This can ensure their survival and reproduction to the greatest extent.

Why does activation of the DRN-BA circuit increase only the social interaction time of mice, but does not affect other anxiety-related behavior?

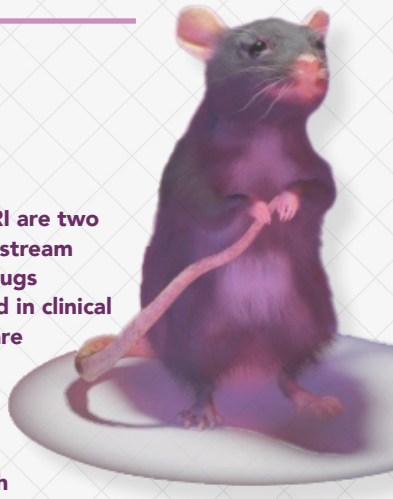
Li's group: Sociability is regulated by HTR1B, while other anxiety-related behaviors are regulated by HTR1A. Why activating DRN(5-HT)-BA does not reduce anxiety-related behaviors other than sociability is probably due to the high affinity and low expression of HTR1A within the BA under physiological conditions.

Is it possible that local Pyr neurons and PV neurons, as excitatory and inhibitory neurons, interact within BA to induce different types of anxiety-related behavior?

Li's group: It is possible.

How will this discovery of anxiety behavior guided by circuit specific molecular mechanisms help guide clinical diagnosis and the treatment of anxiety disorder?

Li's group: Our research found the differing neural circuits and molecular mechanisms for different behavioral phenotypes in anxiety states. This suggests that there is a certain potential for treating anxiety disorders from the perspective of symptomology. However, regarding the process from anxiety state to anxiety disorder, more data is needed to show what changes occur in these neural circuits and molecules between the DRN and BA, and whether HTR1A and HTR1B can be therapeutic targets for different anxiety disorder phenotypes.



SSRI and SNRI are two kinds of mainstream anxiolytics drugs currently used in clinical setting that are related to serotonin regulation, but both of these act with no specific target. What is the relationship between the local serotonin level within DRN-BA circuit and the global serotonin level of an individual?

Li's group: That's a good question. For the time being, I'll take "individual global serotonin" to mean the whole brain's serotonin. We tracked collateral projection of DRN-BA 5-HT neurons and found axon terminals in other parts of the brain and revealing DRN 5-HT neurons that project not just to the BA, but also project to many other parts of the brain. When these neurons are activated, it is possible that not only the 5-HT level of BA will increase, but also the 5-HT level of other brain regions. However, the 5-HT system also has a complex and sensitive regulation mechanism including aspects of negative autoreceptor feedback. Therefore, the relationship between 5-HT level in the specific neural circuit and the level of 5-HT in the whole brain is not clear at present.

XIAOMING LI'S RESEARCH GROUP

The long-term goal of Professor Li Xiaoming's laboratory is to study different synapses and neural circuits to find target molecules for treating neuropsychiatric diseases such as anxiety, depression, and schizophrenia, and to provide corresponding treatment strategies.
Brief Introduction of Research Content
(1) The neural circuits of emotion and affective disorders
(2) Study on the pathogenesis of anxiety, depression, schizophrenia, and other neuropsychiatric diseases

Compulsive overeating – uncovering the brain dynamics of losing control around food.

High-fat diet-induced maladaptive responses in the anterior paraventricular thalamus lead to compulsive sucrose-seeking.

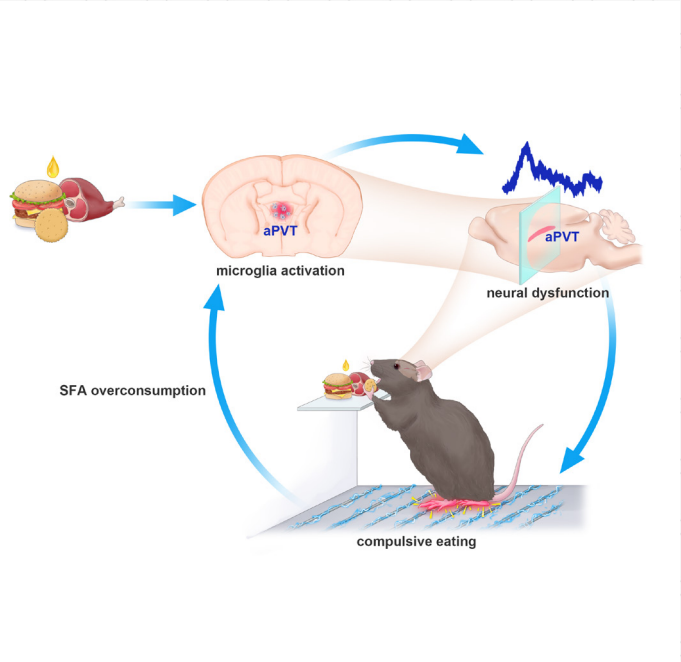
High-caloric food may trigger hedonic eating behavior. As overconsumption of palatable food is one of the most important factors leading to obesity, elucidating whether and how excessive caloric intake causes adaptive changes in the reward circuitry is of particular interest. Consumption of excessive high-fat diet (HFD) has been shown to induce compulsive-like feeding in rodents. However, the neuroadaptive responses in the reward centers produced by high fat consumption that underlie compulsive palatable food-seeking remain obscure.

Yu-Dong Zhou's team from the BBMI Center has recently published a research paper in ***Nature Neuroscience*** (2022), revealing that HFD enhances threat-cue-induced responses of excitatory neurons in the anterior paraventricular nucleus of the thalamus (aPVT) to promote compulsive sucrose-seeking. Notably, the elevated cue-triggered neuronal activity in the aPVT results from HFD-induced microglia activation.

Zhou's group developed an HFD-induced compulsive sucrose-seeking animal model in a Skinner box, where mice were trained to press a lever to obtain a sucrose reward and a conditioned punishment was subsequently established by pairing a cue light with electric foot-shock. How will the mice response to the cue light trigged by lever presses? Are they going to keep pressing the lever to consume sucrose or simply freeze in fear of electric foot-shock? It turns out that unlike mice fed chow, which stop pressing the lever after seeing the light, mice fed HFD keep pressing the lever to seek sucrose, mimicking the key symptom of compulsive eating. Further, using optogenetic or chemogenetic manipulation and in vivo photometry recording methods, the team established that the activity level of excitatory neurons in the aPVT determines the motivation to obtain the sucrose reward in the presence of the cue predicting the aversive stimulus.

As one of the nuclei located in the midline thalamus, the PVT lies just ventral to the dorsal third ventricle (D3V), and it is possible that the PVT contains sentinel cells that monitor metabolic factors in the cerebrospinal fluid. Indeed, the team found that HFD caused a significant increase in the number of Iba-1+ microglia in the aPVT. Chronic palmitic acid infusion in the D3V promoted microglia proliferation and induced compulsive sucrose seeking in chow mice. Systemically or locally inhibiting microglia activation abolished compulsive sucrose-seeking in HFD mice.In summary, these exciting results imply that anti-inflammation therapies may control diet-induced overeating. Future studies are needed to unravel further microglia-neuron interactions in the aPVT. The team also plans to investigate how aPVT neurons process reward-seeking information in approach-avoidance conflict.

Cheng J, Ma X, Li C, Ullah R, Wang X, Long J, Yuan Z, Liu S, Fu J, Chen Z, Shen Y*, Zhou Y*. Diet-induced inflammation in the anterior paraventricular thalamus induces compulsive sucrose-seeking. ***Nature Neuroscience***. 2022 Aug;25(8):1009-1013.



The graphic summary for high-fat diet-induced compulsive eating behavior in mice

What is compulsive-feeding behavior? How is it different from regular feeding?

Zhou: Our paradigm examined the feeding behaviors in conflict situations in which mice must balance the seeking of benefits with the avoidance of danger. Mice that are aware of danger, but still choose to eat rather than avoid risk, are then considered to display compulsive behavior. It is generally believed that there are two feeding behaviors: homeostatic and hedonic. We hypothesized that a high-fat diet may cause a shift to hedonic feeding. Interestingly, we found mice fed a high-fat diet did not significantly increase the regular food-seeking, but rather significantly increased the food reward-seeking in the conflict scenario. These results indicated that mice would only eat more palatable food, regardless of potential negative consequence. This behavior is most likely the reason for obesity caused by high-fat diets, and holds many similar hallmarks to addiction scenarios. However, unlike addictions, the compulsive behavior induced by a high-fat diet did not seem to have a strong negative reinforcement effect. When we restored the normal diet, the motivational food-seeking quickly returned to normal levels.

Your work has elucidated the role of the anterior paraventricular thalamic nucleus (aPVT) in inducing compulsive feeding upon a high-fat diet. What role might the PVT play in the neural circuits of compulsive eating?

Zhou: The PVT can regulate sleep and other biological processes, as can other thalamic nuclei. As it is clearly part of the brain's reward system, previous studies have also pointed out that PVT is closely related to compulsive drug-seeking behavior. The PVT has a long anterior-posterior axis and the posterior region is also involved in the processing of stress and other aversive information. We hypothesize that in the conflict scenario, the PVT acts like a gate and is responsible for transmitting the reward-seeking decision results from the upstream cortex to the downstream subcortical regions. Any abnormality in this process could then lead to biased information, giving rise to compulsive behavior. Our study was the first time the PVT had ever been demonstrated to be linked to food-seeking in approach-avoidance conflict. We also found that only the anterior paraventricular nucleus (aPVT) played a clear role in this process.

What role does the microglial activation and neuro-inflammation play in the compulsive feeding loop caused by high-fat diet?

Zhou: Our results suggested that, within the PVT the activation of microglia is limited to its anterior section (the aPVT). We speculated that this is because of the proximity of the aPVT to the third ventricle, thus allowing easier entry of lipid molecules. Microglia may therefore play a role in monitoring and responding to the entry of lipid molecules, and then produce some factors that act on neurons. This is, of course, remains only a superficial and initial explanation. Our current research only demonstrates that the PVT can respond to macro nutrients, including glucose, amino acids and lipids, and that such processes are closely related to microglia. Previously, it has been generally believed that food-induced microglial activation mainly occurred in the hypothalamus but our research is beginning to expand this concept. However, this is clearly still an ongoing investigation. We are still trying to clarify how microglia are activated and how microglia affect neurons in these processes.

The obese population in modern society is increasing. Excessive intake of high calorie food is one of the reasons that leads to obesity. How will this research help the obese population recover their health?

Zhou: This is also a matter of great concern to us. We are preparing to cooperate with many other researchers to explore whether there are changes in certain brain regions in the obese population. These changes may serve as a marker to indicate potential risks of obesity. Our research shows that anti inflammation may be an effective method to treat obesity. Whether some nonsteroidal anti-inflammatory drugs can inhibit appetite and control weight is also under investigation. Overall, the PVT clearly plays an important role in compulsive behavior. In the future, it may be possible to change the activity pattern of the PVT through transcranial magnetic stimulation and other methods. This treatment might be very helpful in the diagnosis and treatment of addiction and obesity.

YU-DONG ZHOU'S RESEARCH GROUP

Zhou's lab has a long-term interest in investigating the pathogenesis of neurodevelopmental disorders and metabolic diseases. As many neurological and metabolic conditions are triggered by immune challenges, Zhou's lab is particularly interested in understanding the regulatory effect of immune signaling on functional development of neurons and synapses. Two major ongoing projects are: 1) deciphering key inflammatory signaling cascades in brain circuit development and remodeling; 2) exploring the adaptation of a midbrain reward circuitry in response to diet-induced metabolic inflammation.

Uncovering positive feedback circadian neuronal circuits regulating sleep depth

Sleep is one of the most prevalent physiological behaviors in the animal kingdom and the circadian clock is understood to be a dominant regulator of sleep and sleep patterns. Circadian genes were first identified in Drosophila, and then later confirmed to be a relatively conserved genetic feature active throughout the animal kingdom. However, whilst Drosophila has only about 150 central circadian neurons, the mammalian biological clock regulation center, located in the SupraChiasmatic Nucleus (SCN) of the hypothalamus, is comprised of more than 20,000 neurons. Representing less than 1% of number of neurons than that in mammals, the regulatory mechanisms behind the sleep-wake cycles of Drosophila are relatively well studied and understood. By contrast, those of higher animals remain far less explored.

Classical studies have emphasized that the mutual inhibition between different brain regions controls the state transition between sleep and wakefulness. However, it remains unknown whether the circadian neurons and the pro-sleep brain regions form a positive loop to maintain sleep. In May 2022, **Fang Guo** and his team from BBMI Center published their latest research paper titled "*Recurrent Circadian Circuitry Regulates Central Brain Activity to Maintain Sleep*" in the journal ***Neuron***. The study revealed that the positive loop in the Drosophila brain consists of three neuronal layers: DN1s, APDN3s, and CLs. The APDN3s are the link between circadian DN1s and non-circadian CLs, and the latter is closely connected to the mushroom body (MB) γ lobes, which are involved in sleep regulation.

Previous studies from Dr. Guo's team have shown that Drosophila dorsal circadian neurons (APDN1s) are involved in sleep initiation and maintenance. Despite this finding, the pattern of their connections to downstream circadian neural circuits had remained unclear. In the present study, our researchers identified the complete DN1-APDN3-CL-DN1 positive feedback loop, beginning with the currently unstudied DN3 circadian neuron subsets, which also project to the MB in higher brain regions of the brain, thereby maintaining the deep sleep state in Drosophila.

Using a new split-GAL4 technique, Dr. Guo's team identified three different subtypes of DN3 circadian neurons. One of the clusters represents APDN3s labeled with only 2-3 neurons. Optogenetic activation of APDN3s significantly induces sleep in Drosophila. Using trans-Tango and functional imaging, the team found that APDN3s act as a links between upstream circadian neurons (DN1s) and downstream non-circadian neurons (CLs). CLs, by receiving output from circadian neurons, cause the own Ca^{2+} to exhibit a circadian oscillation patterns, peaking at night. This pattern is very similar to the Ca^{2+} oscillations of DN1 and DN3.

It was found that calcium signaling in the CL neurons was maintained at a high level long after APDN3 activation. The researchers thus speculated that CLs may be part of a self-sustaining circuit. In both mouse and Drosophila brains, recurrent circuits are involved in maintaining the internal state of the animal. In the Drosophila brain, CLs and DNs may also form an excitatory feedback loop to continuously promote sleep. To test this conjecture, using trans-synaptic tracking techniques the researchers further demonstrated that CLs can feedback to upstream DN1s, thereby forming a positive loop of DN1-APDN3-CL to maintain sleep by gradually accumulating and sustaining sleep-promoting signals.

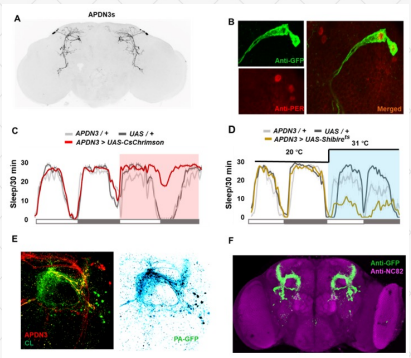


Figure 1: Sleep-promoting APDN3 circadian neuronsacting on CL neurons

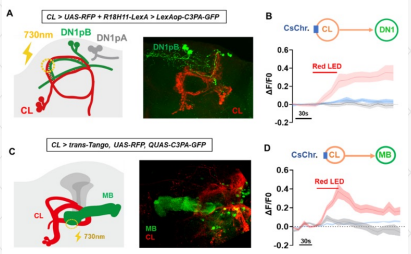


Figure 2: Optogenetic coupled calcium imaging technique to identify functional connections between CLs and downstream neurons

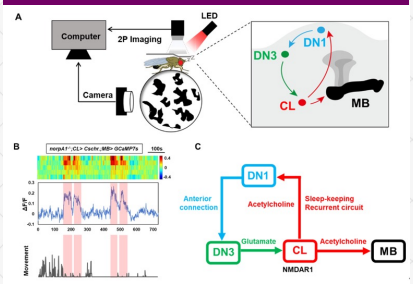


Figure 3: In vivo calcium imaging technique identifies a positive feedback loop acting on the MB to promote sleep

Subsequently, the team used trans-synaptic PA-GFP and in vivo calcium imaging to demonstrate that CLs release acetylcholine to activate MB γ lobes in order to drive sleep. MB apoptosis induced by hydroxyurea blocked the pro-sleep effect induced by CLs, indicating that the MB is necessary for CL-induced sleep. The researchers further verified this in live flies using real-time calcium imaging and motor coupling paradigms, showing that the activation of CLs leads to elevated calcium activity of the MB, accompanied by a prolonged resting state in Drosophila. Ultimately they were able to demonstrate that recurring release of the DN1-APDN3-CL loop activates MB brain regions, thereby causing Drosophila to fall asleep.

In summary, this research has identified for the first time a positive feedback loop in the Drosophila brain containing circadian neurons that regulate the activity of higher brain regions in the MB and play an important role in maintaining sleep depth. The positive recurrent loop reported in the paper is a groundbreaking discovery that provides a more comprehensive understanding of the neural mechanisms underlying sleep and circadian regulation. It also delivers a fascinating new perspective on the relationship between deep sleep and higher cognitive functions since the MB is also a higher brain region for learning and memory storage in the Drosophila brain.

As the downstream region in the brain of Drosophila, this article points to the mushroom body which has been long considered the center of learning and memory. What is the relationship between sleep regulation, learning and memory?

Fang Guo: We still don't know exactly to what extent, if any, deep sleep is related to learning and memory. The current research simply reveals the tip of the iceberg. In this paper, we activated a circuit and observed regular oscillation in the mushroom body of Drosophila. Whether such oscillation contributes to better memory formation remains unclear, though we suspect that it may. Previous studies have shown that manipulating the activity of the mushroom body, such as making it insensitive to external stimuli, memory consolidation in Drosophila. Humans are also less sensitive to external stimuli during deep sleep. Whether and even how these findings are linked together is an area of interest for us, though it is not the primary focus for our future research.

Other sleep-related circuits have been identified before. How does this differ from the new findings? Which one plays the more important role?

Fang Guo: After I first established my laboratory, the first paper we published in ***Neuron*** was primarily relating to the circuit connections between circadian neurons and the sleep homeostasis brain regions. Hindered by the lack of sufficient genetic tools to label and analyze the whole circadian circuit, we were only able to analyze a few subgroups, luckily stumbling upon a relatively important one essentially by accident. By contrast, in the recent ***Neuron*** article, we used the split-GAL4 technique to perform a more complete and systematic screening. This allowed manipulation of every circadian neuron giving a clear description of the whole circuit. We then focused upon a particularly recurrent circuit. This, once activated, would sustain the hyperactivity and would bring the drosophila into a more and more sleepy physiological state with each repetition. Compared with the initial study, this current study was better prepared and enabled the mapping out of the whole circuit, despite the previous finding being relatively more interesting.

Drosophila is a very small bodied species, yet technologies such as optogenetics, two-photon imaging can be applied on it. Is it possible to record the activity of multiple brain regions simultaneously in a tiny model organism like Drosophila?

Fang Guo: The techniques in our laboratory are now relatively mature. We have been able to generally record whole-brain calcium imaging for a while now, enabling the scanning of the key brain regions of Drosophila over a relatively short time period. The more critical question now is how to simulate the scene that Drosophila encounters in the environment under two-photon microscopy. We can place the fruit fly on a air-supported ball and use the software to record its trajectory, calcium signaling, movement speed, and other indicators, so that numerous brain regions can be recorded synchronously. However, the recording environment is dark. We need to now consider how to observe and record Drosophila's social behavior, including courtship and fighting, under a more realistic brighter environment.

Can the emotions of Drosophila be studied? What indicators can be used to reflect its emotional states?

Fang Guo: Yes. For example, Professor David Anderson of the California Institute of Technology is a leading expert in the field of Drosophila emotions. He studied how neurotransmitters like dopamine and conservative neuropeptides such as tachykinin regulate emotions including anger and fear in Drosophila. Flies behave similarly to humans when they're angry. They have certain patterns, such as opening their wings, like a human "flapping and clawing," and they also fight. There are many genetic tools available for studying Drosophila, and each neuropeptide has its strain for easy manipulation and fast detection.

How should the findings from the study of Drosophila and other model organisms be translated into clinical practice?

Fang Guo: The generalization from animal models in biology to humans is a question that researchers in many fields are interested in. Genetically, the conservation of Drosophila and human genes is about 60%. For example, the four key circadian genes we are looking at are conserved from Drosophila to human. Drosophila also has many advantages such as convenient feeding, low rearing costs, abundant genetic tools, complete analysis of the whole brain connectome, and mastery of the topological connection structure between neurons. We can therefore answer the most basic questions about humans using Drosophila models, such as the mechanisms of sleep, circadian rhythm, learning and memory, etc. However, it is very difficult to directly transfer the result from basic research in Drosophila to humans. There are other promising studies using monkeys and other non-human primates, but here cost and ethics becomes a much bigger issue. We really should find middle ground models to answer the various differing questions using the most suitable model organisms, and eventually transform these into results that can be applied to clinical practice.

Sun L, Jiang R, Ye W, Michael Rosbash, Guo F*. Recurrent Circadian Circuitry Regulates Central Brain Activity to Maintain Sleep. Neuron. 2022 Jul 6;110(13):2139-2154.e5.

FANG GUO'S RESEARCH GROUP

Fang Guo's lab has long been engaged in the elucidation of circadian loop mechanisms and the regulation of physiological processes, such as sleep and metabolism, by studying biological clocks. Using cutting-edge optogenetics, neural circuit tracing technology, in vivo long-term calcium imaging technology and cellular molecular biology they have conducted profound analysis of circadian neural loops at both cellular and loop levels. Their previous research results have been published in leading journals such as ***Nature***, ***Neuron***, ***eLife*** and ***PNAS***.

Epilepsy and ion transmembrane transport

Epilepsy is a common nervous system disease. It is characterized by recurrent seizures caused by abnormal discharges of neurons. The worldwide incidence of epilepsy is about 1%, and the pathogenesis of epilepsy includes brain trauma, stroke, brain tumors, genetic defects, and other features. The transmembrane transport of ions plays a critical role in the ion homeostasis of neurons and the stability of membrane potential. Genetic mutations of various ion channels (such as sodium and potassium channels) and ion transporters (such as potassium chloride co-transporters and chloride ion transporters) may result in hereditary epilepsy. This facilitates these channels and transporters to be important drug targets for the treatment of epilepsy.

Guo Jiangtao's lab focuses on epilepsy-related ion transmembrane transport proteins where they systematically study the structure and mechanism of potassium chloride co-transport KCC and potassium ion channels using Cryo-EM Single Particle Analysis. A series of original research results and related publications have laid a solid foundation for future research and development of antiepileptic drugs targeting KCC and KCNQ2.

Potassium-chloride cotransporter KCC2 mediates the coupled export of potassium and chloride across the plasma membrane and plays an important role in maintaining chloride ion homeostasis in postsynaptic inhibitory neurons. The mutation of KCC2 can lead to increased intracellular chloride ion concentration and depolarized membrane potential in inhibitory neurons, resulting in persistent action potential and epilepsy. Therefore, the development of KCC2 agonists has become an important research direction in the treatment of epilepsy. In October 2019, the Guo lab reported the first high-resolution cryo-EM structure of human potassium-chlorine cotransporter KCC1 in ***Science*** (Figure A). The researchers revealed the dimer structure of KCC1, defined one potassium and two chloride binding sites, and proposed a model of coupled transportation of potassium and chloride. One year later, the researchers reported the full-length structures of human potassium-chloride cotransporter KCC2-4 in ***Science Advances*** in December 2020 (Figure B). They elucidated the auto-inhibition mechanism of KCC2-4, as mediated by the N-terminal peptide binding in the substrate binding pocket, providing novel prospects for the antiepileptic drug discovery and development targeting KCC2. In the follow-up research, they expect to design allosteric modulatory agonists based on the structure of KCC2 by weakening the binding of the N-terminal inhibitory peptide.

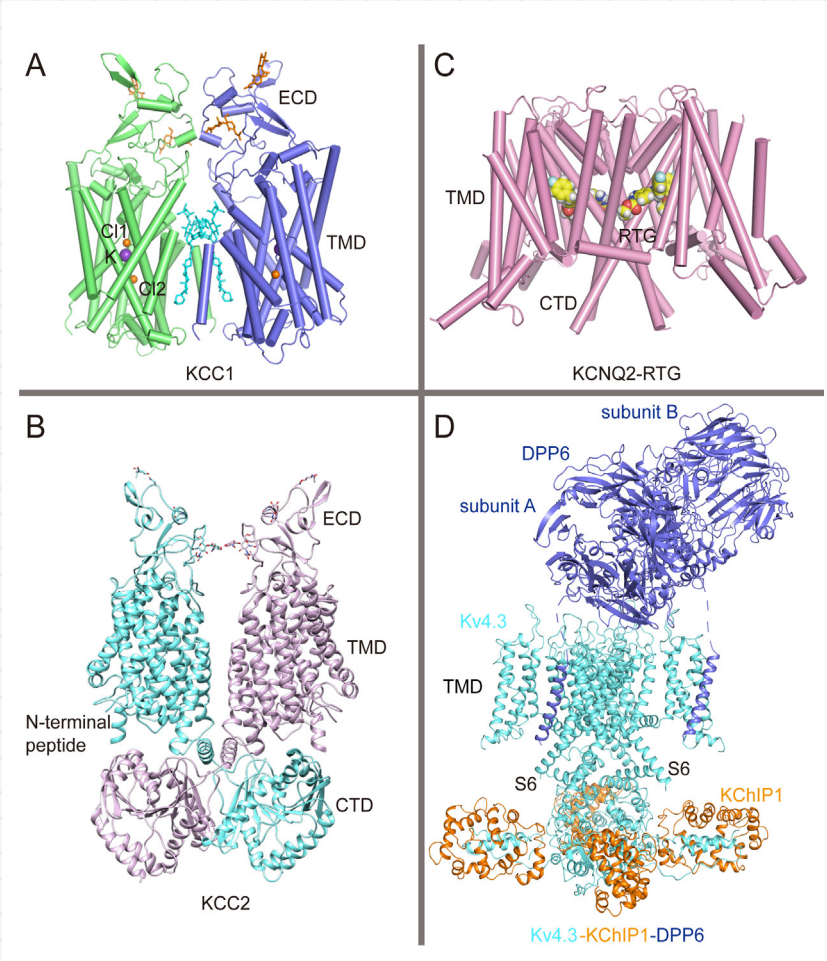


Figure Structures of ion transmembrane transport proteins related to epilepsy

A, potassium-chloride cotransporter KCC1; B, potassium-chloride cotransporter KCC2; C, potassium channel KCNQ2-RTG; D, potassium channel Kv4.3-KChIP-DPP6

Voltage-gated potassium channels mediate the efflux of potassium upon membrane potential depolarization. These channels play key roles in maintaining the stability of neuronal membrane potential and are closely related to nervous system diseases, such as epilepsy and pain. Guo's lab studied several voltage-gated potassium channels and made progress on KCNQ2 and Kv4.3. Potassium channels KCNQ2 and KCNQ3 mediate the neuron M current. Genetic mutation of KCNQ2 could lead to benign familial neonatal convulsion and epileptic encephalopathy. Retigabine (RTG) is the first drug targeting the KCNQ2 channel to treat epilepsy, and it is used as an adjuvant therapy for adult refractory partial seizures. However, retigabine can cause certain side effects such as pigmentation in patients' eyes and skin due to its poor selectivity. Guo lab published a research paper in ***Cell Research*** in January 2021 (Figure C), reporting the

structures of human KCNQ2 in the apo state or in complex with the activators retigabine and ztz240. This study revealed the binding sites of retigabine and ztz240, elucidated the activation mechanism of the two ligands, and provided the structural basis for the development of new antiepileptic drugs. The potassium channel Kv4.3 mediates the somatic dendritic current ISA of neurons, which is closely related to neuropathic pain, epilepsy, and other diseases. Kv4.3 is regulated by the auxiliary subunits KChIP and DPLP. Guo lab published a research paper in ***Cell Research*** in January 2022, reporting the structure of Kv4.3, KChIP, and DPLP complexes (Figure D). This research revealed the structures of the Kv4.3, Kv4.3-KChIP eight-subunit complex, and Kv4.3-KChIP-DPP6 ten-subunit complex, defined the structural basis of Kv4.3 regulation by KChIP and DPP6, and laid the foundation for the subsequent development of modulatory molecules for Kv4.3.

Over recent years, thanks to the development and application of molecular genetics, electrophysiology, optogenetics, Cryo-EM Single Particle Analysis, and other technologies, the understanding of the molecular mechanism of epilepsy has advanced. Focusing on epilepsy, Guo's lab has studied the structure and mechanism of KCC and potassium channels, which not only revealed the structural basis for the physiology and pathology of these two types of proteins but also provided a solid foundation for drug discovery. In the future, based on the structure of transmembrane transporters and with the help of artificial intelligence, precise drug design and screening of antiepileptic drugs should be facilitated to greatly promote the treatment of epilepsy.

1. Liu S#, Chang S#, Han B#, Xu L, Zhang M, Zhao C, Yang W, Wang F, Li J*, Delpire E*, Ye S*, Bai X*, Guo J*. Cryo-EM structures of the human cation-chloride cotransporter KCC1. ***Science*** 366, 505–508 (2019).

2. Xie Y#, Chang S#, Zhao C, Wang F, Liu S, Wang J, Delpire E*, Ye S*, Guo J*. Structures and an activation mechanism of human potassium-chloride cotransporters. ***Sci Adv*** 6, eabc5883 (2020).

3. Li X#, Zhang Q#, Guo P#, Fu J, Mei L, Lv D, Wang J, Lai D, Ye S, Yang H*, Guo J*. Molecular basis for ligand activation of the human KCNQ2 channel. ***Cell Research*** 31, 52–61 (2021).

4. Ma D#, Zhao C#, Wang X, Li X, Zha Y, Zhang Y, Fu G, Liang P*, Guo J*, Lai D*. Structural basis for the gating modulation of Kv4.3 by auxiliary subunits. ***Cell Research*** 32, 411-414 (2022)

GUO JIANGTAO'S RESEARCH GROUP

The Guo lab mainly focuses on the structure and mechanism of ion channels, transporters, and other important membrane proteins using biophysical and biochemical methods such as Cryo-EM and X-ray crystallography. Over recent years, research achievements have been made related to the molecular mechanisms of the potassium-chloride co-transporter KCC; the potassium channel and two-pore channel TPC; and the TRP channel. Seminal research papers have been published in the top international journals such as ***Nature*** and ***Science***. In Aug 2022, the Guo lab also reported the structures and molecular mechanism of the transporter PIN of the plant hormone auxin in the Nature journal, representing a milestone in the field of auxin biology.

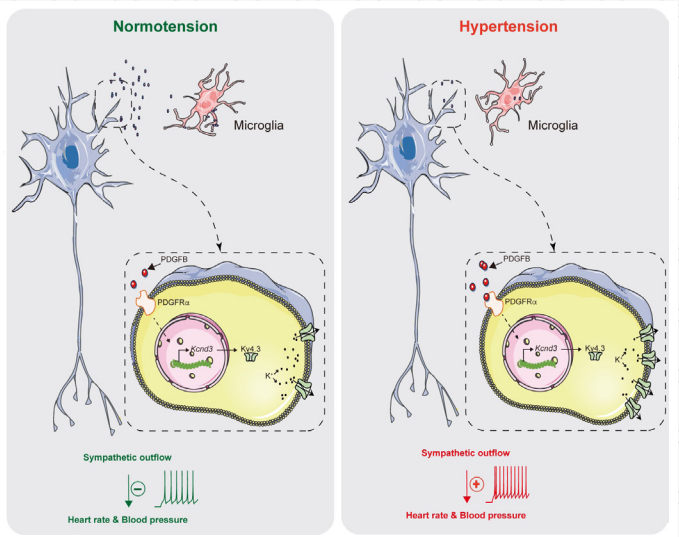
Microglia,

the 'levee' of sympathetic outflow?

Hypertension, AKA the "silent killer", is a major risk factor for life-threatening cardiovascular diseases such as heart failure, heart attack, and stroke. It also contributes to neurodegenerative diseases *e.g.* Alzheimer's disease. Famous characters in history have been impacted considerably by this condition. In the great gathering of leaders from World War II, President Roosevelt, Prime Minister Churchill, and Chairman Stalin (from the United States, United Kingdom and Soviet Union, *respectively*), all suffered from hypertension, with President Roosevelt's blood pressure continuing to rise steadily during the progress of the war leading to his death from complications stemming from his severe hypertension in 1945.

If we look back 70 years, healthcare professionals did not realize the lethal effects of hypertension. Since then, many breakthroughs have contributed dramatically to our understanding and management of this condition. Life-style related risk factors, such as high salt diet, have also now been identified. Meanwhile, safe and effective anti-hypertensive drugs such as beta blocker, diuretics, Ca^{2+} channel inhibitor, ARB or ACEI, have been developed to treat hypertension. Despite these advances, there are still ~10% of hypertensive patients with conditions that are refractory to current therapy and are therefore named "resistant hypertension". Clinicians can carry out a comparably aggressive approaches to treat these patients by interventions such as renal denervation, a minimal invasive procedure to permanently lesion the sympathetic nerves controlling the renal arteries through a radiofrequency balloon generator. This strongly indicates the importance of sympathetic nerve activity in controlling or propelling hypertension.

Ongoing sympathetic nerve activity is generated by a couple of key brain regions in the brain. Dr. **Peng Shi**'s research group focuses on the paraventricular nucleus (PVN), a critical nucleus locating bilaterally surrounding the 3rd ventricle in the hypothalamus. It is comprised of pre-sympathetic neurons projecting down to the brainstem or spinal cord to regulate sympathetic outflow. Abnormal discharge of PVN pre-sympathetic neuronal activity participates in multiple cardiovascular diseases such as hypertension, heart failure and/or stroke. What causes the PVN neurons to switch from physiological to the pathological state remains unclear. Previous work from Dr. Shi's laboratory indicates that microglia, the resident immune cells in the central nervous system (CNS), participate in sympathetic outflow and cardiovascular function. Microglia have been shown to support homeostatic functions in the CNS including those of neuronal circuitry formation, synapse formation/pruning, neurogenesis, and myelinogenesis. Recent work published on ***Immunity*** by Peng Shi's group shows that microglia directly modulate PVN pre-sympathetic neuronal firing in a paracrine fashion. Platelet-derived growth factor B (PDGFB) is dominantly expressed in microglia in the adulthood brain. By constitutively releasing PDGFB, microglia negatively modulate PVN pre-sympathetic neuronal activation by promoting the expression of Kcnd3, a gene coding an alpha subunit (Kv4.3) of the outward K^+ channel. Disruption of the Microglia^{PDGFB}-Neuron$^{Kv4.3}$ pathway leads to the susceptibility to hypertension development. This study unravels a new understanding that resident microglia directly regulate neuronal intrinsic activity and highlights a non-immune function employed by microglia in maintaining homeostasis, not simply for just the central nervous system, but also for the whole body.



Microglia-derived PDGFB promotes Kv4.3 expression, the aphal subunit of potassium channel, to regulate the excitability of PVN neurons and sympathetic tonicity.

Bi QQ, Wang C, Cheng G, Chen N, Wei B, Liu X, Li L, Lu C, He J, Weng Y, Yin C, Lin Y, Wan S, Zhao L, Xu J, Wan S, Zhao L, Xu J, Wang Y, Gu Y*, Shen X.Z.*, Shi P*. Microglia-derived PDGFB promotes neuronal potassium currents to suppress basal sympathetic tonicity and limit hypertension. ***Immunity***. 2022 Aug; 55,1-17.

PENG SHI'S RESEARCH GROUP

Autonomic dysfunction has been implicated in many cardiovascular and neurodegenerative diseases. Combining multi-disciplinary techniques including cardiovascular function assessment, electrophysiological recording, and immunological analysis, Dr. Shi and her team have been focusing on delineating the cellular and molecular mechanism(s) by which sympathetic tonicity has been altered. In the past, a major project in the lab is to understand how microglia, the primary immune cells in the CNS, participate in autonomic neuronal activity in both physiological and pathological states, e.g. hypertension and related-cardiovascular diseases.

Traumatic brain injury in a military context

Neurology in nature, and psychiatric manifestations

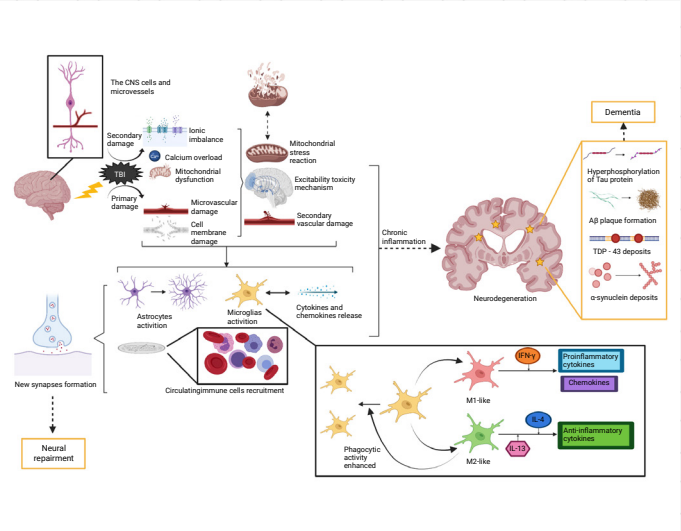
After the World War I, the specific concept of military-based traumatic brain injury (TBI) was gradually established, leading to the birth of military psychiatry. Military-related TBIs include concussion, blast injury, chronic traumatic encephalopathy, among others. Military TBI accounts for the vast majority (more than 80%) of all TBIs, and have been clearly associated with military operations such as shooting, exposure to explosive weapons, etc. Whilst the majority of military TBIs are classified as relatively mild, epidemiological statistics show an extremely high incidence of military related TBIs with a prevalence of somewhere between 20-30% among all military personnel. In addition, military TBI is characterized by atypical clinical manifestations, poor long-term prognosis, and incidences of sequelae in many patients, all of which create a serious burden on the national social health system.

A key review was published in ***Military Medical Research*** in 2022 by **Shaohua Hu** and his team, in which epidemiology, molecular mechanisms, diagnosis and treatment progress, and comorbidities were all reviewed and summarized. The long-term prospect of "strengthening the cross integration of neurology and psychiatry in scientific research, so as to promote the precision medicine in the field of military TBI" was particularly emphasized.

Whilst military TBI is neurologic in nature, it is primarily psychiatric in its manifestation. Typical manifestations of military TBI include neurological symptoms such as headache, vomiting, and dizziness, as well as psychiatric symptoms such as depression, irritability, and suicidal tendencies. With the development of molecular medical research, it has been confirmed that the pathogenesis of military TBI often involves damage to the blood-brain barrier, brain edemas, axonal ruptures, neuroinflammation, hyperphosphorylation of Tau protein, accumulation of abnormal proteins such as Aβ42, and other similar aspects. These pathological mechanisms have conceptual crossover with some neurodegenerative diseases such as Alzheimer's disease (AD).

The standardized diagnosis of military TBI has yet to be perfected. Currently, most patients are initially diagnosed by scale assessment (such as the Glasgow Coma Scale, Neurobehavioral Symptom Questionnaire, etc.). Meanwhile, neuroimaging techniques such as CT, fMRI and DTI can more specifically reveal any abnormalities in anatomical structure, biochemical metabolism, or functional connectivity in the brain of patients. For example, increased thalamic volume, altered cingulate cortex connectivity, and decreased prefrontal cortex activity, have been previously observed in military TBI patients. It has been reported that biomarkers derived from serum or cerebrospinal fluid, such as neuron-specific enolase, myelin basic protein, vascular endothelial growth factor, or exosomes, can be used for clinical typing, judging the severity of brain injury, and assessing long-term prognosis.

However, the injured areas are often difficult to accurately characterize and locate in the brains of military TBI patients, and complex neuropsychiatric comorbidities (such as AD, depression, anxiety, and sleep disorders) add further complexity and enhance clinical difficulties. At present, the main therapeutic goals of military TBI diagnosis and treatment remain broadly defined in the basic control clinical symptoms, the improvement of quality of life, and optimization of long-term prognosis. In this way, it is urgent to establish a more specific, scientific, rigorous and feasible military TBI diagnosis and treatment system, so that patients can regain more complete social functions over shorter time periods than the current system facilitates.



Neuroinflammation after Traumatic Brain Injury

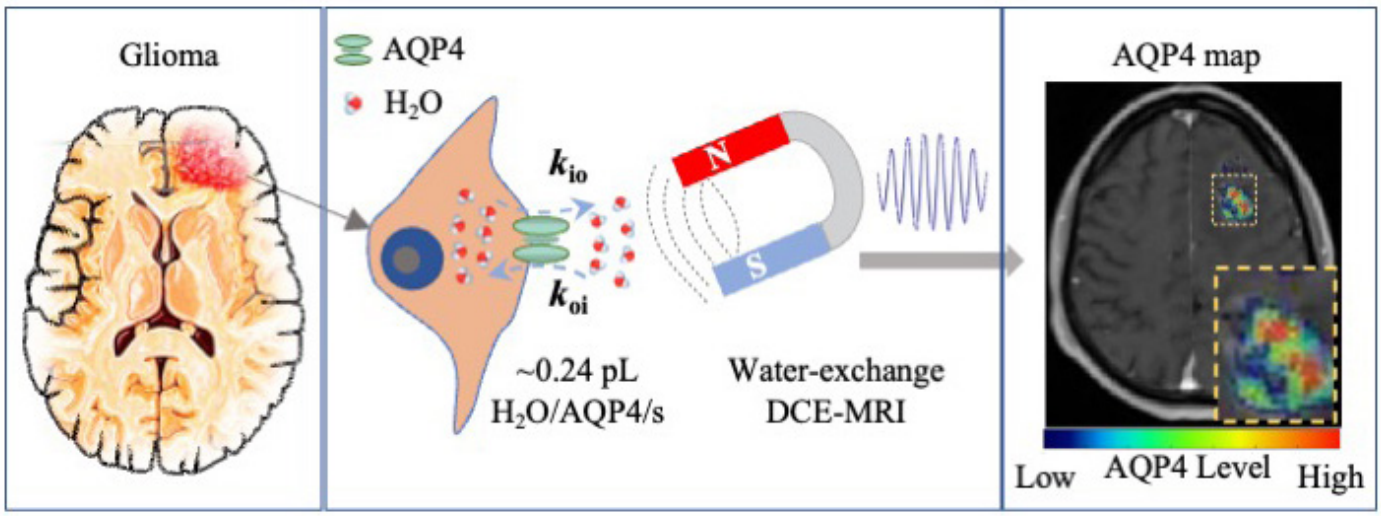
Kong L, Zhang R, Hu S*, Lai J*. Military traumatic brain injury: a challenge straddling neurology and psychiatry. ***Military Medical Research.*** 2022 Jan 6;9(1):2.

SHAOHUA HU'S RESEARCH GROUP

Dr. Hu and his team focus on biological and clinical psychiatry, particularly as related to affective disorders and neuro-cognition. They have long been committed to the study of pathogenesis, emerging biomarkers, development of therapeutic methods, and the clinical transformation of basic research. Their work has led to the development of novel innovative experimental methods, leading interdisciplinary research, and the provision of scientific evidence relating to the use of precision medicine in the field of psychiatry from many new perspectives.

The new AQP4-MRI method

Providing a high-resolution and treatment sensitive prediction for gliomas



AQP4 signal-amplification and detection strategy in MRI and its application as a clinical diagnostic therapy resistance tool.

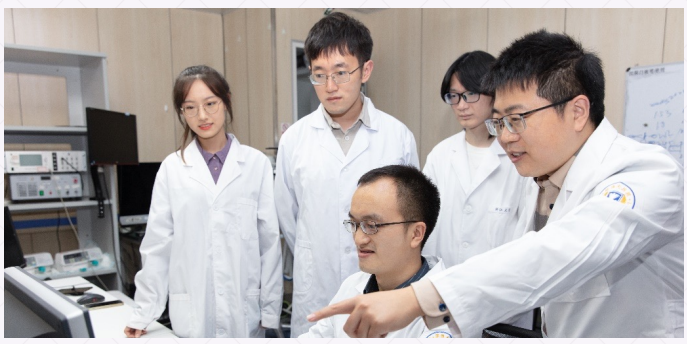
The glioma is the most common primary tumor of the central nervous system and represents one of the most highly heterogeneous and intractable of diseases. Aquaporin 4 channel (AQP4), a water molecule selective membrane protein expressed in glioma cells, dominates tumor migration, proliferation, and drug resistance. At present, biopsies followed by direct pathological analysis is the only known method to quantify the expression level of AQP4. However, there are huge intra- and inter-tumor differences in the expression of AQP4 and a simple biopsy does not give any clear picture of the spatial arrangement of such an expression. Therefore it is remains an urgent priority to develop molecular imaging techniques for in-vivo and non-invasive quantitative detection of AQP4 expression for clinical operation.

Recently, Professor **Ruiliang Bai**'s team from the BBMI center and Professor **Yingchao Liu**'s team from Shandong Provincial Hospital jointly published a research article in the internationally recognized journal ***Nature Biomedical Engineering***, reporting their development of new in-vivo visualization technology for aquaporin 4 (AQP4). Previous studies have shown that the single-channel water permeability of AQP4 could be as large as 0.24 pL per second (the volume of a glioma cell being ~10 pL) and much higher than other aquaporins. This indicated the potentially important contribution of AQP4 to transmembrane water exchange. Accordingly, the teams then were able to demonstrate that the transmembrane water-efflux rate (kio), as measured using new shutter-speed DCE-MRI technology that the team themselves developed, provided an accurate imaging biomarker of AQP4 expression in gliomas. The technology was then successfully applied to demonstrate the heterogeneity of AQP4 expression intra- and inter-tumors in glioma patients, and to confirm that tumor tissue with lower AQP4 expressions had a far higher treatment resistance. This validated the reliability and high precision of this new technology. The researchers explained that this AQP4 MRI technology can be now applied to clinical MRI examination and is expected to be rapidly and widely implemented in a clinical setting, providing a strong new imaging tool for the diagnosis, prognosis, and therapeutic evaluation of gliomas.

Jia Y, Xu S, Han G, Wang B, Wang Z, Lan C, Zhao P, Gao M, Zhang Y, Jiang W, Qiu B, Liu R, Hsu Y, Sun Y, Liu C, Liu Y*, Bai R*. Transmembrane water-efflux rate measured by magnetic resonance imaging as a biomarker of the expression of aquaporin-4 in gliomas. ***Nature Biomedical Engineering***. 2022 Nov 14.

RUILIANG BAI'S RESEARCH GROUP

Ruiliang Bai's lab focuses on three key areas: (1) Inventing "bloodless" functional MRI contrast mechanisms to facilitate direct, speedy, and accurate detection of neurons for application towards whole brain functional mapping; (2) Developing fast multi-dimensional MRI relaxation or diffusion spectroscopy for tissue microstructure characterization; and (3) Studying water exchange dynamics in healthy and pathological cells, tissues and the brain itself, with particular focus upon using and developing MRI detection technology for this purpose.



Time-restricted feeding can prevent and rescue obesity-related drowsiness during daytime

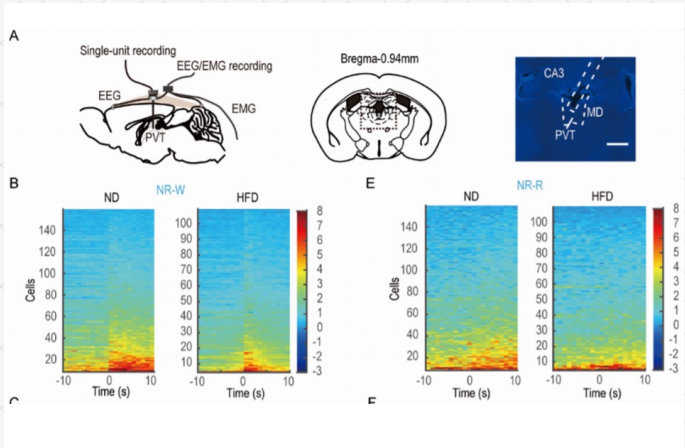
Obesity as a result of a high-fat diet (HFD) is a life-threatening condition of increasing global concern. Daytime drowsiness is a common characteristic of obese patients in whom vigilance and attention are significantly weakened, thus adversely affecting their quality of life. Previous studies have demonstrated that genetic- or HFD-induced rodent models of obesity also exhibit excessive drowsiness during particular phases of the circadian cycle. However, time-restricted feeding (TRF) has been seen to alleviate metabolic disturbances in obese mice, restoring normal clock gene oscillations of peripheral tissues, and improving obesity-related irregularities of sleep-wake cycles. However, the mechanism underlying this phenomenon remains unknown.

On October 16, 2022, joint research by **Haohong Li**'s team from the MOE Frontier Science Center for Brain science and Brain-Machine Integration of Zhejiang University and **Luoying Zhang**'s team from Huazhong University of Science and Technology, yielded an article entitled "*Time-Restricted Feeding Is an Intervention against Excessive Dark-phase Sleepiness Induced by Obesogenic Diet*" presented online in ***National Science Review***. This paper depicted a novel mechanism by which time-restricted feeding alleviates excessive HFD-induced drowsiness during the active phase of the circadian cycle. It focusses upon the paraventricular nucleus of thalamus (PVT) which spans the entire rostral thalamic midline and displays distinct functions along the anterior-posterior axis, including those related to wakefulness, emotion, and motivation. The PVT was also seen to be involved in the regulation of feeding behavior by interacting with circulatory signals.

Previous studies have suggested that the PVT is sensitive to energy balance. Hypoglycemia upregulates the activity of the PVT neurons that project to the nucleus accumbens (NAc), leading to rectal responses. Conversely, the administration of a glucagon-like peptide-1 receptor agonist into the PVT reduces the activity of these neurons, leading to an anorectic effect. Previous studies in rats have shown increases in the expression of c-fos, a marker of neuronal activity, in the PVT during the dark (active phase of waking rats) compared with light periods.

The PVT is one of the components of the thalamocortical arousal system. Upon receiving broad excitatory inputs from the sleep-wake regulatory network, it then activates the cerebral cortex to promote arousal. In humans and rodents, abnormality in the PVT disrupts the integrity of wakefulness and induces drowsiness. Recent studies have shown that the PVT is also associated with arousal independent of light-dark cycles. C-fos expression in the PVT also increased in the presence of palatable food during persistent darkness. Therefore, the researchers speculated that feeding behavior might participate in maintaining wakefulness during the active phases by activating PVT neurons.

This study characterized the increased drowsiness during the active phase in obese mice as induced by HFD. The provision of HFD chow ad libitum shortened wakefulness and increased wake fragmentation in mice during their active phase. Free intake of a HFD also reduced the excitability of PVT neurons, disrupted both PVT synaptic transmission, and upset the excitation/inhibition balance. However, TRF prevented and reversed such effects of HFD-induced obesity on PVT and arousal. Such a rescue of the activity of PVT neurons enabled prolonged wake durations in obese mice and TRF in the active phase improved the fragmentation of wakefulness. TRF in the active phase also attenuated HFD-induced impairment of PVT synaptic activity, the therapeutic effect of which was dependent on the duration of eating or starvation.



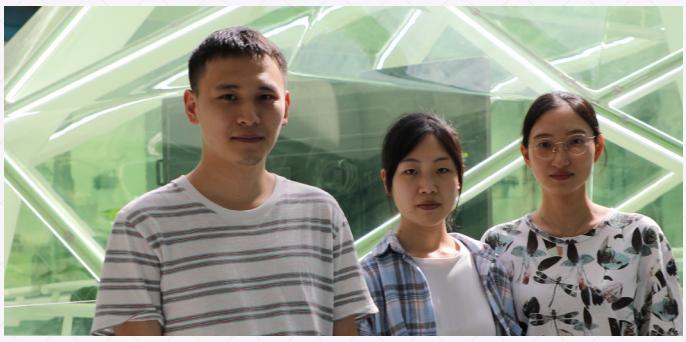
Sleep-wake transition-related firing in the PVT is disrupted by AL HFD feeding

These results revealed a previously unknown mechanism underlying obesity-related drowsiness during daytime, and may represent a non-drug intervention that could be applied to the treatment of human obesity.

Wang X, Xing K, He M, He T, Xiang X, Chen T, Zhang L*, Li H*. Time-Restricted Feeding Is an Intervention against Excessive Dark-phase Sleepiness Induced by Obesogenic Diet. ***National Science Review***. 2022 Oct 16; online.

HONGHAO LI'S RESEARCH GROUP

Haohong Li's Group is dedicated to the study of neural circuits of sleep-wake regulation and the neural mechanisms of network oscillations. His research group has revealed that the paraventricular nucleus of the thalamus is an important brain center for sleep and wakefulness regulation and has verified the effect of arousal regulation on learning and memory. Related work has been published in ***Nature Neuroscience, Neuron, Nature Communications, Current Biology*** and ***Cell Reports***.



Glucose utilization as fuel for microglia -the brain's busy bees.

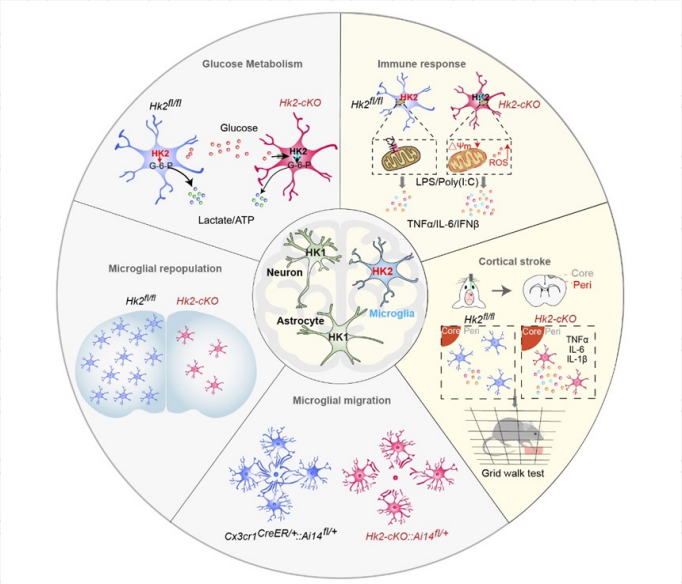
New revelation of the dual roles of hexokinase 2 in shaping microglial function by gating glycolytic flux and mitochondrial activity

Microglia, the brain's "busy bees", continuously survey their microenvironment by extending and retracting their ramified processes to maintain brain homeostasis. Upon disease or injury, microglia quickly alter their morphology, extending their processes towards the disease/injury sites to clear damage. Upon particularly acute depletion or disease conditions, microglia will even undergo rapid proliferation to clonally expand their numbers, resulting in restoration of the homeostatic pool (repopulation), or formation of microglia clusters surrounding disease sites (microgliosis). These dynamic features require microglia to possess a unique bioenergetic profiles to facilitate such a remarkable plasticity. However, little is known about the specific molecular determinants that metabolically and bioenergetically shape microglial function.

The brain mainly uses glucose as its energy or fuel. Hexokinase (HK), by catalyzing the phosphorylation of glucose to glucose-6-phosphate (G6P), is the first rate-limiting enzyme in glucose utilization. Four main HK isozymes, HK1, HK2, HK3 and HK4, with differing biochemical features and catalytic activities have been identified. Among them, HK1 and HK2 also associate with the outer mitochondrial membrane (OMM), allowing preferential access to mitochondrial ATP to promote glycolysis. Nevertheless, how HKs specifically become involved in microglial function and brain diseases remains poorly understood.

Zhihua Gao and **Shumin Duan**'s team from the BBMI Center have just published their latest research results in ***Nature Metabolism*** (2022). By systematically analyzing the metabolic regulators in different brain cell types, the team unexpectedly found that whilst HK2 is selectively expressed in microglia, HK1 is predominantly expressed in neurons and astrocytes. HK2 is the most active HK isozyme. The ablation of HK2 disrupts the microglial glycolytic flux. This results in an energy-deficient state, attenuated microglial surveillance, and delayed microglial repopulation. HK2 is notably and robustly elevated in immune-challenged and disease-associated microglia (DAM) to promote glycolysis in multiple disease models. However, in an ischemic stroke model HK2 ablation aggravates the inflammatory responses and perpetuates brain damage. Such pro-inflammatory effects upon HK2 deletion are also associated with impaired mitochondrial function and reactive oxygen species (ROS) accumulation.

Zhihua Gao and Shumin Duan's team have revealled that HK2 is a genetically programmed metabolic marker in microglia. By utilizing HK2, microglia are able to achieve a maximal glycolytic flux and adaptive capacity to instruct cellular metabolism and support diverse functions in response to differing stimuli. Moreover, HK2 also plays a role in dynamically regulating mitochondrial function and fine tuning microglial immune responses under different states. This study reveals an important mechanism, by which microglia control the intracellular metabolism and immune response through HK2 to adapt to environmental stimuli. This study also provides insights into the mechanism of altered metabolic patterns observed in multiple neurodegenerative diseases and may shed light on therapeutic strategies that could lead to metabolic interventions.



The dual roles of HK2 in shaping microglial functions

Hu Y#, Cao K#, Wang F#, Wu W, Mai W, Qiu L, Luo Y, Ge W, Sun B, Shi L, Zhu J, Zhang J, Wu Z, Xie Y, Duan S*, Gao Z*. Dual roles of hexokinase 2 in shaping microglial function by gating glycolytic flux and mitochondrial activity. ***Nature Metabolism***. 2022 Dec 19;online.

ZHIHUA GAO'S Research Group

Prof. Zhihua Gao's team is particularly focused upon exploring the role of neural-immune interactions and the effect of the neuroendocrine network on brain development and brain disease. Her group mainly focuses on how microglia and magnocellular neuroendocrine cells contribute to brain development and to emotional and social behaviors.

An uphill climb for neuroscience - how does our brain perceive and encode for slope walking?

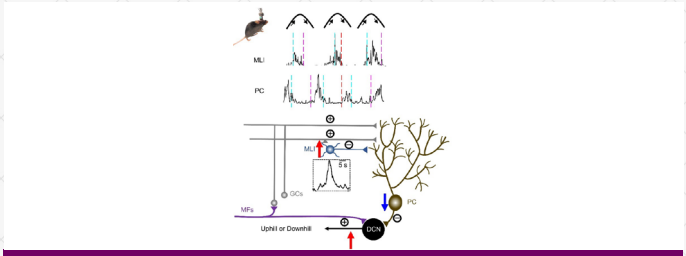
Development of single-cell resolution calcium imaging in free-behaving mice to uncover the mechanisms of the vermal cerebellum during slope walking.

Hiking or stair climbing is controlled by the vermal cerebellum. Although our daily movement takes place in 3D environments, most movement-related studies, especially those on the striatum, cortex, and cerebellum, have been carried out using experiments conducted on flat surfaces.

The cerebellum is widely recognized as a brain area that receives and integrates external and internal sensorimotor contextual signals during movement. By integrating afferent signals from the spinal cord and vestibular system, the cerebellum then participates in controlling head movement, balance, posture, and response to gravity, during locomotion. However, how the brain, especially the cerebellum, perceives and coordinates locomotion on ramps and slopes remains poorly understood.

Through calcium imaging using a miniaturized microscope, the team of **Xinjian Li**, **Lixia Gao** and **Ying Shen** from the BBMI Center visualized mice locomoting on slopes and established a calcium method to visualize the neuronal activity of the cerebellum. Using such techniques, they were able to uncover the role of the vermal cerebellum in slope walking. They found the neuronal activities of molecular layer interneurons (MLIs) in vermal cerebellum were enhanced specifically during uphill and downhill locomotion. In addition, a subset of MLIs were activated either during entire uphill or during entire downhill positions on the slope. Furthermore, the uphill and downhill behaviors could be decoded by MLI activity. This finding, as published in the journal of ***Advanced Science*** in 2022, provided a new method to demonstrate the function of the cerebellum in both motor and non-motor related behaviors, and identified a micro-circuit in the vermal cerebellum for regulating ambulatory behavior in a 3-dimensional terrain.

When walking on a slope or hiking in variable environments, we need to perceive up/down, slope inclines and slope positions to adjust for many different kinds of locomotion behaviors. To further determine the function of the cerebellum in slope walking, the research team imaged the MLI activity at 15°, 30° and 45° slopes. They found that some vermal MLIs would stably discharge during ramp locomotion, regardless of the degree of the inclination. However, some other neurons displayed increased neuronal activity or decreased neuronal activity with increasing slope inclinations. These results proved that MLIs not only differentiate the slope shape, but also differentiate the slope degree and extent of inclination. The research team also imaged the neuronal activity of the cerebellar output neurons known as Purkinje cells (Pcs), and found MLIs and PCs were activated in a counter-balanced manner during ramp locomotion. Furthermore, PCs displayed dichotomous activation patterns along the peak of the slope, which may represent the ramp walking or ramp environment through their population level activity. Finally, the team inactivated the vermal cerebellum using chemogenetic methods and proved that the vermal cerebellum is necessary for ramp locomotion. These results provide direct evidence that the vermal cerebellum plays important roles when navigating inclines.



Working model to explain the micro-circuit in the vermal cerebellum during ramp walking

Dr. Xinjian Li comments: The activity of MLIs is very stable during ramp walking. We guess this kind of activity may also be stable for other kinds of locomotion behaviors in other cerebellar regions. Other works have already shown that the cerebellum has similar activity to that of the motor cortex during proficient motor behaviors. Therefore, the cerebellum may be an ideal brain region to be incorporated into the design of brain-machine interfaces.

The neuronal activity of granule cells during ramp walking and the possible coding mechanism of the cerebellar and motor cortex in slope walking will be the next focus of our team's research.

Lyu C, Yu C, Sun G, Zhao Y, Cai R, Sun H, Wang X, Jia G, Fan L, Chen X, Zhou L, Shen Y,* Gao L* and Li X*. Deconstruction of Vermal Cerebellum in Ramp Locomotion in Mice. ***Advanced Science***. 2022 Nov 14;e2203665.

XINJIAN LI'S RESEARCH GROUP:

Motor behaviors are the final output of our brain and are crucial for the survival of most animals. Xinjian Li's group is dedicated to uncovering the neuronal mechanisms of locomotion behaviors in complex environments, as well as those related to spatial navigation, speech/language, and in diseases and disorders with marked deficiencies in such areas. Using cutting-edge calcium imaging, electrophysiology, optogenetics and other methods the team is particularly active in uncovering motor-related behaviors at the circuit level.

Small vessels: big problems!

Imaging and manipulating the microvascular architecture from mice to primates.

Small vessels contain diverse cellular components and interact with a large variety of brain cells including neurons, astrocytes, pericytes, microglia. Such small vessel systems dynamically supply region-specific oxygen and glucose while also transporting their metabolic waste products for eventual elimination. Dysfunction of such small vessels, together with any related insufficiency in blood supply, can result in irreparable damage to the brain tissue and lead to cerebrovascular diseases and neurodegenerative disorders.

The team of **Wang Xi** joined with with **Anna Wang Roe** from the BBMI Center and **Jun Qian** (College of Optical Science and Engineering, Zhejiang University) to utilize a bright aggregation-induced emission (AIE) probe DCBT to achieve deep in vivo three-photon fluorescent imaging of the macaque cortical microvasculature. This was published in ***Biomaterials*** in Oct 2022. Three-dimensional maps of the cortical microvascular network were acquired with large depth of up to 980 μm. The blood flow velocity of capillaries could then be precisely calculated up to ~600 μm beneath the pial surface.

In humans and nonhuman primates, the structure of vascular organization is quite different from that in mice. The cerebral cortex is functionally organized at mesoscale; that is, there are cortical columns of submillimeter sizes. Their clustered functional organization predicts that the oxygen and energetic demands are also necessarily clustered. This also suggests that the vascular blood supply may have an organization that follows this mesoscale organization.

Using various confirmatory indicators, the research team were firstly able to demonstrate that DCBT nanoparticles had no significant toxicity for nonhuman primates. They were then able to design and build a three-photon fluorescent microscopy system for the stable imaging of non-human primate brains. For the first time, three-dimensional maps of the cortical microvascular network were acquired with large depth up to 980 μm in a living macaque monkey. This might be the largest imaging depth obtained on the cortical microvasculature of macaque monkey by in vivo microscopic imaging methods at a micron resolution. Lastly, 3D reconstruction of the cortical microvascular network was performed, and similarities and differences between various parameters of brain structure between monkeys and mice were compared. This result provided a simple but pilot study of brain structural comparison of different species, and proved that in vivo large depth 3PM vascular imaging had great application potential for further brain research.

Almost concurrent to this research, in Oct 2022 the team of Wang Xi and Anna Wang Roe proposed a highly flexible and reproducible approach of precision ultrafast laser-induced photothrombosis (PLP) in Small Methods. This PLP approach employed a 1070 nm laser which was modulated as repeated spiral scan for Rose Bengal (RB) excitation. This allowed for the fast, precise and well-controlled, production of occlusions in a single target vessel while monitoring the related vasculature networks in real-time. This approach enhances the power of single-vessel occlusion paradigm, providing high success rates for the productionof occlusions in various vascular types.

The spiral scan pattern was applied for RB photoactivation, permitting fast ROS generation and negligible photodamage. The 1070 nm femtosecond laser used for photothrombosis, provided excellent penetration depth and permitted deep-layer vascular occlusion and helped to reduce out-of-focus excitation. This is the first time that a combination of a 1070 nm femtosecond laser with spiral scan pattern has been attempted with this PLP method providing flexible parameters for occlusion and high success rates of

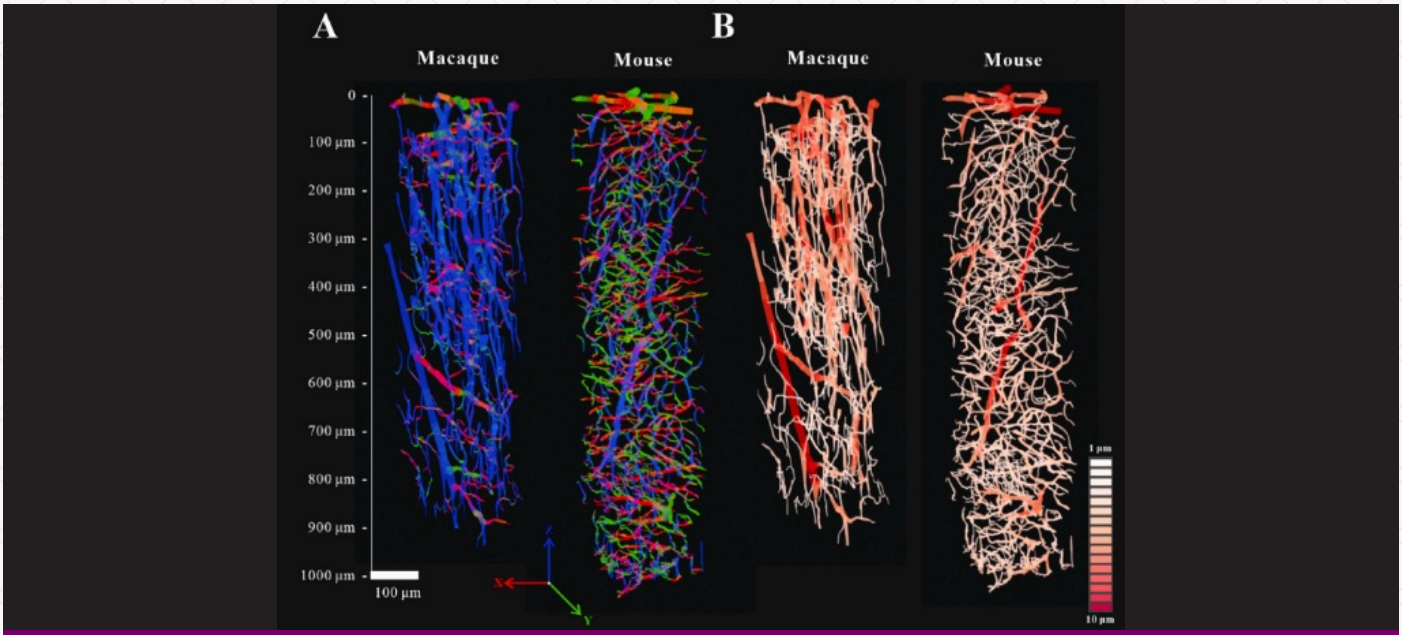


Figure 1 Structural differences of the cortical micro-vasculatures between macaque monkey and mouse

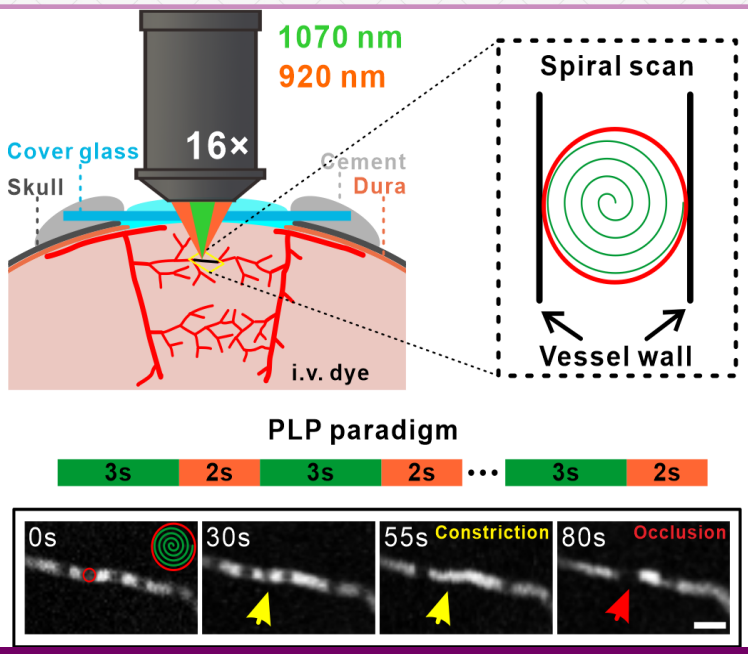


Figure 2 Illustration of the Precision 1070 nm Ultrafast Laser-induced Photothrombosis (PLP) of Depth-targeted Vessels

occlusion production in various vascular types (capillary, artery, and vein), sizes (3-500 μm diameter), and depths (up to 800 μm), even in non-anesthetized mice. In summary, the PLP method provides a practical, precise, and depth-selected single-vessel photothrombosis technology with commercially available optical equipment, which could be critical for deepening our understanding of vasculature function in health and in disorders.

With these approaches, coupled with simultaneous multiphoton cellular imaging methods focused upon the cortex both at rest and in stimulated states (e.g. sensory stimulation, optogenetics, infrared neural stimulation), it will be possible to dissect the directed relationships under different contexts (e.g. feedforward vs feedback contexts). These methods offer fundamental new tools for the investigation of the cortex and the microvascular contribution to brain function and links a large body of fMRI literature with single vessel and single neuron functions.

1.Zhu L, Wang M, Liu Y, Zhang W, Zhang H, Anna W*, Xi W*. Precision 1070 nm Ultrafast Laser-Induced Photothrombosis of Depth-Targeted Vessels In Vivo. ***Small Methods***. 2022 Oct 26;e2200917.

2.Zhang H, Zhu L, Gao DS, Liu Y, Zhang J, Yan M*, Qian J* and Xi W*. Imaging the Deep Spinal Cord Microvascular Structure and Function with High-Speed NIR-II Fluorescence Microscopy. ***Small Methods***. 2022 May 22; e2200155.

3. Zhang H#, Fu P#, Liu Y#, Zheng Z#, Zhu L#, Wang M, Abdellah M, Qian J*, Anna W*, Xi W*. Large-depth three-photon fluorescence microscopy imaging of cortical microvasculature on nonhuman primates with bright AIE probe In vivo. ***Biomaterials***.2022 Oct;289:121809.

ANNA WANG ROE/WANG XI'S RESEARCH GROUP

(1) Development of a new imaging tool on the 2P/3P platform to reveal the architecture and function of microvascular systems in vivo, and to provide new methods to manipulate on the vascular system in vivo including precision ultrafast laser-induced photothrombosis (PLP).

(2) Comparisons and dissections of the neurovascular mechanisms between mice and primates, studying small vessel disease in mice models, and studying the neurovascular coupling mechanism with fMRI BOLD signals in primate models.

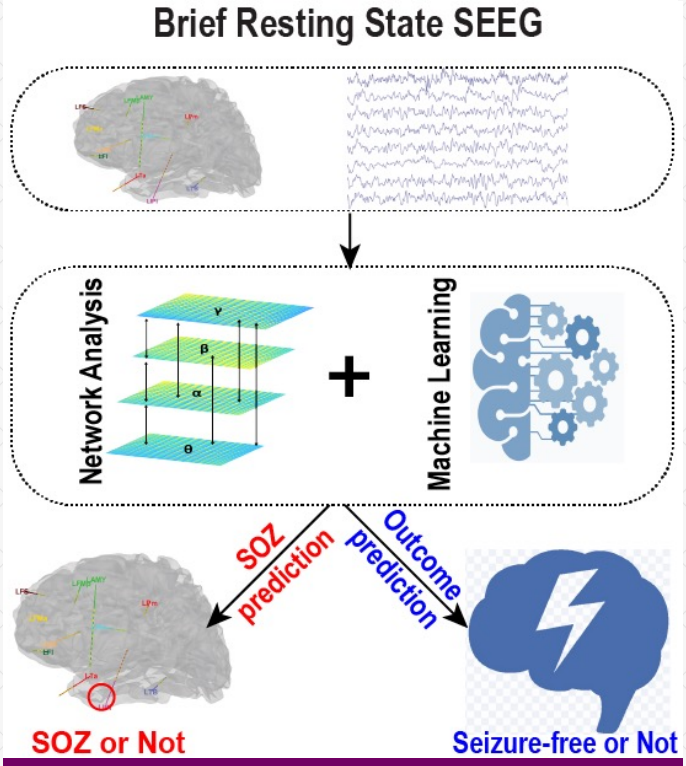
Interictal SEEG resting-state connectivity localizes the seizure onset zone and predicts seizure outcome

Epilepsy is one of the most common neurological diseases, impacting about 70 million people globally. At least one-third of epilepsy patients become drug-resistant and potential candidates for surgical resection or treatment using neuromodulation. The key to successful epilepsy surgery relies on accurate localization and safe removal of the epileptogenic zone (EZ). An integral component for the delineation of the EZ is the seizure onset zone (SOZ) which is the area of the cortex that initiates clinical seizures and is determined predominantly by intracranial investigation. Although surgery and neuromodulation have been proven effective in seizure reduction, there is still a significant room for improvement.

Stereotactic-electroencephalography (SEEG) is a well-established and safe neurosurgical approach to record ictal/interictal brain activity. The golden standard of localization of epileptogenic brain regions in clinical practice typically depends on capturing multiple seizures during the intracranial monitoring process. This may take multiple days or even weeks to complete. As such, a method which can estimate the SOZ and predict prognosis outcomes from the analysis of brief, resting-state data segments, would have tremendous clinical value and represent a significant step forward.

In May 2022, **Haiteng Jiang** and his team from the BBMI /Mental Health Center, Affiliated to the School of Medicine of Zhejiang University (Hangzhou Seventh People's Hospital), published their latest research results in ***Advanced Science***. This research may negate the troublesome requirement for prolonged monitoring of seizure signals during the diagnosis and treatment of epilepsy. Using ten-minute resting-state Stereotactic-electroencephalography (SEEG), combined with advanced brain network analysis methods and machine learning algorithms, they developed a new method to localize the SOZ and predict prognosis outcome with an accuracy of 90% (Figure 1).

With a cohort of 27 drug-resistant epilepsy patients, the team were able to estimate the information flow via directional connectivity and inferred the excitation-inhibition ratio from the 1/f power slope. They hypothesized that the antagonism of information flow at multiple frequencies between SOZ and non-SOZ brain areas would underly the relatively stable epilepsy resting state and could be used to indicate the related disrupted excitation-inhibition balance that characterizes epilepsy. Furthermore, they speculated that the strength of antagonisms would reflect the intrinsic epileptic network characteristics, which could then be eventually associated with seizure outcome. The team found more excitability in non-SOZ regions compared to the SOZ, with dominant information flow from non-SOZ to SOZ regions. Greater differences in resting-state information flow between SOZ and non-SOZ regions were clearly associated with favorable seizure outcome. By integrating a balanced random forest model with the resting-state connectivity, their method localized the SOZ with an accuracy of 88% and predicted the seizure outcomes with an accuracy of 92%, using a clinically determined SOZ.



Interictal SEEG Resting-State Connectivity Localizes the Seizure Onset Zone and Predicts Seizure Outcome

Overall, this study suggests that brief resting-state SEEG data can significantly facilitate the identification of SOZ and may eventually facilitate the prediction of seizure outcomes without requiring long-term ictal recordings.

Jiang H, Kokkinos V, Ye S, Bagic A, Richardson M, He B(2022). Interictal SEEG resting state activity and connectivity localize seizure onset zone and predict seizure outcome. ***Advanced Science***: e2200887

HAITENG JIANG'S RESEARCH GROUP

Haiteng Jiang's team has long been committed to the development of novel brain information analysis methods, the exploration of cognitive and brain disease mechanisms, and to their clinical translations. The laboratory uses multimodal functional brain imaging methods (MEG/EEG/ECoG/SEEG/MRI), machine learning and neuroregulatory techniques to study cognitive and brain diseases (depression/epilepsy), to promote the development and translational application of systems neuroscience.

Revealing the mesoscale networks of non-human primates in vivo

Structure determines function. How does the functional organization of the brain produce perception, thought, and behavior? To answer this question Dr. Anna Wang Roe and her team study the organization and connectivity of the functional modules (roughly 200 μm in size) in the cerebral cortex of nonhuman primates. Such a study can reveal how these modules underly both visual (form, color/brightness, depth, and motion) and tactile (texture and shape) perception.

On May 27, 2022, Professor **Anna Wang Roe** and **Jiaming Hu**'s team from the BBMI Center published a research paper entitled "functionally specific and sparse domain based micro-networks in monkey V1 and V2" in the internationally renowned online journal ***Current Biology***. Their work revealed fundamental mesoscale connectional architecture in the primate visual cortex.

The Macaque monkey's cerebral cortex consists of roughly 109 neurons organized into roughly 105 clusters (columns) of 104 neurons each. Previous anatomical evidence has shown that neurons within single columns (which share similar functionality e.g., preference for color, orientation, motion, and depth information) have connections with other clusters of similar functionality. Anna's research group hypothesized that these connected clusters comprised what they call a 'columnar micro-network' in the brain, and that such micro-networks are common units of connectivity in the visual cortex.

To address this hypothesis, Dr. Hu Jiaming in Anna's research group developed an in vivo method of studying mesoscale functional connections. For this, they developed a focal electrical stimulation method to activate single functional columns and used intrinsic signal optical imaging to map the evoked connections to other columns. When applied to visual area 2 (V2) in the macaque monkey visual

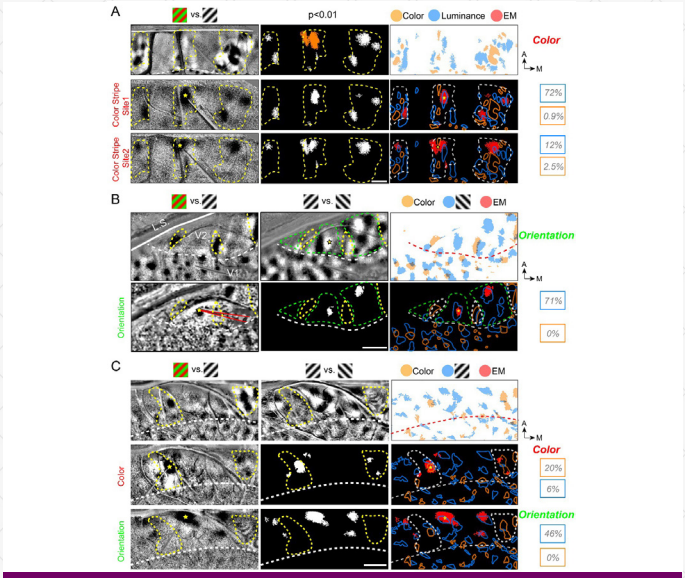


Figure 1. Specificity of EM response pattern.

Stimulation in different stripes produces activation at different connected sites (A. stimulation in a color stripe; B. Stimulation in an orientation stripe; C. stimulation in color and orientation stripes).

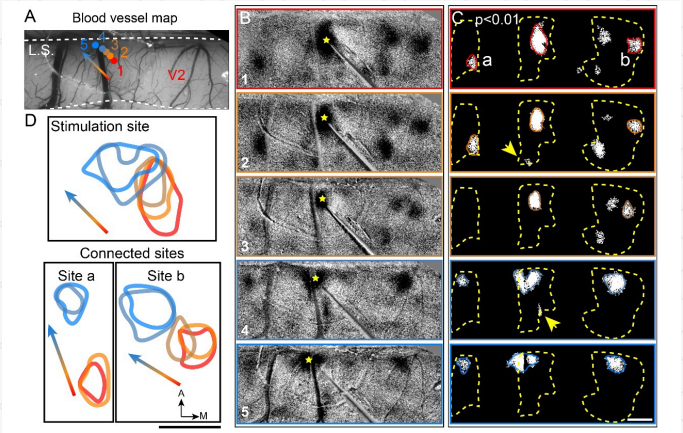


Figure 2. Shifting progressions (from red to blue) at activation sites a and b (see C) as electrode advances from location 1 to location 5.

cortex, this revealed that standard columnar microcircuits do indeed exist to integrate both local intra-areal (V2-V2) and inter-areal (V2-V1) information. They then discovered that such micro-circuits are common across networks that process color and orientation information. Furthermore, moving the electrode and successively stimulating different points in the cortex lead to the activation of micro-networks that shifted depending on the position of stimulation (Fig.1).

Such data introduced the perspective that there are basic micro-network units in the brain that are common and operate across different aspects of functionality and that the architecture of the brain is comprised of these fundamental micro-networks. These findings add significantly to our fundamental understanding of how network architecture is built into the primate brain.

Hu JM, Roe AW (2022) Functionally specific and sparse domain-based micro-networks in monkey V1 and V2. ***Curr Biol***, 32(13):2797-2809.e3.

ANNA WANG ROE'S RESEARCH GROUP

Anna Wong Roe's team use multiple cutting-edge approaches in nonhuman primates to understand mesoscale networks in the brain. These include implanted 'windows on the brain', ultrahigh field MRI machines, optical imaging, single and multielectrode recording arrays, anatomical tracing methods, and focal brain stimulation using both optogenetics and near-infrared lasers. She believes that using multidisciplinary approaches (including computation and mathematical approaches) to understand the brain will lead to an understanding of brain architectures underlying intelligent behavior.

The Academic Annual Conference of the MOE Frontier Science Center for Brain Science and Brain-Machine Integration

Academic Annual Conference

This academic annual conference is hosted every 2 years by the BBMI Center. It has its focus upon interdisciplinary integration and the sharing academic excellence. The 2022 academic annual conference of the MOE Frontier Science Center for Brain Science and Brain-Machine Integration (BBMI) had its grand opening on November 4th, 2022 at the Zijingang Campus of Zhejiang University.

The 2022 academic annual conference continued to focus on interdisciplinary integration, covering a wide range of cutting-edge fields in emotional disorders, mental illness, gliomas, brain-machine intelligence, and neuromorphic computing. The conference specially invited Professor Haoxin Xu from the Liangzhu Laboratory, who is also the professor and QiuShi lecturer of Zhejiang University, to give a keynote presentation. His lecture focused on the field of biomedical translational applications aiming to inspire young researchers to come up with innovative ideas in the biopharmaceutical industry. In the 'Young Doctoral Forum', outstanding postdoctoral researchers from different fields shared their achievements. A number of excellent PIs who had joined the BBMI Center over the recent two years also presented their work, bringing diverse inspirations and insights. Experts and attendees engaged in in-depth thinking and enthusiastic exchanges during the conference, promoting further cross-center collaborations among and between research centers.

The BBMI Center actively connects with national strategies, promoting the vibrant development of China's brain-machine integration technology through practical actions and fruitful achievements. On the road ahead, the BBMI Center will continue to push forwards, anchored to the new coordinates of China's "Brain Science Plan," accelerating the progress of interdisciplinary research, persisting in original innovation and innovation output, and focusing on the strategic goal of creating a high plateau for life, health, science, and technology. In this way the BBMI Center will continue to deepen reforms, actively explore innovation, and achieve new breakthroughs.

Research progress

- **179** papers were published.
  Among them, **68** papers were published in high-level journals including ***Nature, Nature Neuroscience, Neuron***, etc.

- A total of **42** scientific research projects were approved.
  These included **30** "*Major Projects*" and **4** *Science and Technology Innovation 2030-Brain Science and Brain-inspired Artificial Intelligence Key Projects*, the latter of which were initiated and lead by the BBMI.

Talent resource development

- **5** PI from the BBMI have been approved for the The Excellent Youth Overseas Project with an approval rate reaching **63%**.

- **1** National Science Fund for Distinguished Young Scholars, **1** National Science Fund for Outstanding Youth Scholar, and **1** national youth talent support program were also approved.

Achievements and Awards

Top Ten Academic Progress Award of Zhejiang University in 2021

2022 L'Oreal-UNESCO For Women in Science Awards

National March 8th Red-Banner Pacesetters

The First Prize of Zhejiang Province Natural Science Award

The eleventh "Three-dimensional Talent Cultivation" Teaching Model

The BBMI Academic Reports

2022 Second Half

Professor Haoxin Xu

Qiushi Chair Professor, LiangZhu Laboratory & Zhejiang University Medical Center
Dean, School of Basic Medical Sciences, Zhejiang University
Professor (Adjunct), Department of MCD Biology, the University of Michigan

November 4th,2022

Molecular physiology of lysosomes

More than 50 human diseases collectively called lysosome storage diseases (LSDs) are the result of problems in trafficking to, degradation within, or export from lysosomes. Emerging evidence suggests that common neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are also lysosomal (dysfunction) disorders. Dr. Xu has developed a unique research program for understanding the cell biology of lysosomes, and its relationship to lysosomal storage disorders and common neurodegenerative diseases such as AD and PD. This program combines electrophysiological and imaging approaches typically used to study plasma membrane ion channels with molecular and biochemical approaches typically used to understand organelle function. The combined approach has allowed his lab to find eight lysosomal ion channels (Ca^{2+}, Na^{+}, K^{+}, Fe^{2+}/Zn^{2+}, Cl^{-}, and H^{+}) and identify the activating cellular cue for each of them.

Professor Qiufu Ma

Chair Professor and Director of the Center for Systems Physiology and Biomedical Electronics at Westlake University

November 18th, 2022

The architecture of the somatosensory system and its significance in pain research

Pain is a common clinical symptom associated with a variety of diseases, yet pain research is currently facing a translational crisis. Professor Qiufu Ma has been dedicated to studying pain pathways, and his research group has analyzed the neural mechanisms of acupuncture in alleviating inflammation and pain. In this lecture, Professor Ma discussed the separation and interaction of the somatosensory system in terms of its anatomical and functional architecture. On the one hand, it can be used to detect external threats. On the other hand, it can monitor the integrity of the internal systems of the body. One of the reasons for the low success rate of pain translation is the incorrect use of behavioral analysis. Using and optimizing traditional acupuncture therapy and other methods to address the disease origins that lead to redundant pain pathways may help with translational success.

Parallel development of medical education and research Leads the development of mental health specialties

Interview with dean Li Tao

You have been engaging in the basic and clinical research of schizophrenia for a long time. What are the characteristics of schizophrenia, and how is it different from other common mental illnesses such as depression and anxiety?

Li Tao: Schizophrenia, depression, anxiety, bipolar disorder, etc. are all common mental illnesses in clinical practice. Compared with depression, the incidence of schizophrenia is relatively low, approximately 0.5% to 1% globally. Schizophrenia is a severe mental disorder, and patients with schizophrenia often have psychotic symptoms such as hallucinations and delusions. The typical characteristics of schizophrenia mainly include cognitive impairment, such as the occurrence of paranoid delusions. Schizophrenia patients may also exhibit cognitive problems such as attention and memory issues and abnormalities in executive function. These often occur together with emotional problems, which can include depression-like dark moods or emotional indifference, which is significantly different from that of depression. Such factors provide many barriers to social interaction and some patients may actually choose not to interact with virtually anybody. A very small number of patients display impulsive aggressive behavior, sometimes related to physical attack, often induced by psychotic symptoms such as hallucinations and delusions.

What are the current key issues that need to be addressed in the research of schizophrenia?

Li Tao: While schizophrenia research has been ongoing for over a hundred years, the exact causes and mechanisms of the disorder still remain unclear. With advancements in technology, especially over the past 30 years, and with increased attention towards the study of mental illness, schizophrenia is now considered a neurodevelopmental disorder as it can be highly correlated with key aspects of neurodevelopment.

Neurodevelopmental disorders have a significant genetic background to the point that they are considered as genetic disorders. The heritability of schizophrenia, for example, can reach 80%. However, it is important to note that neurodevelopmental disorders are not only inherited, but also due to environmental factors during mother's pregnancy and postnatal period, and additionally linked to social factors that can significantly impact neurodevelopment. Therefore, the interaction between genetics and the environment is an important issue to be studied in the mechanism of schizophrenia. Research has also found that there is a rapid decline in brain function in older patients with schizophrenia, which suggests a connection between schizophrenia and neurodegeneration.

However, current clinical diagnostic systems have not yet incorporated these neurobiological findings. As in other mental illnesses, the diagnosis of schizophrenia is still based on phenomenology, meaning that it is the symptoms such as hallucinations and delusions that are used as the primary diagnostic criteria. Nevertheless, I believe that it will be soon possible to apply some specific related biomarkers to its clinical diagnosis.

Professor Li Tao, a PhD supervisor, holds dual PhD degrees in Psychiatry and Psychiatric Genetics. She is currently the Dean of the Affiliated Mental Health Center of Zhejiang University School of Medicine (the Seventh People's Hospital of Hangzhou), and a distinguished professor of the BBMI center and Zhejiang University School of Medicine. As a recipient of the National Outstanding Youth Fund she has a special allowance from the State Council. For many years, she has dedicated herself to investigations relating to clinical diagnosis and research into the etiology of common mental and psychological disorders. Her research, with significant focus upon molecular genetics and the biological phenotypes of common mental disorders, has led to the revealing of a number of related causes and mechanisms and facilitated the establishment of both objective biological diagnostic markers for mental disorders and the carrying out of personalized treatments. She has presided over dozens of national and international cooperation projects, published over 300 SCI research papers, and edited or co-edited several professional textbooks and reference books.

You mentioned that genetic factors are an important cause of schizophrenia and you have been dedicated to finding the genetic code of schizophrenia. What specific impact do genes have on the onset of schizophrenia, and what are the challenges in this area of research?

Li Tao: Our team has been carrying out research on the genetics of schizophrenia for the past two to three decades. In the early days, research could only be carried out on a few candidate genes, but with the development of technology over the past ten years or so, we can now carry out research from a genome-wide perspective. Currently, it is believed that schizophrenia is not disease arising from a single-gene, and there is no so-called specific schizophrenia-causing gene. However, there are two types of gene mutations related to schizophrenia. The first of these involves variations which are relatively common in the population. Although each locus of these variations has a relatively small effect, their accumulative effects may increase the susceptibility of the population to schizophrenia. Hundreds of common mutations have been discovered so far, but it is not yet clear how these accumulations lead to an increased risk of developing schizophrenia. The other type involves rare gene mutation variations, (from less than 1‰ to 1%), and once these mutations occur, the probability of suffering from schizophrenia becomes very high. With the development of technology, there are now fast and economical means of discovering such gene variations in the population. Through multi-center cooperation, large-scale cohort studies can now be established. In this way, the problems that have plagued us can be gradually solved. I think the most important problem in current research is how we should define schizophrenia. Genetic research first requires a clear definition of the disease phenotype being studied and the related genes being analyzed, but currently there is a lack of objective biological indicators for the diagnosis of schizophrenia. Therefore, the susceptibility genes that have been found may only be those associated with some phenotypes in schizophrenia, and not the entire disease. Therefore, I think that subsequent research should divide schizophrenia patients into subtypes and analyze the genetic basis of different subtype patients. Only with a better understanding of the genetic basis of schizophrenia can we provide a more accurate diagnosis and more effective treatment.

What are the effects of environmental factors on mental illness, and what is the relationship with genetics?

Li Tao: Environmental factors and mental illness have a close relationship. Environmental factors include social development, personal life experiences, major events, etc. These can affect a person's mental and emotional state and in turn affect the development and onset of mental illness. We recently conducted a review to analyze the impact of social environmental changes in mainland China over the past 30 years on the public's mental health. This process was somewhat hampered by the fact that most studies on this topic have been animal-based studies, and there were very limited studies on humans. Some international studies have focused on this issue in humans, but they have not been able to give an adequate explanation of the causal relationship between environmental factors and genetic factors. Currently, studies are finding that environmental factors can affect gene expression via the influence of epigenetic modifications such as methylation of genes. But again, these studies are mainly based on animal studies. Currently, it is still difficult to conduct studies based on humans because it is based not only on autopsy samples but also the collection of environmental information from patients prior to death. The accuracy of the current means of detecting environmental factors, such as peripheral blood tests, still requires further discussion and development.

Your recent work has also focused on the impact of brain connectivity networks on schizophrenia, how do these studies help in the diagnosis and treatment of schizophrenia?

Li Tao: In the past it was believed that there were no significant organic changes in mental illnesses such as schizophrenia. This lay in contrast to neurodegenerative diseases such as stroke and epilepsy which clearly showed significant organic changes. However, over recent decades, rapid advancements in related research and technology have allowed us to understand that the nervous system of schizophrenia patients may also have undergone such changes. Using magnetic resonance imaging (MRI) technology, we have now found changes in brain structure and functional connectivity in schizophrenia patients. Initially, we could only compare brain structures, such as differences in the size of a particular brain region. However, with the more recent increase in resolution of MRI, functional connectivity research has become possible in which the functional connection between one brain region and another can be investigated. This has resulted in the discovery of significant changes in the functional connectivity of schizophrenia patients. We now hope to use the analysis of these aspects of structure and functional connectivity to reveal the changes in the brains of schizophrenia patients. Of course, current imaging technology is not yet at the molecular and cellular level, but it can still be combined with genetics and other means to carry out research to better explain the molecular mechanisms of genetic factors. Changes in brain imaging can also serve to highlight intermediate phenotypes between those of genes and diseases, helping us to explain how genetic factors lead to the appearance of clinical symptoms. I believe that this type of research is important for advancing the research on the molecular mechanisms of schizophrenia.

You mentioned that there are different subtypes of schizophrenia in patients, does this also bring difficulties to clinical treatment? How should this issue be addressed?

Li Tao: This is indeed a major challenge in the treatment of schizophrenia. Currently, most psychiatric drugs work on the dopaminergic system, which is also a

dominant target for our clinical treatment of schizophrenia. In this, the assumption is first made that the patient's dopamine system is somehow impaired. However, this assumption may not actually be true in all cases because such treatment is only effective for some patients. We lack individualized treatment, so our current research on improving schizophrenia treatment is now beginning to emphasize precision and personalization. For example, if patients can be classified based on genetic or imaging methods before treatment, we may find differences and be able to predict, using the genetic background or imaging aspects of patients, whether they are likely to be sensitive or insensitive to treatment. Currently, the pharmaceutical development field is also analyzing those who are insensitive to conventional treatment, hoping to find a target more suitable for them.

As a specialized mental health hospital, what do you think are the differences in responsibilities between the Seventh People's Hospital of Hangzhou and comprehensive hospitals in terms of mental health care?

Li Tao: As for myself, my three roles of doctor, teacher, and researcher have remained unchanged. The West China Hospital, where I previously worked, was a comprehensive hospital and its psychiatry department was ranked among the best in the country. It was large in scale, responsible for the routine diagnosis and treatment of mental illnesses and capable of treating severe mental disorders such as schizophrenia. Compared to specialist hospitals, the biggest difference in the psychiatry departments of comprehensive hospitals is their clinical practices, which often involve interdisciplinary consultations and communication with other departments. Hangzhou Seventh Hospital is a specialist hospital for mental illness, also of a large scale, with rich experience in treating common mental illnesses and coping with difficult and complicated cases. Founded in 1954, the hospital officially became a subsidiary of Zhejiang University School of Medicine last year. It is currently undergoing a transformation, hoping to be developed into a research-oriented hospital. To this end, we have introduced many young talents involved in connecting clinical practice with basic research, and aiming to make breakthroughs in early discovery, accurate diagnosis, treatment, and into the causes and mechanisms of mental illness.

As the largest specialized hospital for mental and psychological illnesses in Zhejiang Province, the Seventh People's Hospital of Hangzhou carries out social services such as psychological health education. What is the significance of this part of the work?

Li Tao: Currently, the public's understanding of mental and psychological illnesses remains fairly poor. Increasing the effort in public awareness can help the public to have a deeper understanding of our work and provide a pathway for them to seek help when required. Increasing public to understanding of mental health can also enable people to conduct a level of self-assessment. If an individual's mental health is highlighted to be in a potentially problematic state, he or she can sometimes recover by self-assessment and then seeking consultation. This is also an important component of mental health care. Just like a person that realizes that they may be in a danger category for diabetes, and therefore avoids illness by increasing exercise and controlling diet, the same applies to the mental state. It is hoped that in the future the public can similarly prevent the occurrence of serious mental illnesses through initiating some early intervention measures.

The Seventh Hospital has taken on a brain-computer interface project. What changes could it bring to the diagnosis and treatment of mental illnesses?

Li Tao: Brain-computer interfaces in the field of mental illness is very promising for both detection and treatment. Currently, the main methods for treating mental illnesses are divided into three categories: medication, psychotherapy, and physical therapy. Some of the physical therapy techniques are related to brain-computer interfaces. At present, some untreatable diseases, such as certain types of depression and obsessive-compulsive disorders, are also treated with non-invasive or invasive brain-computer interface techniques. For example, the use of sound, light, and electrical stimuli can intervene and adjust brain function. Currently, brain imaging technology is rapidly advancing, and we hope to provide a basis for personalized physical therapy through detecting the individualized localization of the patient's affected areas in combination with physical therapy. This will hopefully achieve better effects for different patients.

What other ways, besides brain machine modulation, could the Zhejiang University Brain Machine Key Laboratory's brain machine technology be potentially helpful in the field of mental illness diagnosis and treatment?

Li Tao: In the field of brain-machine interfaces, more interdisciplinary assistance is needed to break through and truly integrate different technologies to solve clinical problems. For example, some cutting-edge technologies in engineering and computer science may be potentially applicable to clinical medicine if the doctors became aware of them and expressed their needs. Currently, the most difficult issue to find those who hold interdisciplinary talents that can link such fields of engineering and computer science with that of clinical medicine. In my opinion, Zhejiang University's current training program is very good in this respect. The cooperation between neurosurgeons and brain-machine experts has already achieved some important results, and cooperation with psychiatry is also well underway. Everyone needs more interaction and communication. The Seventh Hospital has now established a research ward. If there are some new technologies that are highlighted for potential application to the clinical setting, we remain very willing to cooperate.

Interdisciplinary cohesion boosts mental illness research

Interview with chief physicianand director Shaohua Hu

You have conducted many aspects of clinical and basic research on the diagnosis and treatment of bipolar disorder. What kind of mental illness is bipolar disorder and what are its characteristics?

Shaohua Hu: Bipolar disorder is a mental health condition that causes extreme mood swings that include emotional highs (mania or hypomania) and lows (depression). Bipolar disorder and depression are both affective disorders. In the early years of research not much distinction was placed between these two psychiatric disorders. However, with more recent developments in biological research, the pathogenesis of bipolar disorder became noted as distinct from that of depression, with differing clinical phenotype, prognosis, and medication. The transition in this occurred in 2013. Upon the publication that year of the international Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) this separate classification then became fully recognized. More recently we have been conducting a secondary analysis of the burden of disease data published by the World Health Organization in collaboration with Professor Peige Song of the School of Public Health, Zhejiang University. We found that the prevalence of bipolar disorder had stabilized at about 0.49% from 1990 to 2019, but the number of patients with bipolar disorder had continued to increase proportional to global population growth. Disability adjusted life year (DALY) was used to estimate the burden of bipolar disorder, which reflects both damaged healthy years and premature deaths due to illness. According to such a measure we found that the burden of disease for bipolar disorder is in fact increasing, probably related to the preponderation of adolescents who are currently affected by bipolar disorder. In general, bipolar disorder is clinically characterized with a high rate of relapse, disability, suicide, and chronicity. At the same time, type I bipolar disorder is noted as an inherited disorder, often resulting in lifelong illness.

What are the current challenges in the management of bipolar disorder?

Shaohua Hu: The first is to deal with the high rate of misdiagnosis and missed diagnosis. The manifestations of bipolar disorder are diverse with the early phenotypes of bipolar disorder often including symptoms such as depression, compulsive behavior, or eating disorders, which cannot be accurately identified by psychiatrists and are easily misdiagnosed. Some patients with obvious somatic symptoms may also visit other departments. Thus, some cohort studies have indicated that it takes 8-10 years on average for bipolar disorder to be definitively diagnosed. A second clinical challenge is inadequate access to diagnosis and treatment. Bipolar disorder is prone to relapse, and the effect of simple pharmacological treatment is not good. Alternatively, the diagnosis and treatment often remain inaccurate, and some patients have side effects and recurrences after medication.

Shaohua Hu, is Professor of Psychiatry in Zhejiang University, a chief physician, a leading talent in scientific and technological innovation group of the "Ten Thousand Talents " program of Zhejiang Province, has received the Zhejiang high-level medical innovative talent award, is a Class A clinical top young talent of Zhejiang University, and is head of Mental Health Center of the First Affiliated Hospital of Zhejiang University School of Medicine.

Your recent work has focused on the role of the gut microbiota in bipolar disorder. How did you come up with the idea to understand bipolar disorder from the aspect of the gut microbiome?

Shaohua Hu: I don't think we can treat mental illness simply as a neurological disorder. In fact, cardiovascular and cerebrovascular diseases are the leading causes of death in mental diseases such as bipolar disorder, depression, and schizophrenia. This is due to the systemic inflammatory states, metabolic disorders, immune disorders and other conditions which may be caused by or related to mental disease. In addition, many psychiatric disorders are often accompanied by disfunction of other systems. For example, 60% of patients with bipolar disorder have metabolic syndrome. Therefore, I prefer to treat mental illness as a systemic disease. To fully understand the biological mechanisms of mental illness, we must look at the whole body rather than just the brain. Therefore, we have established a bipolar disorder cohort since 2016 to collect multi-omics biological samples including blood samples. Our team has been focused on gut microbiota since 2016, when the concept of gut-brain axis was just emerging. We soon noticed that patients with bipolar disorder display abnormal gut microbiota during depressive episodes. Along this line, we have found some very meaningful phenomena, such as the changes in the structure and diversity of intestinal flora in patients with bipolar disorder. In parallel, we have also carried out some functional exploration. We transferred the gut microbiota of bipolar disorder patients into the gut of mice, and later found that these mice also developed bipolar disorder phenotypes.

What are your current concerns in gut microbiota research in bipolar disorder, and how do they help in the diagnosis and treatment of bipolar disorder?

Shaohua Hu: At present, we hope to identify some bacteria specifically associated with bipolar disorder, clarify their roles in bipolar disorder, and further elucidate their related neuropsychiatric pathological mechanisms. For example, we recently noticed that a single bacterium was abnormally elevated in the gut of patients with bipolar disorder and subsequently decreased after treatment. We hypothesized that it might stimulate macrophages under the intestinal wall to release some chemotactic factors into the brain, which then could affect the function of key nuclei and neural circuits in the brain. These studies are expected to provide accurate markers for the early diagnosis of bipolar disorder. In collaboration with Beijing Anding Hospital, we then established a cohort study comparing the gut microbiota of patients with the depression phase of bipolar disorder and those of patients with major depression disorder. We found that their gut microbiota had similarities, as well as some characteristic differences. If these results can be translated in the future, gut microbiota should be able to provide powerful scientific evidence for the identification and prediction of mental disorders. We also compared the gut microbiota composition of patients with bipolar disorder who had a good response to those who did not respond well to clinical treatment. There were some interesting features. Future studies in this area may help us use the gut microbiota strategy to predict the efficacy of drugs.

You often post some popular science videos on the short video platform. Do you think popular science works well towards public understanding and is also an important part of the work for psychiatrists?

Shaohua Hu: I think mental health is also a public health issue. For example, a depressed patient has on average a great impact on at least 6 people around him. Therefore, for mental illness, primary prevention is particularly important. From the perspective of medical students, this is also a part of social service work. On the one hand, I make short videos to help publicize and educate about diseases. I truly hope these can be applied to help prevent diseases in the future and help adults and adolescents cope with the pressure and stress in their lives.

What can the public do for themselves regarding the primary prevention you just mentioned?

Shaohua Hu: For some high-risk people with a family medical history of hyperactivity or borderline personality disorders, early prevention is crucial. This is because once the symptoms of an affective disorder occur, the patient's mood will be extremely vulnerable. For those of younger ages, we hope that parents play a role in understanding and guiding children's cognition. For adolescents themselves, we hope to be able to help them minimize negative emotions and understand their own mental state in order to self-diagnose and self-evaluate. It is also important to improve the ability to cope with stress. We hope that we can encourage adolescents to be able to diversify their ways of dealing with stress and know when and how to actively seek for help. For those at high risk, we encourage them to establish a routine. This is because a significant feature of mental diseases such as bipolar disorder involves disruption of biological rhythms. Irregular routines easily cause sleep, eating, mood, and other problems. Many people who are prone to mental illness tend to be adventuresome and impulsive, so planning and predictability in life are important.

What do you think about the future direction of the mental health?

Shaohua Hu: In fact, when I was new to the mental health, neither the public nor those working in the field of neurology paid much attention to the development of mental health. Many patients were also holding significant misunderstandings about mental health, and preferred to simply visit doctors from the neurology department. However, our increase in knowledge, the public's understanding of mental illness has deepened and it is less taboo to talk about mental illness. In addition, the prevalence of anxiety and other diseases has increased since the COVID-19 pandemic. In general, the social demand for mental health departments is gradually increasing, and there is a great potential for development. As Chinese

president Xi Jinping said, health is the foundation of social progress, a hallmark of national prosperity and the common pursuit of the broad masses. Mental health is therefore crucial in improving personal well-being and building a comprehensive health system. However, we have also seen that traditional mental health is based on symptomatology and psychology, and that the explanation of mental diseases from biological mechanisms starts late and has limited understanding. We need biology to provide some clear objective indicators to help in the diagnosis and treatment of mental health diseases.

What technologies do you think are noteworthy in the future development of the discipline of mental health, and what changes might they bring?

Shaohua Hu: One is artificial intelligence and brain-like computing. Both of these disciplines can assist in the diagnosis of mental illness. For example, using emotion recognition technology to capture the patient's micro-expression may provide a good complementary reference role in addition to the traditional 'conversation/inquiry' diagnostic route. In the rehabilitation process of mental illness, the rehabilitation of social function is particularly important. VR technology can also provide some practical scenarios to help patients with this aspect of rehabilitation. The second area of interest is neural regulation. We are doing a lot of work on this area as well. For example, robot-guided repetitive transcranial magnetic stimulation (rTMS) has successfully been applied to achieve automatic navigation using a robotic arm. We are also working with Professor Yueming Wang and Professor Ke Si of the BBMI to develop deep brain stimulation (DBS) related technologies. All of these techniques hold great promise, but their implementation must be based on a sufficient understanding of the phenotypes and neural mechanisms of psychiatric disorders to enable precise interventions. Immunotherapy is also an important development direction. In our recent collaboration with Dr. Wei Chen, Professor of the Basic Medicine School at Zhejiang University, we found that peripheral macrophage subsets differ between bipolar disorder and depression. Future immunotherapy approaches targeting these features look very promising. Previous studies have also reported the use of tumor necrosis factor monoclonal antibody in patients with treatment-resistant depression. I believed that immunotherapy may be a very promising treatment for certain psychiatric disorders, including bipolar disorder.

What kind of scientific research model do you think the BBMI provides, and how does it help your clinical research work?

Shaohua Hu: As I mentioned earlier, we have extensive collaboration with the BBMI in the area of neuronal regulation. To quote one example, in November last year, the DBS project in cooperation with Professor Yueming Wang recruited a patient who had been struggling with treatment-resistant depression for over 20 years. We implanted electrodes and intermittently stimulated the lateral habenula, which significantly improved his depression symptoms. This project is in its second round, and we hope to conduct further successful trials with patients with bipolar disorder. Another aspect is cooperation with basic research. Some drugs already discovered in basic research could potentially be quickly verified for clinically use and repurposed towards mental health treatment. Any problems such as with side effects in clinical practice, could be fed back into the system and returned to the level of basic research level for optimization. We are cooperating with Professor Hailan Hu of the BBMI in this mode, which is very necessary and efficient.

▲

Interest is the best teacher and cooperation is the cornerstone for development

Tongchao Li is an Assistant Professor at the MOE Frontier Science Center for Brain Science and Brain-Machine Integration of Zhejiang University. He received his BS degree in Biology from Tsinghua University and subsequently completed his PhD at Baylor College of Medicine, working in the laboratory of Dr. Hugo Bellen, a Drosophila geneticist and member of the National Academy of Sciences. He then worked as a postdoctoral fellow in the laboratory of Dr. Liqun Luo, a neurobiologist, also a member of the National Academy of Science at Stanford University. Dr. Tongchao Li's research interests are focused on the study of neural circuits and single cell transcriptional profiling. In particular, he has developed an in vitro brain organism imaging system, which has provided a powerful tool to study the cellular and biological bases of neural circuits. His has published research as the first or corresponding author in ***Cell, Current Biology, eLife, PLoS Genetics, JoVE***, and other prestigious journals. He won the Pathway to Independence Award (K99/R00) for the NIH and is now a Guest Editor of JoVE.

Dr. Li is interested in **studying the cell biological mechanism of neural circuit development using time-lapse imaging, and rare disease of neural development.**

Interdisciplinary cooperation is a cornerstone for the future of research

"I believe that interdisciplinary cooperation is essential for the future of brain science research, and I always encourage my students to participate in academic exchanges." Speaking of his time of cooperation with Nobel Prize winner Eric Betzig, Dr. Li shared his story of having lunch with Eric Betzig at an academic conference in Cold Spring Harbor. At that time, Professor Eric Betzig was looking for a collaborator for in vivo experiments and Dr. Li's work required a lattice light sheet microscope with adaptive optical correction. Over such opportunities for mutual collaboration they hit it off immediately. "So rather than specializing in one subject, I would like my students to communicate regularly to learn from each other's strengths." In such a way, Dr. Li continually emphasizes the importance of cooperation. When discussing how to break down barriers and communicate effectively in the cooperation process, Dr. Li explains that it is important to first identify the concerns of collaborators, the difficulties they encounter, what roles that we can play to help, and also understanding that it is always essential to reflect on problems from multiple angles, cultivating the possibilities to think in different ways.

Problem-oriented and systematic research

Dr. Li pointed out that good PhD student should graduate with the ability to solve practical problems, while postdocs should be able to identify new scientific problems. “New problems are hidden in life, not in literature, and always need to be sought out with curiosity and the ability to think ‘outside the box’”. "I come up with a lot of new ideas every day," said Dr. Li, "and I learned from Dr. Liqun Luo how to screen them and put them into practice". Scientific research may be a long and arduous effort. "What made Dr. Luo's team different is that they don't limit themselves to using existing tools, but if needed can commit to the development of novel tools, or repurpose tools from other areas, to work on new problems, always enjoying such challenges." Dr. Li spoke of his post-doctoral experience with great respect for his supervisor. The ability to solve practical problems is so important in research. When Dr. Li was using the light-sheet microscope, it often took him a long time to find the location of the sample, so he asked the experienced Professor Eric for advice. Professor Eric located the sample with the help of a mobile phone camera. Dr. Li exclaimed: "Practice clearly goes so much deeper than theoretical knowledge!"

Research is an attitude, not a job

"Many people think of research as the task of climbing to the mountain top," said Dr. Li, shaking his head gently, "but I don't agree”. “I think research is a challenge, but not a task; it's an attitude, not a job." He clearly believes that interest is the best mentor. "My curiosity about the results has driven me to patiently complete otherwise boring dissections on Drosophila for in vitro imaging experiments without torment." By doing so, his passion, curiosity, and hard work have helped Dr. Li to uncover the developmental mechanism of the olfactory circuits in Drosophila and to visualize the neural development of the brain from 3D to 4D. Speaking about why he came back to China and chose ZJU, Dr. Li said: " Hangzhou is a great place to work and live in. ZJU has given me full support for my research; the Center for Brain Science and Brain-Machine Integration is one of the best of such centers in China, in all dimensions of brain science research. As a young scientist, I also feel the positive and happy atmosphere of the scientific cooperation in China, which is very a rare and valuable commodity."

Encouragement and trust create positive feedback between students and teachers

"During my PhD, my supervisor had been so patient and encouraging, which had greatly increased my motivation and self-confidence." Supervisors are there for students to lead their way through research, and provide guidance and encouragement. Dr. Li always hoped he could do the same for his students, trusting that his students would learn to think independently, but not sacrifice their lives for research. "Research shouldn't be competitive. It becomes competitive because new ideas are not being discovered and everyone is still stuck competing on the same old track. I hope my lab members could help each other develop novel thinking and work together in such a way." Dr. Li looks forward to building a harmonious and warm laboratory and exploring the unknown with students who are truly both interested in and devoted to science.

Facing the challenge of emotion regulation requires exploring cross-disciplinary fields

Yuxiao Yang is a PhD supervisor and researcher at the BBMI center. He has also been selected for a national young talent project. He graduated with a bachelor's degree in electronic engineering from Tsinghua University in 2013 and received his PhD in electrical engineering from the University of Southern California in 2019. From 2020 to 2022, he served as a tenure-track assistant professor in the Department of Electrical and Computer Engineering at the University of Central Florida. He mainly engages in neural engineering research in the fields of neural coding and neural modulation and has rich research achievements. He has published in leading international academic journals as the first or co-first author, including two cover articles in ***Nature Biotechnology*** and ***Nature Biomedical Engineering***, and has received awards such as the IEEE EMBC Best Paper Award in 2015 and the International Brain-Computer Interface Research Award in 2019.

His main research areas include **brain-computer interfaces, treatment of brain disorders, neural encoding and decoding, adaptive neural modulation, and artificial intelligence.**

Conducting Scientific Research that Integrates Medicine and Engineering

Yuxiao Yang majored in electronic engineering and information theory in his undergraduate studies. He hoped to apply the knowledge of information theory in the field of medicine, thereby promoting the theory into practice and ultimately benefiting mankind. Therefore, during the process of applying for a Ph.D. after graduation, Yang was firmly determined to devote himself to biomedical research. However, it was a chance encounter with the field of brain-computer interaction that really opened up the particular direction of his research path. During his studies abroad, Yuxiao Yang's vision was broadened by the tremendous energy of cross-disciplinary collision and the blending of the fields of life-science, medicine, and engineering. In such a multi-disciplinary environment he successfully decoded human emotional changes using intracranial neural signals and constructed a neural control model to accurately predict neural activity. He then integrated the design of closed-loop deep brain stimulation algorithms to develop new therapies for treatment-resistant depression and other brain disorders. Yuxiao Yang has clearly expressed that he believes the scientific spirit of seeking truth, focusing, and being practical, building a knowledge system, and promoting cross-disciplinary cooperation, are the "magic weapons" for him to achieve fruitful results.

Confronting the Challenge of "Emotion Regulation" by Enhancing "Cross-Disciplinary" Cooperation.

When it comes to research goals, Yuxiao Yang points: "The field of emotion regulation holds both opportunities and challenges. I hope to cooperate with scholars from different fields in the future to truly transform the emotion regulation algorithm into a medical product that benefits humanity." The population of patients with depression is large, and traditional drug treatment and deep brain stimulation have certain limitations. Therefore, Yuxiao Yang hopes to use a closed-loop control method, that is, using neural signals to detect patients' emotional changes in real time and permit automatic adjustments to the pattern of electrical stimulation based on these changes to achieve precise treatment. However, this plan still faces many challenges. In addition, Yuxiao Yang hopes to achieve "cross-disorder emotion regulation" in the future, benefiting other patients of mental disorders. Looking to the future of brain-computer interfaces, Yuxiao Yang stated: "The seamless interconnection and integration of brain-inspired computing and the brain itself is the ultimate goal of the brain-computer intelligence field." However, this still faces many challenges. Can we efficiently collect neural activity with high-quality electrodes? Can we prepare low-power and high-performance chips? How to design stable, efficient, and accurate algorithms? How to prepare a long-term usable integrated system? Progress in these research areas require in-depth cross-disciplinary cooperation and Yang hopes to contribute his own strength to this end.

Persisting in Morality and Cultivating a New Generation of Researchers.

"Establishing character and educating people is the responsibility of teachers." Yuxiao Yang emphasized that success starts with being a good person. The way students conduct themselves, their mode of thinking, and their attitude are of utmost importance. A diligent, practical, and positive attitude is the first driving force for progress. For students who plan to devote themselves to scientific research, the road to research may be full of difficulties, but the process of overcoming difficulties is often also a process of learning and growth. In this regard, Yuxiao Yang shared his own experiences, the most important of which is to always maintain a curious mind in scientific research. Pursuing hotspots alone will only make the road narrower and narrower. It is only by finding an area of interest and persistently exploring it that one can more easily "break through." In addition, Yuxiao Yang believes that interdisciplinary study is also a wise choice. Transferring knowledge and integrating it with those of other fields would be a good personal decision for anyone choosing scientific research as a career. If one is determined to persist, it is necessary to establish a research direction that combines interest and advantages, and to plan for future career development.

Keep digging, keep harvesting

Yang SHI is a principal investigator in both MOE Frontier Science Center for Brain and Brain-Computer Integration (BBMI). He has been selected for the national young talent project. Dr. Shi received his PhD degree from the Institute of Biophysics, Chinese Academy of Sciences in 2018, and conducted his postdoc program in the MRC Laboratory of Molecular Biology (MRC-LMB) in 2018-2022 (under tutors Dr. Michel Goedert and Sjors H.W. Scheres). Dr. Shi has published several articles as the first author in journals such as ***Nature*** (3, with 1 cover article), ***Acta Neuropathologica***, ***Nature Communications***, ***Science Advances*** and many others.

Dr. Shi' s research interests are focused on **structures and mechanisms of amyloid protein assemblies in neurodegenerative diseases, and PET ligand recognition mechanisms of amyloid filaments**.

Untangling scientific puzzles with electron microscopy

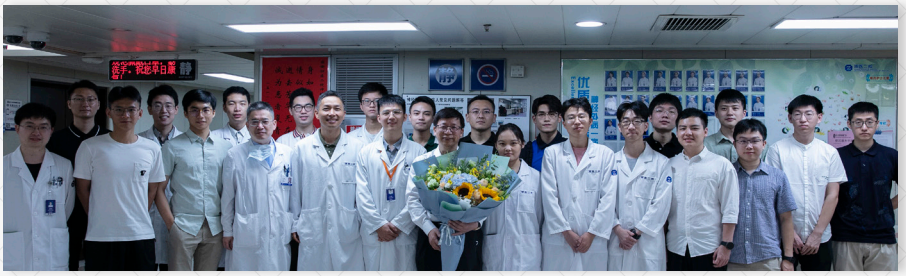
The electron microscope has long been the window through which Dr. Shi has peered into the biological world. During his 2011 master's program in the school of life science, conducted under the supervision of Prof. Qinfen ZHANG at Sun Yat-sen University, Dr. Shi's electron microscope based studies were focused upon uncovering the packaging process of baculoviruses. In 2014, Dr. Shi then joined Prof. Fei SUN's group at the Institute of Biophysics, Chinese Academy of Sciences, studying the molecular mechanism of bacterial photosynthesis. For more than 10 years, Dr. Shi has been following the resolution revolution in cryo electron microscopy and its application into our understanding of ever-smaller molecules and more elaborate biological processes. Such studies have resulted in many scientific breakthroughs.

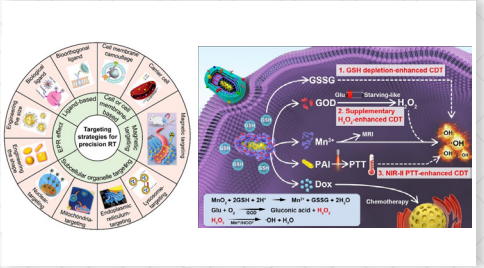
Exploring the mysteries of protein structure for human health

Human diseases have been the best "teacher" for scientific improvement. "Though it is interesting to study the basic biological progress in other organisms, such as photosynthesis, scientific issues related to human diseases have given me a particular sense of responsibility and mission", declares Dr Shi. Exactly this concept had previously promoted Dr. Shi's 4-year work on neurodegenerative diseases in MRC-LMB. By then systemically analyzing the folds of tau filament from more than 10 tauopathies, Dr. Shi was able to conclude that the structural characteristics of tau filaments can be used to facilitate the categorization, diagnosis, and identification of neurodegenerative disorders.

Creating a win-win mode for teacher-and-student cooperation

In the opinion of Dr. Shi, the abundant scientific experience of teachers and the courage and vitality of the students to explore the unknown provides a complimentary partnership. Thinking while learning can usually inspire new ideas for study, making it a virtuous circle for scientific research. Talking about why he chose the BBMI center, Dr. Shi said Zhejiang University presides over the construction of the National Human Brain Bank For Health And Disease and possesses rich patient samples and excellent research teams. What's more, the facility level cryo-electron microscopy platform is due to be greatly improved by the end of the second phase of its construction, opening up exciting potential for future work. In addition, the chief scientist of the BBMI center, academician of the Chinese Academy of Sciences, Prof. Shumin DUAN, has offered constructive help. For the focus of his following work in the BBMI center, Dr. Shi plans to expand our understandings on structures and mechanisms of amyloid protein assemblies in neurodegenerative diseases, and PET ligand recognition mechanisms of amyloid filaments.





Prof. Jianmin Zhang's Research group

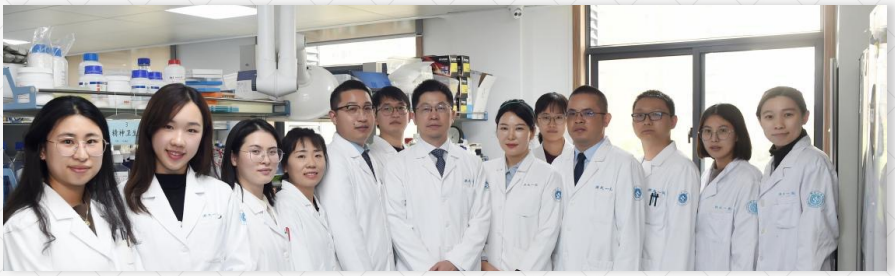
Pan Y, Tang W, Fan W*, Zhang J*, Chen X*. Development of nanotechnology-mediated precision radiotherapy for anti-metastasis and radioprotection. ***Chemical Society Reviews***. 2022 Nov 10. doi: 10.1039/d1cs01145f. Online ahead of print.

Recent breakthroughs in nanotechnology have provided a variety of strategies by which radiotherapy (RT)can precisely and efficiently eradicate local tumors. In this review, we would like to summarize a series of nanotechnology-mediated strategies to achieve precision RT, including tumor-targeted delivery, image-guided precision radiotherapy, exo/endogenous stimuli-responsive nanomedicines for enhanced tumor accumulation/penetration. In add on, this review will also discuss two representative featured applications of precision RT: RT-induced immunotherapy against cancer metastasis and radioprotection of the surrounding healthy tissues. Finally, the current challenges and future prospects of precision RT are also elucidated with the intention to accelerate its clinical translation.

Prof. Yan Zhang's Research group

Huang S#, Xu P#, Shen D#, Simon I#, Mao C, Tan Y, Zhang H, Harpsøe K, Li H, Zhang Y, You C, Yu X, Jiang Y, Zhang Y*, Gloriam D*, Xu H*. GPCRs steer Gi and Gs selectivity via TM5-TM6 switches as revealed by structures of serotonin receptors. ***Molecular cell***. 2022 Jul 21;82(14):2681-2695.e6.

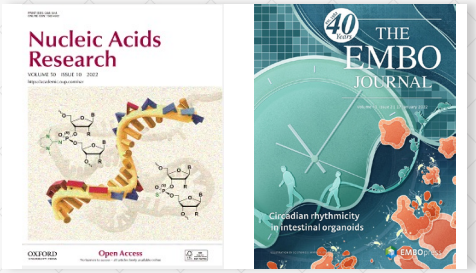
Serotonin (or 5-hydroxytryptamine, 5-HT) is an important neurotransmitter that activates 12 different G protein-coupled receptors (GPCRs) through selective coupling of Gs, Gi, or Gq proteins. We report the structures of the serotonin receptors 5-HT4, 5-HT6, and 5-HT7 with Gs, and 5-HT4 with Gil. The structures reveal that transmembrane helices TMS and TM6 alternate lengths as a macro-switch to determine receptor's selectivity for Gs and Gi, respectively. We find that the macro-switch by the TM5-TM6 length is shared by class A GPCR-G protein structures. These results present a common mechanism of Gs versus Gi protein coupling selectivity or promiscuity by class A GPCRs and extend the basis of ligand recognition at serotonin receptors.



Prof. Shaohua Hu's Research group

Wang Y, Li X, Chee H. Ng, Xu D*, Hu S*, Yuan T*. Risk factors for non-suicidal self-injury (NSSI) in adolescents: A meta-analysis. ***EClinicalMedicine***. 2022 Mar 21;46:101350.

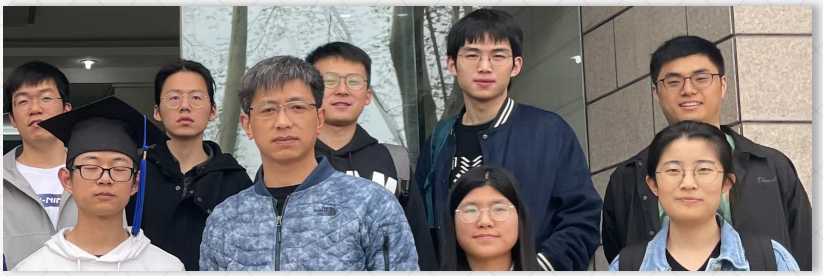
Non-suicidal self-injury (NSSI) in adolescents is a significant mental health problem around the world. Here, we performed a meta-analysis to systematically delineate the risk factors for NSSI. This meta-analysis found that mental disorders, low health literacy, adverse childhood experiences, bullying, problem behaviours, the female gender and physical symptoms appear to be risk factors for NSSI.

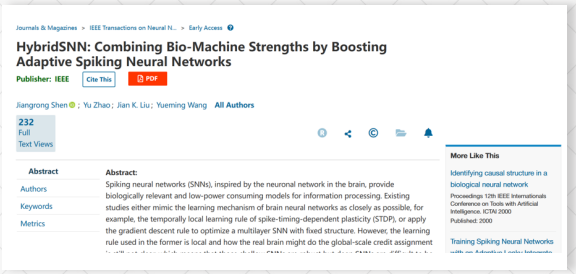


Prof. Wei Chen's Research group

Lei Y#, Fei P#, Song B, Shi W, Luo C, Luo D, Li D*, Chen W*, Zheng J*. A loosened gating mechanism of RIG-I leads to autoimmune disorders. ***Nucleic Acids Research***. 2022 Jun 10;50(10):5850-5863.

In this study, single molecule magnetic tweezers, hydrogen deuterium exchange mass spectrometry and biochemical methods were utilized, from the atomic, single molecule to cell levels, to study the receptor protein retinoic acid induced gene protein I (RIG-I), which plays an important role during innate immunity, depicting its dynamic molecular confom1ation change mode and revealing its molecular mechanism of accurately distinguishing “self ‘and “non self ‘RNAs through its dynamic conformations. This study further revealed the molecular mechanism of immune disorder caused by disease-related mutation of RIG-I, which provides a theoretical basis and technical support for screening drugs for treatment of related clinical diseases.

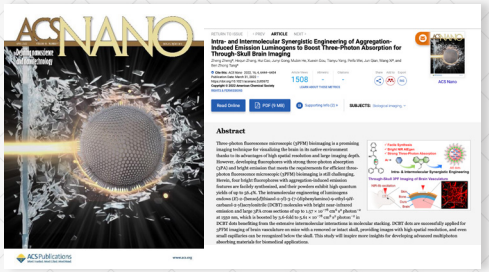




Prof. Yueming Wang's Research group

Shen J, Zhao Y, Liu J, Wang Y*, HybridSNN: Combining Bio-machine Strengths by Boosting Adaptive Spiking Neural Networks. ***IEEE Transactions on Neural Networks and Learning Systems.*** Oct. 2021.DOI: 10.1109/TNNLS.2021. 3131356.

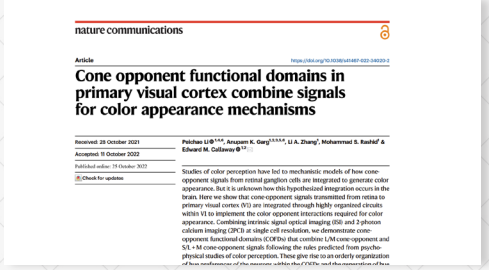
Spiking neural networks (SNNs), inspired by the neuronal network in the brain, provide biologically relevant and low-power consuming models for information processing Existing studies either mimic the learning mechanism of brain neural networks as closely as possible, for example, the temporally local learning rule of spike-timing-dependent plasticity (STDP), or apply the gradient descent rule to optimize a multilayer SNN with fixed structure. However, the learning rule used in the former is local and how the real brain might do the global-scale credit assignment is still not clear, which means that those shallow SNNs are robust but deep SNNs are difficult to be trained globally and could not work so well. For the latter, the nondifferentiable problem caused by the discrete spike trains leads to inaccuracy in gradient computing and difficulties in effective deep SNNs.



Prof. Wang Xi's Research group

Zheng Z#, Zhang H# , Cao H, Gong J, He M, Gou X, Yang T, Wei P, Qian J, Xi W*, Tang B*. Intra- and Intermolecular Synergistic Engineering of Aggregation-Induced Emission Luminogens to Boost Three-Photon Absorption for Through-Skull Brain Imaging. ***ACS Nano.*** April 26, 2022, 16(4): 6444−6454.

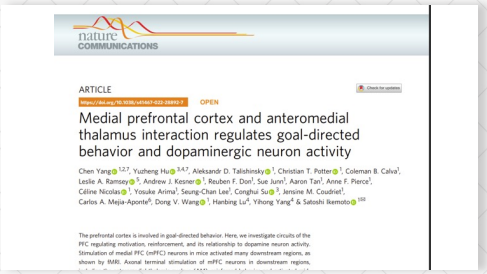
This study uses the intra- and intermolecular synergistic engineering to boost three-photon absorption of AIEgen for ultra-deep 3PFM imaging. The AIEgen dots are successfully applied for 3PFM bioimaging of cerebral vasculature on mice with the removed or intact skull, providing images with high spatial resolution and even small capillaries could be recognized below the brain skull. This work will inspire more insights into the development of advanced multi-photon absorbing materials for bio-medical applications.



Prof. Peichao Li's Research group

Li P#, Garg A#, Zhang L, Rashid M, Callaway E*. Cone opponent functional domains in primary visual cortex combine signals for color appearance mechanisms. ***Nature Communications.*** 2022 Oct 25;13(1):6344.

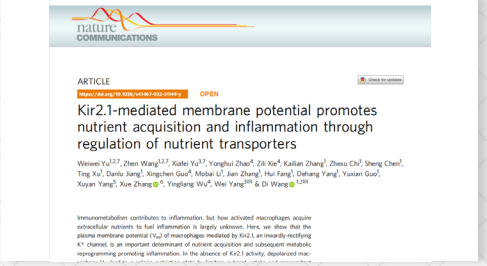
This study shows that cone-opponent signals transmitted from retina to primary visual cortex (Vl) are integrated through highly organized circuits within Vl to implement the color opponent interactions required for color appearance. Combining intrinsic signal optical imaging (ISI) and 2-photon calcium imaging (2PCI) at single cell resolution, we demonstrate cone-opponent functional domains (COFDs) that combine LIM cone-opponent and S/L +M cone-opponent signals following the rules predicted from psychophysical studies of color perception. These give rise to an orderly organization of hue preferences of the neurons within the COFDs and the generation of hue “pinwheels”. Thus, spatially organized neural circuits mediate an orderly transition from cone-opponency to color appearance that begins in Vl.



Prof. Yuzheng Hu's Research group

Yang C#, Hu Y#, Talishinsky AD, Potter CT, Calva CB, Ramsey LA, Kesner AJ, Don RF, Junn S, Tan A, Pierce AF, Nicolas C, Arima Y, Lee SC, Su C, Coudriet JM, Mejia-Aponte CA, Wang D, Lu H, Yang Y, Ikemoto S*. Medial prefrontal cortex and anteromedial thalamus interaction regulates goal-directed behavior and dopaminergic neuron activity. ***Nature Communications***. 2022 Mar 16;13(1):1-20.

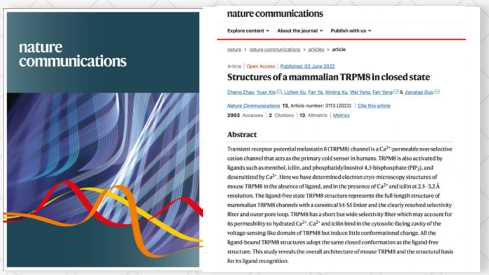
This study integrated multiple techniques including fMRI, optogenetic stimulation, calcium imaging, and physiological recording to investigate how rodents respond to medial prefrontal cortex (mPFC) stimulation. The results showed that stimulating mPFC can induce addiction-like self-stimulation behavior. fMRI data revealed significant activation in many mPFC downstream regions including anteromedial thalamus (AM). Further physiologic and calcium data demonstrated positive feedbacks between mPFC and AM. To explore potential clinical implications of mPFC-AM activation, a task fMRI experiment was conducted in human subjects and activations in the same pathway were seen when subjects viewing reinforcing personalized short videos. Taken together, these results suggest that the mPFC-AMc circuit is critical in reinforcing behavior and might be parts of neural substrates of behavioral addiction.



Prof. Wei Yang's Research group

Yu W#, Wang Z#, Yu X#, Zhao Y, Xie Z, Zhang K, Chi Z, Chen S, Xu T, Jiang D, Guo X, Li M, Zhang J, Fang H, Yang D, Guo Y, Yang X, Zhang X, Wu Y, Yang W*, and Wang D*. Kir2.1-mediated membrane potential promotes nutrient acquisition and inflammation through regulation of nutrient transporters. ***Nature Communications***. 2022 Jun 21;13(1): 3544.

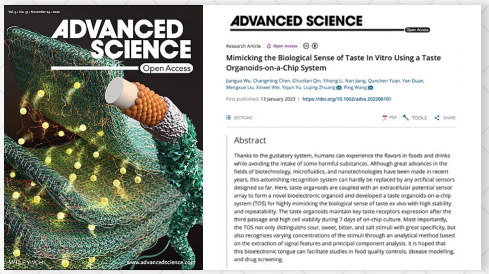
This study shows that the plasma membrane potential (Vm) of macrophages mediated by Kir2.1, an inwardly-rectifying K^+ channel, is an important determination of nutrient acquisition and subsequent metabolic reprogramming promoting inflammation. In the absence of Kir2.1 activity, depolarized macrophage Vm lead to a caloric restriction state by limiting nutrient uptake and concomitant adaptations in nutrient conservation inducing autophagy, thereby suppressing their transcription. Kir2.1-mediated Vm supports nutrient uptake by facilitating cell-surface retention of nutrient transporters such as 4F2hc and GLUT1 by its modulation of plasma membrane phospholipid dynamics. Pharmacological targeting of Kir2.1 alleviated inflammation triggered by LPS or bacterial infection in a sepsis model and sterile inflammation in human samples. These findings identify an ionic control of macrophage activation and advance our understanding of the immunomodulatory properties of Vm that links nutrient inputs to inflammatory diseases.



Prof. Guo Jiangtao's Research group

Zhao C#, Xie Y#, Xu L#, Ye F, Xu X, Yang W, Yang F*, Guo J*. Structures of a mammalian TRPM8 in closed state. ***Nature Communications.*** 2022 Jun 03; 13: 3113.

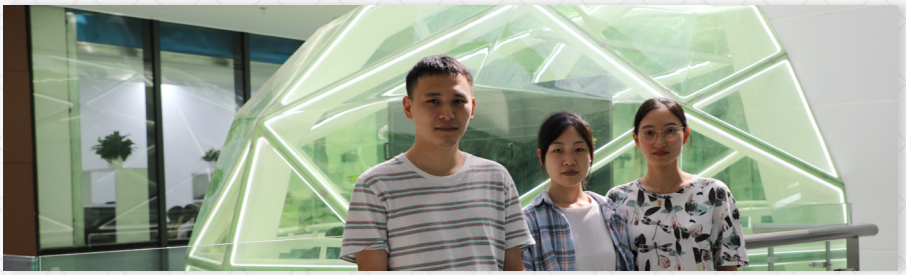
Using the single-particle electron cryo-microscopy technique, this study presents structures of mouse TRPM8 in the absence of ligand, and in the presence of Ca^{2+} and icilin at 2.5 to 3.2 A resolution and reveals the structures and ligand recognition mechanism of mouse TRPM8. By comparing mouse TRPM8 structures with the previously published bird TRPM8 structures, this study provides insights into the interpretation of TRPM8 structures in different states.



Prof. Ping Wang's Research group

Wu J, Chen C, Qin C, Li Y, Jiang N, Yuan Q, Duan Y, Liu M, Yu Y,Zhuang L*, Wang P*. Mimicking the biological sense of taste in vitro using a taste organoids-on-a-chip system. ***Advanced Science***.2022. In press.

Here, we coupled taste organoids with an extracellular potential sensor array to form a novel bioelectronic organoid and developed a taste organoids-on-a-chip system (TOS) for highly mimicking the biological sense of taste ex vivo with high stability and repeatability The taste organoids maintained key taste receptors expression after the third passage and maintained high cell viability during 7 days of on-chip culture. Most importantly, the TOS not only distinguished sour, sweet, bitter, and salt stimuli with great specificity, but also recognized varying concentrations of the stimuli through an analytical method based on the extraction of signal features and principal component analysis. We hope that this bioelectronic tongue could facilitate studies in food quality controls, disease modelling, and drug screening.



Prof. Honghao Li's Research group

Cui Y, Huang X, Huang P, Huang L, Feng Z, Xiang X, Chen X, Li An, Ren C, Li H*. Reward ameliorates depressive-like behaviors via inhibition of the substantia innominata to the lateral habenula projection. ***Science Advances.*** 2022 Jul 8;8(27):eabn0193.

We find that the excitatory projection to the LHb from the substantia innominata (SI), a BF subregion, is activated by aversive stimuli and inhibited by reward stimuli. Furthermore, chronic activation of the SI-LHb cu it is sufficient to induce depressive-like behaviors, whereas inhibition of the circuit alleviates chronic stress- induced depressive-like phenotype. We also find that reward consumption buffers depressive-like behaviors induced by chronic activation of the SI-LHb cu it. The work provide important insights to better decipher LHb processing in the pathophysiology of depression.

Prof. Li Tao's Research group

Liang S, Greenshaw AJ, Li T*, Mao H. Sleep clinic service model with closed-loop management for insomnia. ***Asian J Psychiatr.*** 2022 Jul;73:103158.

Insomnia is a common medical condition associated with other psychological and physiological disorders, and may require long-term treatment and outpatient management. This study introduces an innovative outpatient service model for patients with insomnia, which includes providing medical care before, during and after diagnosis in public hospital clinics, completing prescribed treatments at home and return visits. It is a digital health-based, patient-centred, collaborative care model with closed-loop management. The proposed management strategy may help achieve a balance between the efficiency and the quality of outpatient medical care for insomnia.

Prof. Ruiliang Bai's Research group

Xue S, Cheng Z, Han G, Sun C, Fang K, Liu Y, Cheng J, Jin X, Bai R*. 2D Probabilistic Undersampling Pattern Optimization for MR Image Reconstruction. ***Medical Image Analysis.*** 2022 Apr; 77, 102346.

With 3D magnetic resonance imaging (MRI), a tradeoff exists between higher image quality and shorter scan time. One way to solve this problem is to reconstruct high-quality MRI from undersampled k-space. Recent studies explored effective k-space undersampling patterns and MRI reconstruction methods separately. This study proposes optimization network for 2D undersampling pattern optimization and MR image reconstruction in a retrospective data-driven fashion and under a limited sampling rate. Furthen11ore, we discovered a quantification relationship between the optimized probability distribution of our 2D undersampling pattern and its sampling rate.

Prof. Hao Wang's Research group

Pan L #, Zheng L #, Wu X #, Zhu Z, Wang S, Lu Y, He Y, Yang Q, Ma X, Wang X, Yang H, Zhan L, Luo Y, Li X, Zhou Y, Wang X, Luo J, Wang L, Duan S, Wang H*. A short period of early life oxytocin treatment rescues social behavior dysfunction via suppression of hippocampal hyperactivity in male mice. ***Molecular Psychiatry.*** 2022 Oct;27(10):4157-4171.

This study shows that early lif e bilateral whisker trimming (BWT) subsequently affects social discrimination in adult male mice. Enhanced activation of the hippocampal dorsal CA3 (dCA3) in BWT mice was observed during social preference tests. Optogenetic activation of dCA3 in naive mice impaired social discrimination, whereas chemogenetic silencing of dCA3 rescued social discrimination deficit in BWT mice. Hippocampal oxytocin (OXT) is reduced after whisker trimming. Neonatal intraventricular compensation of OXT relieved dCA3 over-activation and prevented social dysfunction. Neonatal knockdown of OXT receptor in dCA3 mimics the effects of BWT, and cannot be rescued by OXT treatment. Social behavior deficits in a fragile X syndrome mouse model (Fmrl KO mice) could also be recovered by early life OXT treatment, through negating dCA3 over-activation. Here, a possible avenue to prevent social dysfunction is uncovered.

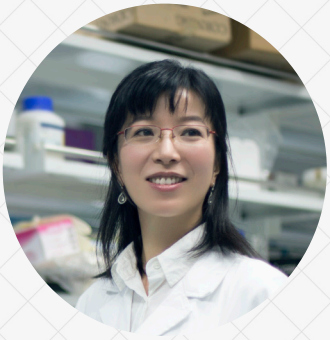
Prof. Aimin Bao's Research group

Guo L, Qi Y, Tan H, Dai D, Balasar R, Sluiter A, Heerikhuize J, Hu S, Swaab D, Bao A*. Distinct oxytocin and corticotropin-releasing hormone system activities of bipolar disorder and major depressive disorder patients. ***eBioMedicine.***2022 Oct;84:104266.

This postmortem study showed that increased expression of oxytocin in hypothalamic paraventricular nucleus (PVN-OXT) and of OXT receptor in the dorsolateral prefrontal cortex were characteristic for bipolar disorder (BD), but not major depressive disorder patients. In addition, activation of PVN-OXT neurons in mice induced BD-like behaviors, the pattern of sex differences was, however, different from that in human brains. It provides a key evidence for symptom-dependent neurobiological pathogenesis and treatment strategy of psychiatric diseases.

Prof. Xiaoming Li

Prof. Shumin Duan



Prof. Hailan Hu

Basic Science Center Project of National Natural Science Foundation

▼ Neural mechanisms and interventions of instinctive behaviors and related psychiatric disorders

The regulatory mechanisms underlying behaviors of has become one of the biggest challenges for humans to understand the nature, break through ourselves, and change the world. Animal behavior patterns can be divided into innate instinctive behaviors and experience-dependent learned behaviors, among which the instinctive behaviors are the basis of experience-dependent learned behaviors. In recent years, the research of innate instinctive behaviors has become a major scientific frontier of multi-disciplinary interests such as life sciences, medicine, and information technology. The interpretation of instinctive behaviors is critical for understanding the diversity and complexity of species evolution, the basic working principles of the brain, the pathological mechanisms of psychiatric disorders and the treatment strategies, as well as the development of artificial intelligence. This will also bring revolutionary breakthroughs and is the key to seizing the international commanding heights in the field of neuroscience. Our research will focus on the critical scientific issue of 'neural mechanisms underlying instinctive behaviors and related disorders' from three aspects: the neural circuitry of innate instrinctive behaviors, the regulatory mechanisms of instinctive behavior interactions, and the pathological mechanisms and interventions of diseases related to instinctive behaviors. The team leader of the research center is Prof. Lin Lu, the member of Chinese Academy of Sciences.

Prof. Binggui Sun

MOST Key Research and Development Program

▼ Investigation of biomarkers to identify the differentiation of human neural progenitors

Implantation of neural pro genitors is a promising method for treating of neurological diseases. Proper identification of developmental stages of these cells is essential to the success of this method. In this study, we will screen candidate markers to identify human neural progenitors at different stages of differentiation. Different populations of the human neural pro genitors selected by these markers will be transplanted to different brain regions of mice, and their survival, migration, differentiation and integration in to the neural circuit will be evaluated with multiple approaches.

Prof. Chong Liu

National Science Fund for Distinguished Young Scholars

▼ The origin and progression of glioma

Glioblastoma (GBM) is one of the most malignant cancers in human. Despite many years of efforts in both basic research and clinical practice, the progresses of diagnosis, prognosis and therapy of GBM are limited. Many questions remain to be addressed in terms of how GBM initiates and evolves, and how we can prognose, prevent and treat this devastating disease. The applicant has been focusing on the important questions pertinent to the developmental origin and progression of GBM. By developing a panel of unique genetic glioma models with high spatiotemporal resolution, the applicant made it possible to visualize the entire process of gliomagenesis, and to manipulate relevant biological functions in a highly precise way. Taking advantage of these powerful tools, the applicant provided the evidence to show that (1) oligodendrocyte precursor cells (OPCs) function as the important cell of origin for gliomas; (2) identified the critical switch molecule to regulate OPC homeostasis; (3) revealed that external sensory experience is an important risk factor for gliomagenesis; (4) described the new paradigm for glioma targeted therapy; and (5) demonstrated that the IGF-1-IGF1R signaling axis is a promising target for glioma treatment. In the future, the applicant will continue working on those questions related to the origin and progression of GBM. By developing novel mouse and pig genetic models, the applicant will systematically delineate the essential biological principles governing these processes. By developing cutting-edge techniques for early cancer diagnosis based on the multiplex in situ mRNA hybridization, the applicant will further examine the pattern of gliomagenesis in the human brain; and identify novel biomarkers for early diagnosis and treatment. The pertinent study will help to understand the mechanism of glioma initiation and progression, and provide the foundation for the diagnosis and treatment of gliomas in patients.

Prof. Yu Qi

Distinguished Youth Program" of Lingang National Laboratory

▼ Neuromorphic chip based brain-computer interface method and system

Brain-computer interface and brain-inspired computing are ushering in an unprecedented period of rapid development, and the deep integration of the two breeds new technological and theoretical breakthroughs. The compatibility of brain-inspired computing and biological neurons in information representation and learning mechanisms is expected to establish new theories and methods for deep brain-computer fusion and collaborative learning, with great research potential. At the same time, brain-inspired computing has great potential in low energy consumption and sustainable learning. The advantages of the brain-computer interface perfectly match the core problems such as high energy consumption and poor long-term stablilty that need to be solved urgently in the widespread implementation of the brain-computer interface, and it is expected to establish a new high-performance brain-computer interface technology. This project gathers the characteristics and advantages of the team in the fi eld of brain-computer interface and brain-inspired computing, focuses on the research of brain-computer interface methods and systems based on brain-inspired computing, breaks through the neuron spike brain information decoding model based on pulse computing and the deep integration of brain and computer Learn theories and methods, establish a brain-computer interface platform system based on brain-like chips, and rely on clinical/ animal platforms for demonstration and verification. This project is a frontier exploration of the combination of brain-inspired computing and brain-computer interface technology. On the one hand, it explores new research paradigms, new theories and new methods for deep integration of brain-computer from a new perspective of brain-inspired computing; on the other hand, it takes advantage of brain-inspired computing. It is of great significance to break through the core problems in the fi eld of brain-computer interface and effectively improve the long-term stability and usability of brain-computer interface.

Prof. Xiaotong Zhang

Key R&D Program of Jiangsu Province

▼ Research and Development of Real-time MRI-guided Surgical Robots for Precise Deep Brain Stimulation

Built upon theories and technologies overarching electromagnetism, control in automation, mechanical design, image and signal processing, and machine learning, the proposed project focuses on the development of new generation real-time MRI-guided surgical robots for precise deep brain stimulation. Specifically, MRI-compatible low-artifact deep brain stimulation electrodes and real-time electrophysiological feedback system will be devised, and the prototype for interventional brain MRI system will be developed, alongside with the navigation platform for surgical planning and deep brain surgery with high spatiotemporal resolution, and eventually towards clinical evaluations and applications.

Prof. Huajin Tang

Key Project of National Natural Science Foundation

▼ **Hybrid brain-inspired architecture system and application verification for emulating biological intelligence**

The brain is an extremely complex intelligent agent with hybrid architectures that can achieve advanced cognition in multi-task environments by multi-modal perception, multi brain-regions collaboration, and hybrid digital-analog computing. However, there is not a unified brain theory like the Turing machine in traditional computing domain. This project dedicates to investigating generic structures and calculation mechanisms of different biological brains and then put forward a minimized, flexible, universal abstract multi-brain regions structure. This project will establish the mapping methods between neuronal activities, neural circuit and perception, decision, behaviors, focusing on the key theories and methods of information representation using spikes, hybrid computing with digital-analog signals, and multi-task learning. In terms of algorithm and model, this project will combine the dynamic gating mechanism of specific neural cu it in the brain, propose the multi-task-oriented cooperative regulation theory and method of multi-brain-regions, and form the cooperative working mechanism of multi — intelligence model for complex applications. In terms of system architecture, a hybrid digital-analog spike coding scheme is proposed for simulating biological intelligent hardware system, and a neuromorphic computing architecture is designed under the resource-limited condition to emulate biological conditions, and the real-time interaction between the neuromorphic system and physical environment is realized by using bionic birds for verification. It is expected to achieve a breakthrough and inspiring results in establishing unified theories and architectures of neuromorphic computing.

Prof. Li Tao

Key Project of National Natural Science Foundation

▼ **Exploring the neuromodulatory effect and neurobiological mechanism of bright light therapy (BLT) combined with mood stabilizer on bipolar disorder**

By focusing on a number of key clinical challenges in the acute episode of the depression phase of bipolar disorder (BD-DEP), including limited treatment options, delayed treatment onset, and poor efficacy, we are going to integrate clinical resources and advanced technology to prospectively evaluate the therapeutic effect of Bright Light Therapy (BLT) combined with mood stabilizers based on our previous research and the experts team; to analyze the changes of clinical symptoms, cognitive functions, and peripheral biological rhythm biomarkers before and after treatments; to depict the multi-dimensional and multi-level pathophysiological changes in brain emotional neural cu it and rhythm neural cu it at the structural, functional, and metabolic levels in details; and to reveal the neuromodulation mechanism of BLT in patients with BD-DEP. Using the INS-fMRI technology innovatively developed by our team members, we will analyze the changes of functional connectivity with high precision in Rhesus monkey brain before and after BLT and maps the functional connectome of light-sensitive neural circuits. We will also establish a composite brain-like model induced by iPSCs derived from BD-DEP patients and comprehensively explore the neurobiological mechanism of BLT in the treatment of BD-DEP from the aspects of composite brain-like single-cell sequencing, brain-like 3D reconstruction, electrophysiological function, and mitochondrial function. This study is oriented to clinical problems and integrate basic and clinical research in order to explore the underlying neurobiological mechanism of the rapid antidepressant effect of BLT. It will also provide a scientific basis for the development of effective and individualized BD-DEP neuromodulation treatment.

Prof. Huan Ma

Key Project of National Natural Science Foundation

▼ **Mechanisms underlying dysregulated plasticity of inhibitory interneurons in impaired cognitive flexibility**

As the comer stone for brain cognitive network during information processing, the dynamic control or plasticity of inhibitory interneurons is thought to be crucial for brain function. The relevant studies, which are the key for understanding mechanisms underlying many brain diseases with cognitive dysfunctions, are the frontier of the current neuroscience research. Recently, the applicant found that gCaMKII, a calcium/ calmodulin kinase highly implicated in human cognitive functions, is the long-sought mediator of long-term synaptic plasticity inhibitory interneurons. Interestingly, the level of gCaMKII decreases in human brain diseases with cognitive flexibility, including schizophrenia, indicating that there might be a causal relationship between dysregulated plasticity of inhibitory interneurons and impaired cognitive flexibility. To address this, the applicant will study the in vivo function of plasticity inhibitory interneurons from three angles: neurotransmitters, neuropeptides, and neuronal network, which is innovatory and distinct from the classic way for studying synaptic plasticity of excitatory neurons. Based on many preliminary data and clinic findings, the applicant will utilize genetically modified mice, electrophysiology, and in-vivo imaging to systematically analyze the link between impaired plasticity of inhibitory interneurons and cognitive flexibility. By executing this project, the applicant hopes that the findings shed light on understanding the correlation between synaptic plasticity of inhibitory interneurons and neuronal diseases like schizophrenia, which should help to develop new drug targets for improving cognitive flexibility in the future.

Prof. Jianhong Luo

Joint Fund Project of National Natural Science Foundation

▼ **Investigation on neural mechanisms and new therapeutic targets for social deficits in Autism Spectrum Disorder**

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by severe social communication deficits and restricted and repetitive behaviors and interests, with 1 % of estimated prevalence in China, a high sab 山 ty rate, no effective treatments, and thus results in serious harm to children effected. ASD is highly heterogeneous in both clinical phenotypes and genetic etiology, including a potential involvement of environmental and epigenetic factors, reflecting tremendous complexity of its pathogenesis. Although investigations using ASD model animals provide evidences for a given associated gene linking changes in neurodevelopment, synaptic functioning, and signaling pathway to pathological processes which eventually leads to behavioral deficits, the neuropathological mechanisms for social defects in ASD remain to be elucidated due to both the complexity of social behaviors themselves and the limitation of research techniques. We are planning in this project to employ technology of in vivo multiple brain region electrophysiological recording and deep analysis, activity -dependent labeling of neuronal assembly and cu it tracing to depict the dynamic of "social brain" network for social events under updated social behavioral paradigms in ASD mouse models. Furthermore, we are planning to examine changes in brain regions, neuron subtypes, neural circuits, and synaptic function comparatively using representative strains of ASD mouse models for identifying the common and distinct features of mechanism for social deficits. And we also are going to explore novel potential therapeutical targets for this disastrous disorder based on our new findings. This project would provide new insights into neurobiological mechanisms underlying normal and pathological social behaviors.

Prof. Benyan Luo

Joint Fund Project of National Natural Science Foundation

▼ **A new method for assessment and neural mechanism exploration of disorders of consciousness based on multi-dimensional stimuli combined with micro-behavior detection**

Accurate assessment and decoding of neural mechanisms in patients with chronic disorders of consciousness (DoC) are important for finding therapeutic targets to improve their level of consciousness. The key to its development is the full activation of the central neural network and the comprehensive evaluation of their remaining brain function. In this project, based on the stimulus paradigm containing multidimensional and multi-level emotional and semantic information, neuroelectrophysiology and neuroimaging methods were used to accurately assess the central response of the remaining level of consciousness in patients with DoC. In addition, we will use a peripheral micro-response monitoring system, including myoelectric sensor and micro-expressions, to decode the intensity of peripheral neural responses under different stimuli. Further on the basis of open loop decoding, we will use brain-computer interface technology to adjust various stimulus parameters and decode in real time and feedback them to the brain of patients, so as to fully activate the remaining brain functions of patients with DoC from low-level consciousness dimension to high-level cognitive dimension in a closed loop. Based on the central perception, semantic function evaluation and peripheral motor function evaluation, we will establish a new level of consciousness evaluation model from "input - central processing - peripheral monitoring" and combine deep learning to analyze the neural mechanism related to the perception and semantics of DoC. This study is helpful to evaluate the remaining level of consciousness in patients with DoC comprehensively and individually and promote the exploration of the neural mechanism of DoC.

Prof. Ruiliang Bai

National Natural Science Fund for Excellent Young Scholars

▼ **Transmembrane water transport MRI in brain and its clinical transfer**

The development of non-invasive measurement technology for key physiological processes in the brain is vital to correctly understanding the working mechanism of human brain and accurately diagnosing brain diseases. Transmembrane water transport process is an important physiological process in the brain, which plays a pivotal role in tissue balance, cell metabolism, and glymphatic circulation system The abnormal function of transmembrane water transport process is also an important pathogenic factor of various brain diseases such as cerebral edema, glioma, and Alzheimer's disease. Starting from a physical background in magnetic resonance imaging (MRI), the applicant has conducted in-depth research on developing quantitative MRI methods of the key transmembrane water transport processes in the brain and the related clinical transfer. The main achievements include: (1) Facing the complexity of the brain tissue environment, the specific and quantitative measurement of the transmembrane transport of water molecules has been successfully achieved through the innovation of magnetic resonance imaging sequences and algorithms; (2) The main molecular pathways and regulatory mechanisms of transmembrane transport of water molecules in the normal brain and the diseased brain have been systematically revealed to solve the problem of unclear physiological significance of this type of technology; (3) Successfully applied this type of technology to the precise diagnosis of brain diseases such as glioma and Alzheimer's disease. In this project, the applicant will further improve the MRI technology for the measurement of the key transmembrane water transport process in the brain clearance function, and explore its clinical value in the early diagnosis of Alzheimer's disease.

Prof. Nai Ding

National Natural Science Fund for Excellent Young Scholars

▼ The cognitive neural mechanism of speech com prehension

Speech comprehension is a high-level cognitive function unique to the human brain. How the brain encodes dynamic and complex speech sequences is a key question in psychology and neuroscience. This project aims to analyze the cognitive neural representations of syllabic and phrasal structures during the process of natural speech understanding. This project mainly covers two aspects: (1) Based on the reverberation scenes, this project will dissociate the cognitive neural representations of speech envelope as a basic auditory feature, and of the abstract speech units related to the perception of syllables; (2) Based on the research of manipulated speech materials, which uncovered the neural representations of phrasal structures generated by the multi-time scale neural oscillations, this project intends to study whether the multi-time scale neural oscillations of the cerebral cortex can represent the dynamically changing complex phrasal structures in natural speech, and to explore how the prosodic cues of speech affect the way phrasal structures are neutrally represented. Through the above-mentioned research, it is expected to establish a new theory on the neural encoding of hierarchical speech structures in the process of natural speech understanding.

Prof. Chong Liu

Zhejiang Provincial Natural Science Foundation of China

▼ Somatic mosaicism atlas in human brain and their relationship with brain disease

Brain tumors and Alzheimer's disease are major diseases that endanger human health, and changes in genetic material are important factors causing these diseases. However, due to the limitation of resources and technical difficulties, the research on somatic mosaicism in human brain multibrain regions is relatively lagging behind. At present, the recognition of somatic mosaic mutations can not locate the spatial location of mutated cells and define the interaction information with surrounding cells. This research is the first time to combine the ultra-deep sequencing technology with the digital multiple fluorescence in situ hybridization technology with single nucleic acid resolution, to develop a panoramic subcellular resolution whole-brain multiomic atlas analysis platform, which integrate the full-exon/whole-genome ultra-deep sequencing, the multiple in situ fluorescence hybridization technology, lock probe technology, artificial intelligence image recognition technology. With this platform, we can fine analyze the distribution of somatic mosaic mutations in tumor, Alzheimer's disease brain and normal brain, gene regulatory networks, key signal pathways and mutation evolution of different cell subtypes, and infer cell migration patterns the gene regulatory network of different cell subtypes, key signal pathways, the evolution of genomic mutations and cell migration patterns. At the same time, we search for disease-specific markers and verified them with animal models. This research provides a theoretical basis for analyzing the fundamental problem of the occurrence and behavioral nature of brain tumors and Alzheimer's disease. It is helpful to predict the occurrence of tumor and Alzheimer's disease based on gene mutation, so as to formulate accurate prevention and treatment strategies at the early stage of disease occurrence.

Prof. Gang Pan

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ Research platform of brain-machine interaction and computation

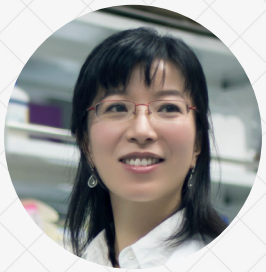
The convergence of the brain and computers has become an important trend of future computing technology. It is also an important frontier topic in the interdisciplinary fi eld of artificial intelligence and cognitive science. Brain-computer integration provides new means for understanding the brain, provides new diagnosis and treatment methods for the brain, and supports the development of new intelligence paradigm. This project will work from three levels: fundamental platform, key technologies, and applications. It focuses on key technologies for brain-computer information interaction and fusion computing, standards and specifications for brain-computer integration, and brain-computer applications. At the same time, it will develop a number of basic and universal platforms for brain-computer intelligence, such as brain-computer I/ 0 sub-platform, brain-computer computing sub-platform, brain-computer clinical and animal sub-platform, to promote the theories, technologies, and innovative applications of brain-computer intelligence.

Prof. Xuhua Wang

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Non-invasive brain-computer fusion applications**

The main research objectives of this project are to explore the effective correlation between the regulation mechanism of neuro feedback intervention and the characteristic indexes of emotional disorders, and to build a model of neuro feedback intervention characteristic indexes for emotional disorders; to try to combine the closed-loop negative feedback control theory to break through the technical bottleneck of traditional methods to achieve accurate quantification and evaluation, so as to achieve personalized and precise neuro feedback intervention for people with emotional disorders. We will study the brain-computer interaction in the process of digital drug therapy, establish the experimental model of brain activity representation and adaptive multitask stimulation, model the relationship between brain activity representation and drug efficacy and evaluation index, and model the encoding and decoding of attention state, build a digital drug system based on brain-computer interface, and conduct validation to improve the current cure rate of ADHD in children. To develop a closed-loop epidural electrical stimulation technique to reveal the mechanism of central neuropathic pain, effectively suppress neuropathic pain and promote functional recovery. To develop a non-invasive neurocircuit activity manipulation-driven sleep and emotion regulation technique by analyzing the signal coupling mechanism between sleep-wake activity and multiple emotion-processing brain regions, as well as the temporal nodes of sleep regulation and key coding patterns of emotion regulation.



Prof. Hailan Hu

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Mechanism-based new treatment strategies for mood disorders**

Mood disorders (depression, anxiety, addiction) are serious mental disorders caused by biological, psychological, and social stress. Due to the limitation in the understanding of pathogenesis and the neuronal molecular mechanism of these diseases, the clinical therapeutic strategies are restricted. Accordingly, this project plans to carry out a study on "mechanism-based new treatment strategies for mood disorders". To deepen our understanding of the neurobiological mechanisms of mood disorders, this project will apply state-of-art techniques such as molecular and epigenetics methods, single-cell analysis, neuronal circuit tracing, in vivo electrophysiology, chemogenetics, and optogenetics, as well as drug screening and other methods in molecular, cellular, and neural cu it levels. In combination with the newly developed neuronal specific label techniques, chemical biology, and computational biology research methods, this project was divided into three topics: (1) New treatment strategies for major depressive disorder and mechanism studies; (2) New treatment strategies for anxiety disorder; (3) Amelioration of the addiction potential of the new treatment strategy. These three topics are integrated. They all focus on the analysis of the pathogenesis of the diseases and the neuronal mechanism behind them, from where we will construct a disease model and exploration of new treatment strategies. In the progress, the individual characteristics and common characteristics of these diseases will be considered to help the precise treatment of the disease.

Prof. Honghao Li

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Remove of the Potential Addiction of New Treatment Approaches**

Emotion disorders including depression and anxiety are severe mental disorders, which resulting from the interaction of biological, psychological, and social stress. Currently treatment effect is poor. In recent years, sub-anesthetic doses of ketamine have been found to have rapid onset, long-lasting and strong antidepressant effects. In addition, studies have also found that endocannabinoids have good application in the treatment of anxiety disorders, which suggesting that the cannabinoid system may be an important class of candidate targets for the treatment of anxiety disorders. Although ketamine and cannabinoids are important candidate molecules for the treatment of depression and anxiety disorders, their clinical application is seriously hindered by their side effects such as addiction and hallucinnations. The current project takes chemical synthesis strategies to obtain small molecule derivatives of ketamine/cannabinoids modified by different chemical groups, and then uses addiction and hallucination detection animal models to analyze the differences in the addictive and hallucinogenic effects of different derivatives, and to clarify the ketamine/cannabinoid Correspondence among different chemical groups and their addictive hallucinogenic side effects. At the same time, with the help of these derivative molecules, the neural mechanism of the hallucinations of ketamine/cannabinoid will be explored. Our work will provide a theoretical basis for small molecule derivatives and drug development with clinical application prospects for the treatment of affective disorders.

Prof. Lijun Kang

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Molecular, cellular and neural mechanisms of visceral mechanoperception**

The communication between brain and internal organs is controlled by complex nervous and hormonal systems, which plays a vital role in maintaining the physiological and psychological homeostasis of the human body. The internal sensory networks are widely involved in the neural regulation of internal changes in the human body, and affect advanced cognitive behaviors, such as memory, emotion and self-consciousness. The molecular and cellular mechanisms of mechanical and chemical signal transduction in many internal organs are still unsolved; The mechanism by which visceral sensory information encodes in the brain and affects our behaviors and emotions is still unclear; The pathogenesis and treatment of visceral pain is still an unsolved problem. Combining the research systems based on C elegans, Drosophila, mouse and other model animals, this project is intended to reveal the regulatory effect of visceral mechanoreceptors on the function of digestive tracts and internal genitalia, and discovery the underlying mechanisms. This project will help us to understand the mechanism of the neural regulation of the homeostasis of human visceral system, and lay a scientific foundation for drug development and the treatment of related diseases.

Prof. Xiaoming Li

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Research on neural circuit mechanism of fear emotion**

The overall goal of this project is to decipher the neural circuit mechanisms underlying fear emotions Four representative brain regions, namely the brain stem, amygdala, hypothalamus and medial prefrontal cortex, are very important in the process of perception, integration, expression and regulation of emotions and are selected as the research subjects. The research deployment and design are carried out on the levels of gene, molecule, cell, neural cu it and function. The purpose of this study was to map the gene and protein expression profiles of the above four important emotional brain regions, and to screen out 5-10 specific molecular markers of each neuron subtype in each brain region, so as to elucidate their structural basis and activity of specific neural circuit and their contributions in fear/anxiety. This project will fully reveal the neural circuit mechanism of fear/anxiety, establish a new theory of fear/anxiety in the brain, and provide a systematic theoretical basis for more accurate diagnosis and treatment of fear-related mental disorders. In addition, this project will provide support for the mechanism study of neural circuit for other brain functions.

Prof. Zhihua Gao

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Neural circuit mechanism of fear express ion in the hypothalamus**

Fear is one of the most fundamental and primitive emotions essential for survival and species reproduction. Aberrant or sustained fear is one of the common clinical manifestations of multiple psychiatric diseases including depression and anxiety. Hypothalamus plays an important role in controlling the expression of fear. Current studies were primarily based on the traditional macroscale brain area-related architecture; thus it is difficult to reflect the complexity of neural cu it formed by highly heterogeneous neurons within the hypothalamus. This project is going to dissect the neural cu it mechanism underlying fear expression from a single-cell basis.

Prof. Haiteng Jiang

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project for Young Scientists

▼ **Digital intelligence precision diagnosis and treatment of severe mental disorders**

In view of the lack of objective and effective classification and diagnosis system for mental diseases, the etiological mechanism is unknown, and other key problems that need to be solved urgently, this project intends to establish a large-scale biological large sample database of major mental disorders (depression/ bipolar disorder/schizophrenia), using EEG data, genetic data, clinical data and multi-dimensional information of clinical assessment, combined with advanced multimodal fusion algorithms and big data retrieval algorithms, to deepen the understanding of the pathological mechanism of severe mental disorders, and develop a digital intelligent precision diagnosis and treatment system for severe mental disorders.

Prof. Aimin Bao

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Construction of human brain bank cooperation network platform in Southeast China**

This project aims to collect high-quality postmortem human brains and related tissues for research. It covers a wide range of neurological and psychiatric disorders as well as controls without brain diseases. All the donations shall have clear informed consent and sufficient medical history. For each case a neuropathological diagnosis report will be made according to the international neuropathological diagnostic standard criteria. All processes are following the international and Chinese ethical laws and regulations, together with the standard operation protocols of international advanced brain banks and of the China Human Brain Banking Consortium. The relevant samples will be sent to brain research groups after approval of a well-documented research proposal. The ultimate aim of this project is to better understand human brain diseases and to provide novel targets for their treatments. In the meantime, a collaborative brain banking network platform will be set up in the Southeastern China (Zhejiang, Anhui, Guangdong, Hainan, etc.). Via providing human brain tissue samples for promoting brain research including China Brain Project, we aim to set up the most precious human brain research infrastructure and technical support platform for brain research in China. In addition, the effects of antemortem parameters on the preservation of molecular subsets (such as DNA, RNA, and proteins) will be determined during the construction of this collaborative network platform, as well as the limits or ava lab 山 ty of advanced neuroscience techniques for human brain tissue study. We will develop the best practice guidelines for quality control and ethics in the construction of human brain banks from sample acquisition, processing and distribution of research.

Prof. Yi Shen

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ **Standardization of Qual ity Control for China's Brain Banking Network**

The core problem of human brain bank construction is what kind of brains can be collected? What kind of brain samples is qualified for brain research? The goal of this project is to establish the standardization of quality control for China's Brain Banking Network, in accordance with international standards, to ensure that China's Brain Banking Network can provide high-quality human brain tissue samples to Chinese brain researches. We will firstly organize a standard quality control team and an academic committee for quality control of neuropathology diagnosis, to supervise the implementation of ethical review and standardized operation of brain tissue processing, storage and sending for research application. In addition, we will supervise and improve the implementation of slice preparation, examination, staining results as well as neuropathological diagnosis. The pathological diagnosis should follow the internationally and domestically recognized diagnostic standards. Secondly, we will regularly carry out relevant training workshops, international and domestic scientific forums on neuropathology to cultivate high-level talents for standard quality control of brain banks. Thirdly, we will build a Digital Pathology Remote Consultation Center that can cover the national brain banks, to improve the quality control and personnel training for China's Brain Banking Network.

Prof. Nai Ding

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ Brain-inspired computational models for language and sequence processing

The project explores the computational neural mechanisms of sequence and language processing through research on brain-inspired mode ling. Mathematical models serve as an important indicator to reflect the development degree of a certain discipline. Accordingly, whether we can describe and explain the phenomena of language evolution with mathematical models is an important indicator reflecting whether we have a valid understanding of the mechanisms underlying language evolution. Efforts to study brain-inspired computational modeling will contribute to complementing the theoretical models of sequence and language processing in offering mathematical description and uncovering possible computational implementation mechanisms. This project plans to build computing models that are more brain-like and can integrate semantic and syntactic information in a better manner, including three kinds of models specifically: a neurodynamic model that matches neuroscience data to describe and explain the differences of distinct species in the capacities to process sequences; a computational model to describe and explain the neurocognitive mechanisms underlying how the human brain integrates semantic and syntactic structures; a brain-inspired computational language model that can integrate syntactic structures, multimodal sensory information, and common sense information.

Prof. Lixia Gao

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ Study on the Brain Mechanism of Speech Development and Speech Communication in Model Animals and the Regulation of Internal and External Factors

Aiming at the scientific problems such as the occurrence, development and neural mechanism of human language, this program uses a variety of animal models (marmosets, mice and birds) to clarify the brain mechanism of animal speech development and speech communication in developmental critical period and adulthood, and to reveal the effects of internal and external factors such as gene and environment on animal speech communication. It includes: (1) the key to the development of budgerigar and the changes of adult speech learning ability, environmental regulation and neural coding mechanism: by comparing the similarities and differences of speech communication behavior, brain mechanism and environmental regulation between budgerigar and marmoset, the evolution process of speech learning and speech communication in different species was clarified from the point of view of comparative biology. (2) effects of speech-related genes on animal speech development and speech communication: the models of transgenic mice and gene-edited marmosets were established to study the role of speech-related genes (such as FOXP2) in speech communication, and to clarify the effects of genes and environment on animal speech development and speech communication. (3) the neural mechanism of environmental influence on speech communication in marmosets during the critical period of development: on the basis of behavioral studies, the cortical neural circuit that produce sounds and perceive conspecific calls during speech communication in marmosets during the critical period of development were further elucidated, and the effects of different speech environments on the plasticity of this neural circuits. (4) Neural characterization of call sequence of marmosets: the neural mechanism of secondary auditory cortex, insular cortex and amygdala to code marmoset calls and call sequences was studied by awake marmoset electrophysiological recording and two-photon calcium imaging.

Prof. Benyan Luo

Science and Technology Innovation 2030 - Brain Science and Brain-Inspired Intelligence Research major project

▼ Evaluation, assistance and rehabilitation of patients with disorders of consciousness based on brain-computer interface

This topic will face the patients with disorders of consciousness, analyze the multi-modal data such as passive multi-sensor stimulation and EEG in sleep state, and develop a brain-computer interface consciousness level evaluation system. Based on active cognitive tasks, build a brain-computer interface multi-dimensional awareness detection system based on emotion induction and recognition and command compliance. Design personalized multi-sensory stimulation and interaction paradigm, and develop multi-modal brain-computer interface assisted communication system. Combined with various neural regulation technologies and active cognitive tasks, a bidirectional closed-loop brain-computer interface wake-up promoting rehabilitation system was built. Establish an integrated platform for brain-computer intelligent awareness assessment, auxiliary communication and rehabilitation, and promote industrialization.

2022 BBMI Selected publications

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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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