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BBMI

Fall and Winter 2024

Research Progress

Brain Navigation:
The Application and Development of Brain Imaging

Message from Chief Scientist

Shumin Duan

Chief Scientist
the BBMI Center

Today, with the rapid development of science and technology, we are increasingly recognizing the brain as the core through which individuals perceive the world. In turn, brain science has built a bridge that deepens our understanding of the relationship between matter and consciousness. We continue to made significant strides not only in comprehensively understanding emotions and feelings and uncovering the mysteries of brain function, but also in laying a solid foundation for the precise treatment of complex disorders and in the related development of more powerful artificial intelligence.

This year marks the Year of the Dragon in the Jiachen cycle, a year in which the BBMI Center has achieved remarkable progress across multiple disciplines, including neuroscience and computer science. Among many other aspects, we have further elucidated the mechanisms of ketamine's action on specific brain regions; discovered new biomarkers for the early diagnosis and staging of Alzheimer's disease; uncovered the detailed mechanisms by which the amygdala complex regulates temporal lobe epilepsy; and created a global trend map of bipolar disorder over the past two decades, bringing new hope to the long-standing challenges of mental health disorders. We have also unveiled the mechanisms underlying dynamic energy supply to the brain; clarified how glial cells regulate neuronal aging and degeneration and how hippocampal pyramidal neurons affect social recognition; leading to breakthroughs in aging and social cognition. In our studies of fear and aggression, we have uncovered new neural circuits that control defensive behaviors through midbrain regulation and basal forebrain projections involved in social anxiety. We have also investigated how food intake regulates fear responses and how the thalamus-amygdala circuit mediates sex-differentiated aggression. With these insights, we no longer fear the unknown. Additionally, we have decoded the structure and molecular mechanisms of the first insect taste receptor and used the fruit fly model to reveal the neuro-coordinated activities of circadian rhythm and temperature regulation. Moreover, through MRI imaging, we have elucidated the processing mechanisms of cortical plasticity in the human brain, significantly improving the quality and accuracy of this imaging technology by introducing medium-waveguides. We have also developed an invasive brain-machine interface system for Chinese character writing. In this, using neural decoding technology, we can convert neural signals into writing trajectories, allowing a robotic arm to write synchronously, thus enabling a high-level paraplegic clinical volunteer to write Chinese characters using only their thoughts. Building on previous years' work, we collaborated with Zhijiang Laboratory to develop the third-generation Darwin brain-like chip, which enhances synaptic connectivity and on-chip learning capacity, offering significant potential for the exploration of novel artificial intelligence hardware.

The BBMI Center aligns with global trends in scientific and technological development and national strategic needs, driving innovation through interdisciplinary research that integrates brain science, brain medicine, and artificial intelligence. Building on a strong scientific research foundation, it focuses on cutting-edge areas such as emotional neural circuits, mental disorders, and brain-machine interfaces, striving to create an internationally leading research platform. The center aims to propel industrial development and achieve world-class breakthroughs in basic research, technological innovation, and translational applications.

The BBMI Center remains steadfast in providing abundant channels for communication and broad development opportunities for talent, working hand in hand with them to shape the future. We have successfully organized the BBMI Annual Academic Conference and the Frontiers in Neuroscience, inviting numerous renowned experts and scholars from both domestic and international fields to share their cutting-edge research achievements and scientific approaches in the center's BBMI distinguished lecture series. Additionally, we have hosted high-level meetings such as the Brain Science and Brain-Like Intelligence Technology Forum , actively engaging young scholars and students to participate, expand their international perspectives, and foster interdisciplinary collaboration.

Three of our teams have won national and provincial natural science awards, while three achievements have been recognized in Zhejiang University's "Top Ten Academic Progresses." Three faculty members were also included in the "Highly Cited Researchers" listed by Clarivate, highlighting the center's strengths and vitality. Furthermore, Professor Hu Hailan is selected as one of Cell Press's "50 Scientiests that Inspire" in the globe serves as an inspiration for all to strive toward greater achievements and pursue their dreams.

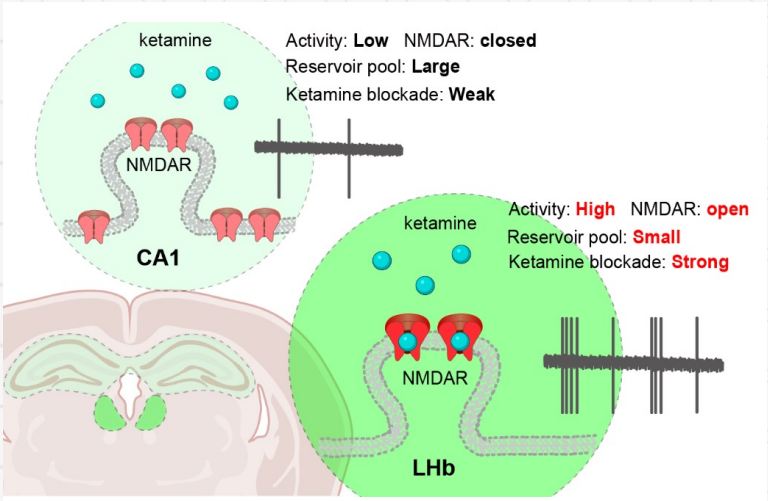
The BBMI Center remains committed to its founding mission of scientific exploration, focusing on the deep integration of basic brain science research and translational applications. Guided by national strategic needs, we prioritize breakthrough research in frontier technologies such as brain-computer interfaces and artificial intelligence, promoting effective translation from basic research to clinical applications. Looking toward the vision of an intelligent society and human health advancement, the BBMI Center continues to deepen international collaboration and engage in high-level scientific research partnerships with global partners. We believe that through our team's persistent efforts, we will make unique contributions in the transformative field of brain science, delivering substantial contribution to human welfare and technological progress.

Locating ketamine's antidepressant effect

Brain region–specific action of ketamine as a rapid antidepressant

Depression is a serious mental illness that significantly threatens human health. The accidental discovery of the antidepressant effects of sub-anesthetic doses of ketamine has revolutionized the field of depression treatment. However, the related neural mechanisms and molecular and brain region targets of ketamine's action, remain unclear.

Covered in two publications in ***Nature*** (2018 and 2023), Professor **Hailan Hu**'s group have elucidated the mechanisms of the rapid and sustained antidepressant effect of ketamine. These studies collectively highlighted the lateral habenula (LHb) as a critical brain region for ketamine's action. In August 2024, Professor Hu's group then published a research article titled *"Brain region–specific action of ketamine as a rapid antidepressant"* in ***Science***. As the third part of their trilogy on ketamine research, this study further answered why the LHb is the primary target region for ketamine's action, further enriching the theoretical framework proposed by this group.



Neural mechanism of brain-region specific action of ketamine

Ketamine specifically inhibits the neurons in LHb

The primary molecular target of ketamine is the NMDA receptor. However, NMDAR is ubiquitously expressed in the brain. This raises an important scientific question: does ketamine simultaneously act on many brain regions, or more specifically target only one or a few primary site(s) which then sets off its antidepressant signaling cascade?

To address this question, researchers administered ketamine to depressive-model mice. One hour after administration, brain slices of LHb and hippocampal CA1 were prepared, and NMDAR-mediated synaptic currents were recorded electrophysiologically. The results revealed that ketamine specifically inhibited NMDAR currents in neurons of LHb, while showing no significant effect in hippocampal pyramidal neurons.

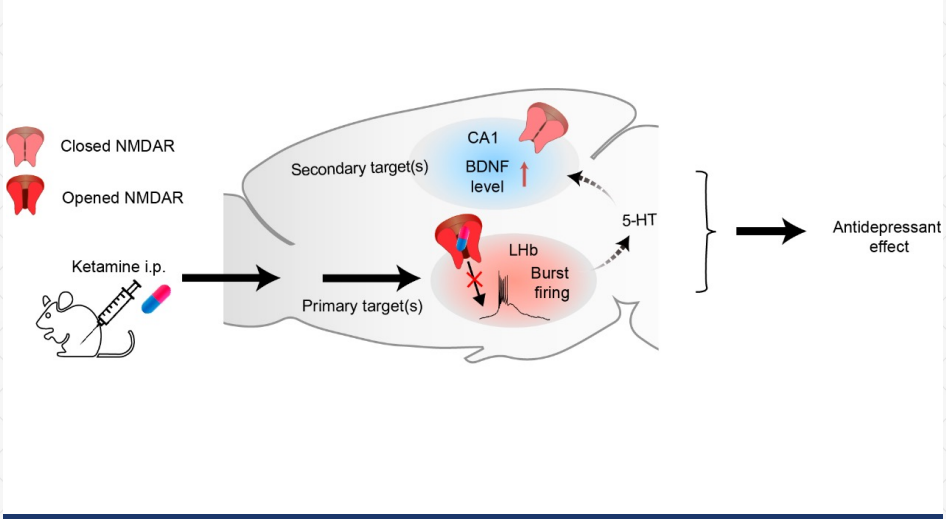
Mechanism of the brain region-specific action of ketamine

Considering ketamine's characteristic as an open-channel blocker, researchers had initially hypothesized that differences in neuronal activity across brain regions could be a contributing factor to this region-specific action. *In vivo* recordings confirmed that, in depressive state, the activity of neurons in LHb was significantly higher than that of hippocampal CA1 pyramidal neurons.

To further validate this hypothesis, researchers employed optogenetic techniques to inhibit the activity of LHb neurons, or used chemogenetic methods to enhance the activity of hippocampal CA1 neurons. These manipulations successfully reversed the ketamine sensitivity of the neurons in these two brain regions.

HAILAN HU'S RESEARCH GROUP

As social animals, our emotions and health are regulated by various social behaviors. The research group led by Hailan Hu is dedicated to investigating the neural bases and plasticity mechanisms of emotions and social behaviors. They employ cutting-edge methodologies, including electrophysiology, optogenetics, and molecular biology, to conduct an in-depth analysis of the neural circuits related to emotions at the nuclear circuit level. Relevant work has been published in internationally renowned journals such as ***Nature, Science*** and ***Cell***.



Antidepressant effect of ketamine

Additionally, the researchers discovered a notable difference between LHb neurons and hippocampal CA1 pyramidal neurons in that the extrasynaptic NMDAR reservoir pool in LHb neurons was significantly smaller than that in hippocampal neurons. They concluded that the brain region-specific action of ketamine depends on the use-dependent nature of ketamine, local neural activity, and the extrasynaptic reservoir pool size of NMDARs.

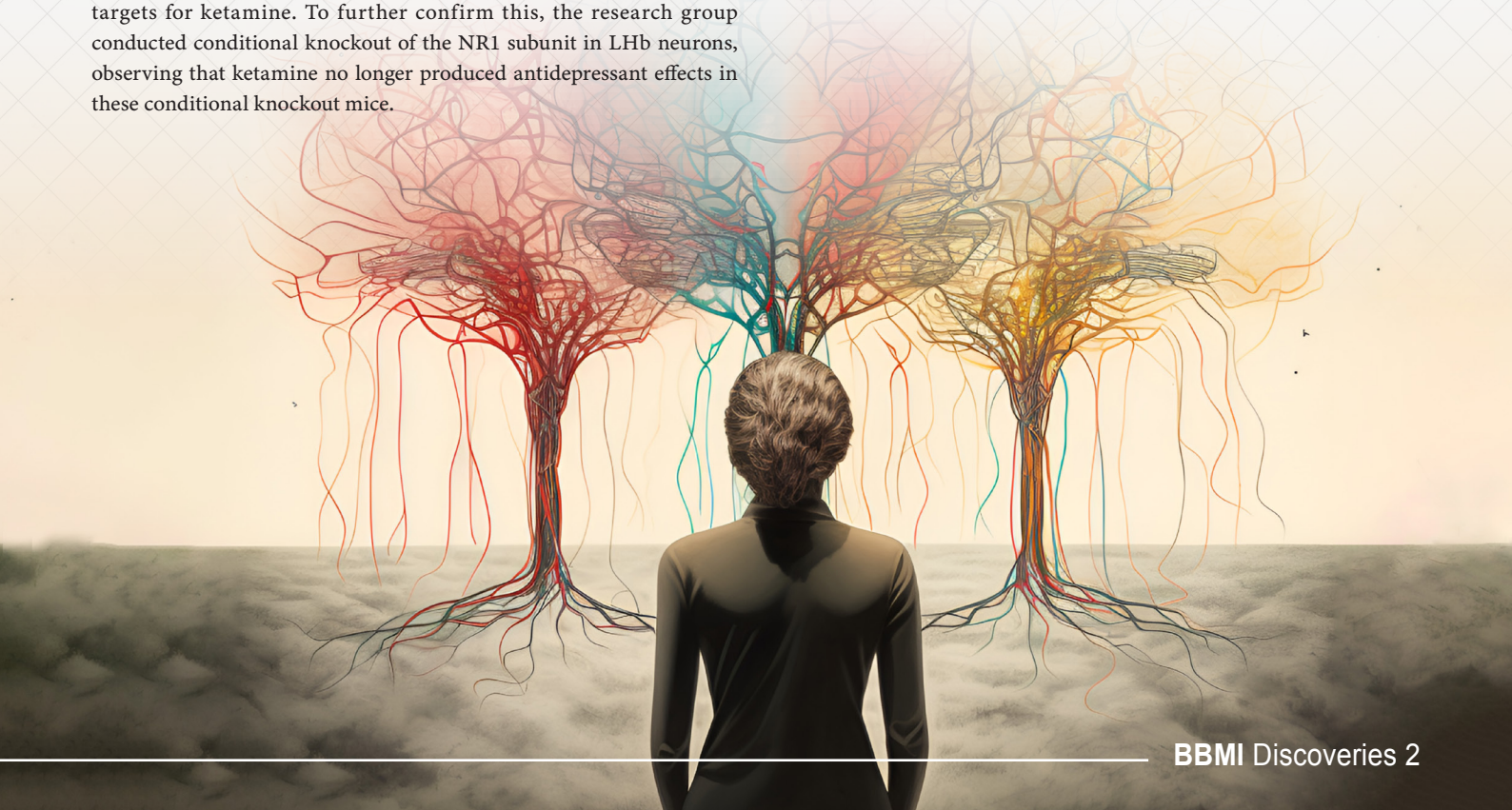
The LHb as the Primary Target Brain Region of Ketamine

The above findings suggest that NMDARs in the LHb are potential targets for ketamine. To further confirm this, the research group conducted conditional knockout of the NR1 subunit in LHb neurons, observing that ketamine no longer produced antidepressant effects in these conditional knockout mice.

Previous studies have suggested that other brain regions are also involved in ketamine's actions. Hu's group found that ketamine leads to an increase in 5-HT and BDNF levels in the hippocampus. However, they found that these ketamine-induced responses were markedly attenuated in conditional knockout mice, suggesting that LHb is the primary brain region, and its effect on the hippocampus, likely represents a downstream response contributing to ketamine's action.

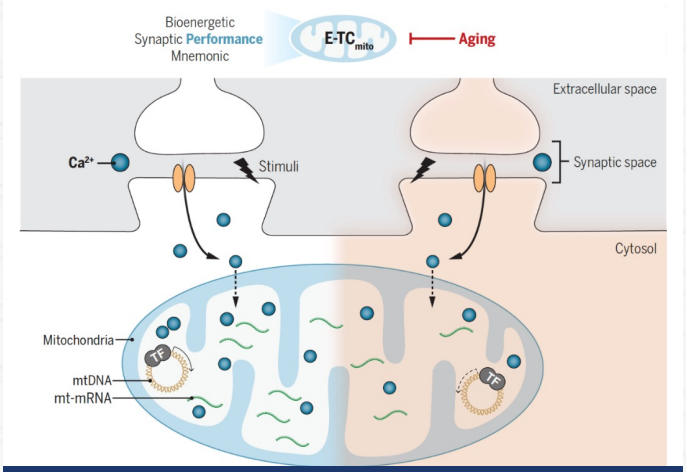
This study was the first to identify the brain region-specific and state-dependent characteristics of ketamine's action, subsequently providing a unified mechanistic explanation. From the perspective of drug properties, it offers a unique angle for researching the antidepressant mechanisms of ketamine and provides theoretical guidance for its clinical use and the development of new antidepressant drugs. The study also explored the cross-talk between the LHb and other brain regions involved in ketamine's antidepressant effects, aiming to connect the theoretical framework proposed by the group with other research in the field. The ultimate goal is to help unravel the mystery of ketamine's antidepressant mechanisms.

Chen, M., Ma, S., Liu, H., Dong, Y., Tang, J., Ni, Z., Tan, Y., Duan, C., Li, H., Huang, H., et al. (2024). Brain region-specific action of ketamine as a rapid antidepressant. ***Science*** 385, eado7010.



Fueling the aging brain

Unveiling mechanisms underlying dynamic brain energy supply: a new path to energy-efficient information processing and combating cognitive aging.



Linking mitochondrial gene transcription with mental activity in an age-dependent manner

As the core organ governing thought and consciousness the brain consumes a highly significant proportion of the body's available biological energy to maintain its critical functions such as learning, memory, and emotion. To maximize energy-efficient operation, the brain must finely regulate this process, achieving massive parallel information processing and storage at as low as possible an energy cost. Whilst this high-efficiency/low-energy capability remains the ultimate goal of supercomputing and AI technologies, the brain's level of efficiency remains currently beyond the technological reach of human engineering. Moreover, energy regulation in the brain is closely tied to human health, the imbalance of which is considered a major risk factor for neurological disorders, particularly in age-related neurodegenerative diseases.

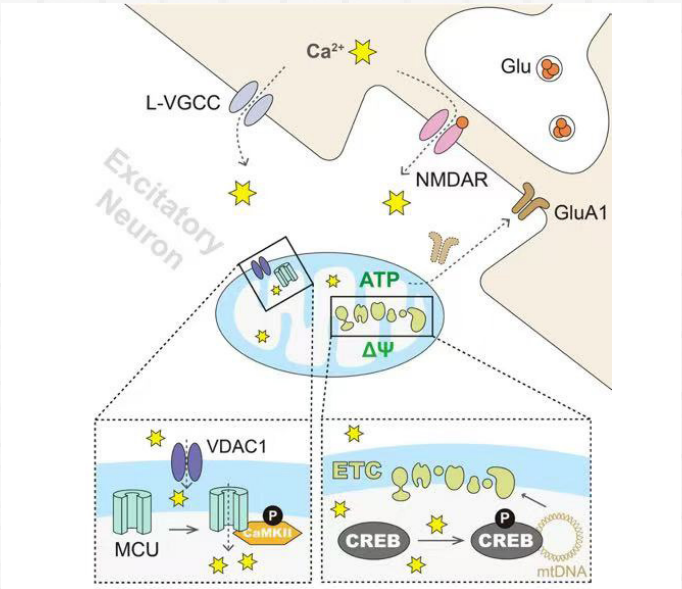
Whether it is the energy crisis posed by AI's high energy consumption or the challenges of cognitive decline in aging populations, these are critical issues for humanity. From a scientific perspective, a better understanding of *"how mammalian brains integrate energy, matter, and information—the fundamental elements of universe"* could offer not only pathways to mimic and potentially even surpass the brain's low-energy/high-efficiency mechanisms, but also opportunities to address age-related challenges. Focusing on this cutting-edge neuroscience question, Prof. **Huan Ma**'s team at Zhejiang University have been investigating the relationship between the neuroplastic regulation of bioenergetics and cognitive aging. Their findings, published in ***Science*** under the title *"Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice"*, provide a novel perspective and theoretical framework for understanding energy-efficient neural computation and may open up potential strategies for combating age-related cognitive decline.

Driving mitochondrial gene transcription with mental activity

The brain's hallmark is its ability to dynamically adjust the strength of neuronal connections based on activity and experience, a mechanism termed 'synaptic plasticity'. This plasticity relies on the activity-driven transcription of nuclear genes which produce new proteins essential for learning and memory. Mitochondria, as the primary energy providers, are unique organelles with their own genome. Mitochondrial transcription is crucial for energy supply and biogenesis. The central question is: Can neuronal activity regulate mitochondrial gene transcription ($E\text{-}TC_{mito}$) in a manner similar to its regulation of nuclear transcription? If so, this coupling could enable coordinated transformation of energy and matter to support

HUAN MA'S RESEARCH GROUP

In Ma lab, we are passionate about studying the brain. Guided by clinical data and using transgenic mouse models, our lab employs electrophysiology, molecular biology, and behavioral analysis to conduct both fundamental and translational research. Our main research focuses include neuroplasticity, learning and memory, aging, and sexual dimorphism. Our findings have been published in prestigious journals such as ***Science, Cell,*** and ***Neuron.***



Fueling memory performance and synaptic resilience via activity-driven mitochondrial DNA transcription

information transmission and storage. Using mouse models, Prof. Ma's team discovered that enhanced neuronal activity, whether during learning or artificially induced, significantly increased mitochondrial gene transcription near synapses. Further investigation revealed that this activity-mitochondrial transcription coupling depends heavily on the mitochondrial calcium influx as induced by neuronal activity. This process is regulated by mitochondrial CaMKII ($CaMKII_{mito}$). Once mitochondrial calcium levels rise, calcium-responsive transcription factor $CREB_{mito}$ binds to the D-loop region of the mitochondrial genome, driving gene transcription. Notably, both CaMKII and CREB are traditionally considered key regulators of nuclear gene transcription. Their newfound role in mitochondria challenges textbook definitions, showcasing their multifaceted functions in the nervous system. By dissecting these mechanisms, the team achieved precise molecular control over activity-driven mitochondrial transcription. They demonstrated that this process is essential for mitochondrial biogenesis, quality control, and the dynamic regulation of energy during neuronal activity. In this way, they have provided a foundation for maintaining both synaptic function and cognitive processes such as learning and memory.

Can "mental exercises" rejuvenate the aging brain?

Research has shown that brain energy supply and cognitive ability decline with aging or neurodegeneration. The team observed that activity-driven mitochondrial transcription coupling weakens in aged brains. Dr. Wenwen Li explains where this understanding led them…*"We speculated whether enhancing this coupling could improve brain function and counteract cognitive aging,"*. Using transgenic mouse models, they then confirmed that suppression of this coupling led to energy deficits and cognitive impairments similar to aging-related neuropathology. To address this, the team developed molecular tools to precisely enhance neuronal activity-mitochondrial transcription coupling. Experiments revealed that prolonged enhancement of this mechanism boosted mitochondrial gene expression during learning, increased energy supply, and significantly improved cognitive performance in aged mice. *"This provides theoretical evidence that mental exercises can counteract brain aging,"* Dr. Li added. Unraveling this fundamental signaling mechanism in neurons not only deepens our understanding of brain function, but also offers a new molecular framework for combating cognitive decline. Related translational research and drug development is now ongoing and beginning to show encouraging early results.

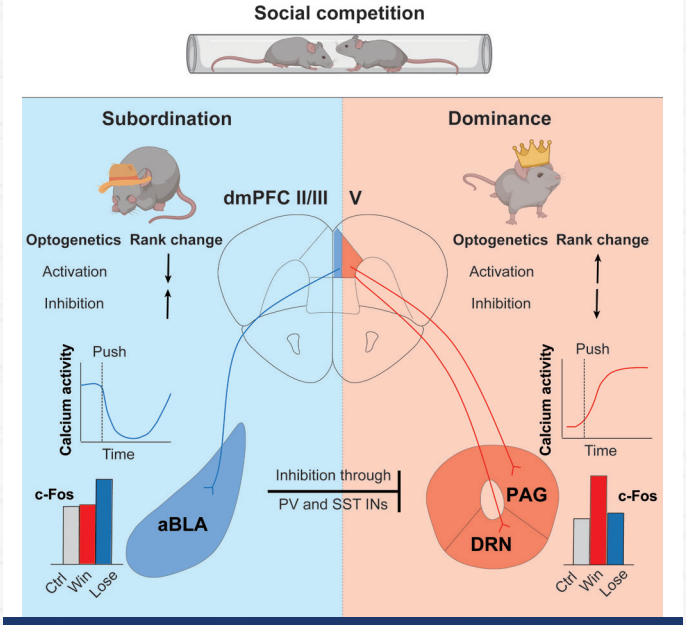
Implications for Energy-Efficient Artificial Intelligence

Elon Musk has highlighted that, beyond chip shortages, energy will be the next bottleneck for AI computation. Could the brain's low-energy information processing inspire solutions to AI's energy demands? Prof. Ma's team have recognized that the evolutionary mechanism of neuronal activity-mitochondrial transcription coupling might hold the key. Unlike traditional computers, which rely on uniform energy supply, the mammalian brain employs a unique *"on-demand"* energy strategy. Mitochondria near synapses act as energy "packets" regulated by local neuronal activity. This discovery suggests that the brain achieves efficient, low-energy computation by dynamically regulating local energy production at each "data node" (synapse). *"Revealing this fundamental coupling mechanism may help AI systems enhance computational efficiency while reducing energy consumption,"* explains Prof. Ma.

Li, W.#, Li, J#., Li, J., Wei, C., Laviv, T., Dong, M., Lin, J., Calubag, M., Colgan, L., Jin, K., et al., Ma, H.*(2024). Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice. ***Science*** 386, eadp6547.

Winning and losing is down to circuit training!

Deconstructing the neural circuit underlying social hierarchy in mice



dmPFC-centric social dominance neural network

Social competition is one of the most common social behaviors in the animal world. It also underlies the basic social organizational structure of social hierarchies. While we know that the dorsomedial prefrontal cortex (dmPFC) plays a fundamental role in regulating social competitions, it remains unclear how the dmPFC orchestrates win- and lose-related behaviors through its downstream neural circuits.

The research team led by Prof. **Hai-lan Hu** has recently published an article titled *"Deconstructing the neural circuit underlying social hierarchy in mice"* in ***Neuron*** on Dec 10th, where they dissect the individual contribution and reciprocal interaction of dmPFC downstream circuits in modulating dominance behavior. This study elucidates that in the dmPFC layer 2/3 neurons projecting to the anterior basolateral amygdala (aBLA) promote losing, whereas layer 5 neurons projecting to the dorsal raphe nucleus (DRN) and periaqueductal gray (PAG) promote winning. Moreover, the lose-related pathway inhibits the win-related pathway through local GABAergic PV and SST interneurons.

In this study, they first systematically screened the c-Fos immunoreactivity patterns in dmPFC downstream brain regions after social competition. They found that winner mice in the tube test competition exhibited a significantly higher number of c-Fos-positive neurons in the dmPFC downstream targets, including the DRN and PAG, whereas loser mice exhibited more c-Fos-positive neurons in the aBLA. Pathway-specific manipulations consistently outlined a dmPFC-centric social dominance neural network in which the dmPFC-DRN and dmPFC-PAG circuits act as win-related pathways. By contrast, the dmPFC-aBLA circuit was seen to act as a lose-related pathway. Interestingly, the activation or inhibition of the aBLA itself yielded similar effects as the manipulation of the dmPFC-aBLA pathway. Accordingly, these win- and lose-related dmPFC circuits showed opposing calcium activities respectively, when mice initiated "effortful" push behaviors in the tube test competition. Further, retrograde tracing study revealed these functionally divergent pathways as anatomically segregated, with the lose-related aBLA-projecting neurons located in layer 2/3 and the win-related DRN- and PAG- projecting neurons located in layer 5 of the dmPFC. The team then further confirmed layer 2/3 neurons to be activated by losing, the optogenetic activation of these neurons leading to competitive failure in mice. Conversely, layer 5 neurons were seen to be activated by winning, with such activation of these neurons leading to competitive success. Finally, *in vivo* electrophysiological recordings demonstrated that lose-related neurons (layer 2/3 projecting to the aBLA) inhibit the win-related neurons (layer 5) whereas win-related neurons (layer 5 projecting to the DRN) do not have any corresponding effect upon lose-related neurons (layer 2/3). This indicates the presence of a one-way functional connection and inhibitory effect from the lose-related neurons to the win-related neurons. *In vitro* brain slice electrophysiology confirmed the existence of this synaptic connection. Activation of the lose-related neurons (layer 2/3 projecting to the aBLA) led to larger inhibitory postsynaptic currents (IPSCs) than excitatory postsynaptic currents (EPSCs) as recorded in the win-related neurons (layer 5 projecting to the DRN), further confirming this inhibitory effect. Such an inhibitory effect was concluded to be jointly mediated by the PV and SST interneurons within the dmPFC.

One interesting speculation of the function of this unidirectional interaction is that a losing mentality may dominate over winning during competitions once animals initiate the idea of quitting or withdrawing from the rivalry. Such an inhibition of the win pathway from the lose pathway may help them execute the idea to end the fight quickly to avoid harm or injury. Such antagonistic interplay may represent a central principle in how the mPFC orchestrates complex behaviors through top-down control.

Xin, Q.#, Zheng, D., Zhou, T., Xu, J., Ni, Z., Hu, H*. (2024) "Deconstructing the neural circuit underlying social hierarchy in mice", ***Neuron*** , doi:10.1016/j.neuron.2024.11.007.

HAILAN HU'S RESEARCH GROUP

Dedicated to studying the neural basis and plasticity mechanisms of emotion and social behavior. They use cutting-edge techniques including imaging, electrophysiology (both *in vitro* and *in vivo*), molecular genetics, and optogenetics to conduct deep analysis of emotion- and social behaviors- and their related neural circuits.

How the brain regulates sex differences in aggressive behavior

A circuit logic for sexual dimorphic aggression in mammals

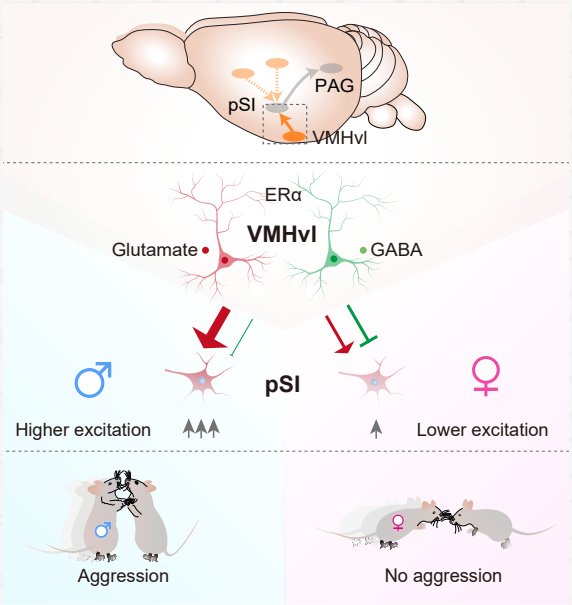
Aggressive behavior is a fundamental instinct that animals rely on to compete for resources, establish dominance, and protect themselves and their groups. It serves as a crucial means to cope with survival and reproductive pressures. Interestingly, significant differences exist in aggression between males and females, males being typically more outwardly aggressive than females across many species. This includes humans, where men often display higher levels of outward aggression than women. While the VMHvl is recognized as a key brain region controlling aggressive behavior, the mechanisms by which it outputs different levels of aggression in male and female animals have remained a mystery.

On July 16, 2024, Academician **Shumin Duan** and Professor **Yanqin Yu**'s team from the School of Brain Science and Brain Medicine at Zhejiang University published a groundbreaking study in the prestigious journal ***Neuron***, titled *"A Hypothalamic-Amygdala Circuit Underlying Sexually Dimorphic Aggression"*. Their research unveils a neural circuit that regulates sex-specific aggressive behavior in mammals involving the pathway from the ventrolateral part of the ventromedial hypothalamus (VMHvl) to the posterior substantia innominata (pSI). In male animals, this circuit exhibits stronger excitatory and weaker inhibitory inputs, leading to increased overall excitability in the downstream pSI region, which in turn results in heightened aggressive behavior.

The research team firstly began by using chemogenetic techniques to activate estrogen receptor-expressing neurons in the VMHvl ($VMHvl^{Esr1}$ neurons). They discovered that the activation of these neurons significantly enhanced aggressive behavior in male mice, while female mice showed little to no change. This finding suggested that $VMHvl^{Esr1}$ neurons play a pivotal role in mediating aggression in males. Further investigation revealed that these neurons primarily project to the pSI region, a part of the extended amygdala known to be involved in emotional processing.

By blocking the activity of pSI neurons, the researchers were then able to inhibit the aggressive behavior induced by the activation of $VMHvl^{Esr1}$neurons. This demonstrated that the pSI is a critical downstream target for the VMHvl in mediating aggression. Additionally, they found that $VMHvl^{Esr1}$ neurons influence the periaqueductal gray (PAG) via the pSI, collectively facilitating the occurrence of aggressive behavior.

Surprisingly, the projections from $VMHvl^{Esr1}$ neurons to the pSI include both excitatory and inhibitory components. However, electrophysiological recordings showed that in male mice, the excitatory projections are stronger and the inhibitory projections weaker, leading to increased overall excitability in the pSI region. This imbalance in excitation and inhibition was concluded to be potentially a key neural mechanism underlying the stronger aggression observed in males. To determine whether this overall excitatory difference exists practically in freely socializing mice, the team conducted *in vivo* electrophysiological recordings of neuronal activity in the pSI. Their results confirmed that male mice receive stronger overall excitatory input from $VMHvl^{Esr1}$ neurons to the pSI than female mice. This heightened excitatory input makes pSI neurons more excitable, thereby inducing stronger aggressive behavior in male mice.



The neural circuit from VMHvl to pSI exhibits stronger excitatory and weaker inhibitory inputs in males

Therefore, this pattern of behavior regulation through the excitation-inhibition balance in such brain circuits provides an exciting new window in the understanding of the neural mechanisms behind sex differences in aggression. It also offers fresh perspectives for comprehending social behaviors and sex-related behaviors more broadly. Since the hypothalamus and amygdala regions are relatively conserved across mammals, this study provides a valuable reference for understanding any brain diseases that display sexual dimorphism and may particularly inform research into conditions such as aggression-related psychiatric disorders that exhibit sex-specific prevalences or characteristics.

Zhu, Z. *, Miao, L. *, Li, K., Ma, Q., Pan, L., Shen, C., Ge, Q., Du, Y., Yin, L., Yang, H. and Xu, X., 2024. A hypothalamic-amygdala circuit underlying sexually dimorphic aggression. ***Neuron***, 112(18), pp.3176-3191.

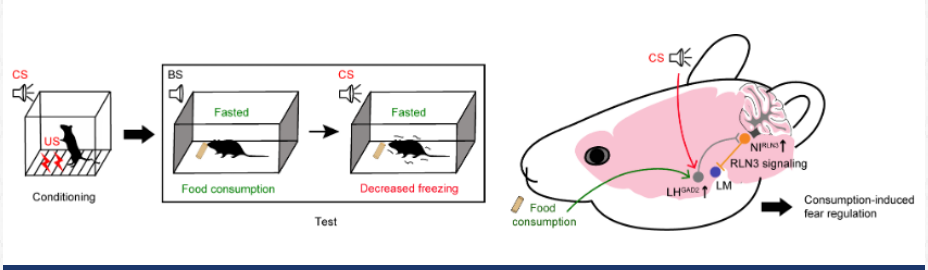
SHUMIN DUAN & YANQIN YU'S RESEARCH GROUP

Specialize in the study of instinctive behaviors and their underlying neural circuits and are dedicated to unveiling how the brain regulates complex behaviors such as sleep and emotions. They employ a variety of advanced technological approaches including chemogenetics, optogenetics, and electrophysiology to uncover the functions and mechanisms of related neural circuits.

Self-preservation is for the well fed!

The hypothalamic–hindbrain circuit implicated in consumption–induced fear regulation

Survival requires organisms to balance nutrient intake with danger avoidance. Many adaptive behaviors take this into account. While energy acquisition drives feeding behavior, exposure to threat induces fear, which can inhibit feeding. For survival, in order to facilitate food consumption, fear may sometimes require active regulation. However, the mechanisms underlying this phenomenon remain unclear.



Theory model of consumption-induced fear regulation mediated by lateral hypothalamic→nucleus incertus→lateral mammillary nucleus circuit

On September 4, 2024, Prof. **Xiao-Ming Li**'s team from the School of Brain Science and Brain Medicine, Zhejiang University published a study in ***Nature Communications***. This study identified a lateral hypothalamic (LH) →nucleus incertus (NI) →lateral mammillary nucleus (LM) circuit involved in modulating fear responses during food consumption.

Consumption-induced fear regulation with LH^{GAD2} involvement

Our researchers first developed a fear-feeding assay, showing a reduction in fear-conditioned stimuli (CS)-induced freezing behavior during food consumption in male mice. Given that the hypothalamus, particularly the LH, is a crucial brain region for processing and balancing potentially conflicting behaviors, researchers examined whether the LH mediated consumption-induced fear regulation.

The results of *Fos* gene analysis revealed a significant increase in the activity of LH^{GAD2} neurons following the fear-feeding assay. GCaMP recordings similarly showed increased LH^{GAD2} activity when fasted mice were exposed to CSs during food consumption. Conversely, LH^{GAD2} GCaMP activity exhibited no significant changes when well-fed mice responded to CSs or when fasted mice began consuming food prior to CS presentation. *Ex vivo* brain slice recordings also revealed that food consumption enhances the excitability of LH^{GAD2} neurons, significantly increasing their activity post-CS presentation. These findings highlight the potential role of LH^{GAD2} neurons in mediating consumption-induced regulation of learned freezing fear responses.

LH^{GAD2}-NI involvement in consumption-induced fear regulation

Our researchers then identified the outputs of LH^{GAD2} neurons that mediate fear regulation through food consumption. Neural tracing and RNAscope experiments revealed that LH^{GAD2} neurons project to the relaxin-3 (RLN3)-positive neurons in the NI. In turn, some NI^{RLN3}-projecting LH^{GAD2} neurons express the *VglutT2* gene. Eelectrophysiological recordings showed that the photogenetic activation of LH^{GAD2} terminals induces excitatory and inhibitory postsynaptic currents in the same NI neurons, activating these postsynaptic neurons. *Fos* gene analysis showed that NI-projecting LH^{GAD2} neurons were activated following the fear-feeding assay. Similarly, LH^{GAD2}-NI GCaMP activity increased as conditioned mice were exposed to CSs during food consumption. Optogenetic manipulation further demonstrated that LH^{GAD2}-NI circuit activity is both necessary and sufficient for food consumption regulation of learned fear. These findings suggest that the LH^{GAD2}-NI pathway mediates consumption-induced fear regulation.

NI^{RLN3} neurons and their LM outputs/RLN3 signaling mediating consumption-regulation of fear

Finally, our researchers confirmed that NI^{RLN3} neurons and their LM outputs/RLN3 signaling mediate consumption-induced fear regulation. NI^{RLN3} neurons were specifically activated following fear-feeding assay and responded to CSs during food consumption. CS-induced increase in NI^{RLN3} activity was also confirmed as controlled by LH outputs. Optogenetic manipulation of NI^{RLN3} activity bidirectionally regulated fear expression during food consumption, and NI^{RLN3}→LM projection mediated this regulation. Neural tracing confirmed that LM-projecting NI^{RLN3} neurons were innervated by LH^{GAD2} neurons, and behavioral experiments showed that RLN3 signaling in the LM partially mediated the fear regulation function of LH^{GAD2}→NI pathway.

Overall, this study found that fear expression is reduced during food consumption, via the involvement of the LH^{GAD2}→NIRLN3→LM pathway regulation mechanism.

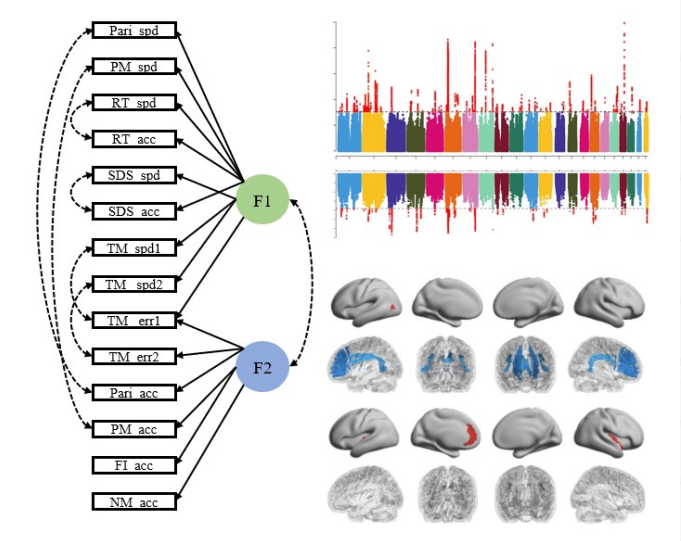
Wang Q.#, Sun R.Y.#, Hu J.X., Sun Y.H., Li C.Y., Huang H.Q., Wang H.*, Li X.M.* (2024) 'Hypothalamic-hindbrain circuit for consumption-induced fear regulation', ***Nature Communications***, 15(1): 7728.

XIAO-MING LI'S RESEARCH GROUP

Facing the significant demand for clinical diagnosis and the call for positive intervention in mental disorders, Xiao-Ming Li's research group focuses on the pathogenesis and clinical translation research of anxiety disorders, depression, and other mental illnesses. They are active in elucidating the pathological mechanisms mediating the occurrence of mental disorders, screening objective diagnostic markers and new therapeutic targets, and establishing new strategies for early prevention, diagnosis, and treatment. Relevant work has been published in journals such as ***Cell, Nature Medicine, Nature Neuroscience*** and others.

Cognitive processing speed and accuracy are intrinsically different in genetic architecture and brain phenotypes

Distinct genetic and neurobiological foundations of cognitive speed and accuracy



Genetic basis for cognitive processing speed and accuracy and genetic association with neuroimaging phenotypes

In psychology and cognitive neuroscience, accuracy and reaction time in specific tasks are commonly used to assess cognitive abilities, reflecting two fundamental dimensions, namely the speed and accuracy of cognitive processing. Cognitive processing speed measures how quickly individuals perceive and process information, typically assessed via reaction time or total task completion time. Cognitive processing accuracy requires coordination of multiple cognitive processes, such as attention and working memory. Variations in these factors have been significantly linked to various cognitive behaviors and mental disorders. Studying their underlying brain structures and genetic bases aids in understanding the mechanisms of cognitive functions and the neurobiological foundations of mental disorders.

The present study used Genomic Structural Equation Modeling (GenomicSEM) based on GWAS data from 14 cognitive measures to estimate cognitive processing speed and accuracy. The results revealed that cognitive measures could be categorized into two latent factors associated with speed and accuracy, respectively. More specifically, the study identified 118 SNPs related to cognitive processing speed and 55 SNPs related to accuracy. Among the 101 known SNPs for cognitive processing speed, 30 were linked to cognitive ability, 24 to intelligence, with reaction times significantly associated. For accuracy, 54 SNPs were related to cognitive ability and intelligence, with one new SNP identified.

Further investigation explored the relationship between these cognitive factors and brain structure. Cognitive processing speed was significantly associated with white matter microstructure, while its links to cortical structure were minimal. Key brain regions involved in speed were concentrated in the visual cortex, which was considered likely attributable to the visual nature of the tasks used. However, accuracy was related to both the anterior cingulate cortex and insula, areas closely associated with executive control and error monitoring.

Additionally, both speed and accuracy exhibited significant genetic correlations with lifestyle and health factors (e.g., smoking, alcohol consumption, sleep, and mental health).

Enrichment analysis revealed that cognitive processing speed was significantly associated with postsynaptic membrane activity, while accuracy was linked to neurogenesis. Gene expressions related to speed were prominent during infancy, a critical period for white matter myelination, whereas accuracy-related genes did not show particularly significant heightened expression at any age. Cell-type specific analysis revealed strong associations with GABAergic cells for both factors, but with each having distinct cell-type foundations.

Finally, using adolescent developmental data from the ABCD study, the research estimated the contribution of genetic scores for these factors to seven cognitive abilities. Findings revealed that cognitive processing speed and accuracy is significantly contributed to multiple cognitive abilities, including language, reaction time, working memory, and executive control. Moreover, these factors differed in their contributions to crystallized and fluid intelligence, with speed favoring fluid intelligence and accuracy more related to crystallized intelligence.

In summary, this study utilized GenomicSEM to reveal two latent cognitive factors—processing speed and accuracy—that differ in their respective neuroimaging features, genetic structures, and associations with behavioral and mental health phenotypes. These findings provide new insights into the neurobiological foundations of cognitive abilities and the relationship between brain health and cognitive development in children.

Li M[#], Dang X, Chen Y, Chen Z, Xu X, Zhao Z, Wu D*. Cognitive processing speed and accuracy are intrinsically different in genetic architecture and brain phenotypes. ***Nature Communications.*** 2024 Sep 6;15(1):7786.

DAN WU'S RESEARCH GROUP

Wu's research group focuses on the development of MRI sequences and medical image processing methods. They have made significant contributions to areas such as the development of fast high-resolution imaging sequences, diffusion MRI for microstructure imaging, and fetal and infant brain imaging. Their work has been published in journals including ***PNAS, Science Advances, Nature Communications,*** and ***Radiology***.

The role of the amygdaloid complex in temporal lobe epilepsy

Neural circuit mechanisms of the posterior basolateral amygdala in regulating temporal lobe epilepsy

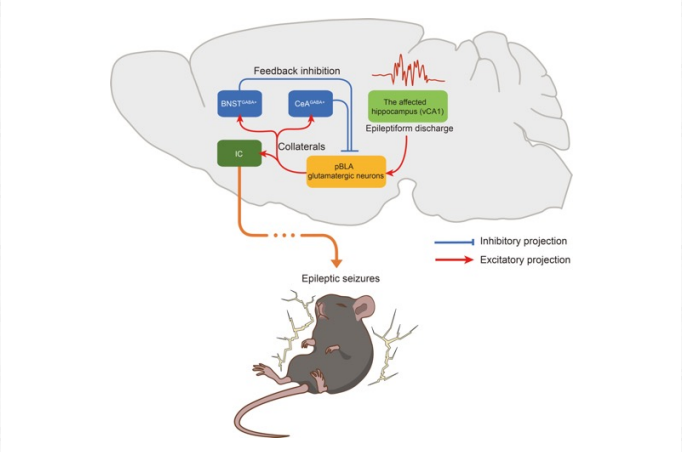
Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy in adults. It is characterized by abnormal neuronal discharges originating in one or more anatomical regions in the temporal lobe (primarily the hippocampus, amygdala, or entorhinal cortex). These abnormal epileptic discharges then spread to other brain regions through interconnected neuronal networks, leading to seizures. Whilst TLE is drug-resistant, neurosurgery remains an effective potential treatment option. However, successful surgical treatment relies on the identification of the precise origin and propagation network of TLE. This is problematic as our understanding of the key neural networks remains limited and imprecise, being largely based on macroscopic scales (e.g., magnetic resonance imaging, intracranial electrode recordings). Such course measurements leave the precise circuit connections that initiate and sustain the spread of epileptic discharges unclear.

On October 30, 2024, the team led by Prof. **Xiao-Ming Li** and **Jiadong Chen** from the School of Brain Science and Brain Medicine, Zhejiang University published a research paper titled *"Posterior Basolateral Amygdala is a Critical Amygdaloid Area for Temporal Lobe Epilepsy"* in ***Advanced Science***. The study revealed the posterior basolateral amygdala (pBLA) as a critical nucleus within the amygdaloid complex active in the regulation of TLE. It also uncovered the distinct roles of the upstream and downstream neural circuits of the pBLA in the modulation of epileptic seizures.

Studies on TLE patients and animal models have reported that the amygdaloid complex is a key brain region controlling TLE. However, the amygdaloid complex consists of multiple nuclei. Within these, the specific nuclei and neural circuits that regulate seizures remain unknown.

In their study, the authors found that optogenetic activation of glutamatergic neurons in the pBLA led to severe seizures and even death. In contrast, activation of glutamatergic neurons in the anterior basolateral amygdala (aBLA) failed to cause any such epileptiform discharges or seizure behaviors. Using anterograde tracing with adeno-associated virus (AAV), the authors then discovered that it is pBLA glutamatergic neurons specifically that collaterally project to multiple downstream brain regions, including the insular cortex (IC), bed nucleus of the stria terminalis (BNST), and central amygdala (CeA). Results of *in vivo* fiber photometry then indicated the calcium activity of the collateral-projecting pBLA glutamatergic neurons was synchronized with EEG signals during acute seizures, correlating their activation with the duration of seizure events.

Among the downstream brain regions of pBLA, the IC was then identified as a critical brain region for pBLA glutamatergic neurons to drive seizures. Apoptosis of IC neurons significantly alleviated seizures induced by pBLA glutamatergic neuron activation. The BNST and CeA are primarily composed of gamma-aminobutyric acid (GABA)ergic neurons. Through viral tracing, RNA fluorescence in situ hybridization, and patch-clamp electrophysiology, the authors found that $BNST^{GABA+}$ and CeA^{GABA+} neurons provide feedback inhibition to pBLA glutamatergic neurons. In normal mice, apoptosis of $BNST^{GABA+}$ or CeA^{GABA+} neurons led to sporadic seizures, suggesting feedback inhibition from these regions to be important



The role of pBLA glutamatergic neurons and their collateral projections in regulating epileptic seizures in TLE

to balance the activity of pBLA glutamatergic neurons. Using rabies virus (RV)-mediated retrograde monosynaptic tracing, the authors found that pBLA glutamatergic neurons receive excitatory inputs from the ventral hippocampal CA1 (vCA1). Optogenetic activation of the vCA1-pBLA neural circuit then induced seizures, demonstrating the vCA1 as a crucial excitatory source driving pBLA glutamatergic neurons to generate seizures. Finally, the authors established mouse models of acute seizures and chronic TLE induced by kainic acid (KA) injection into the hippocampus. This confirmed that apoptosis of pBLA glutamatergic neurons effectively alleviated both acute and chronic seizures in these animal models.

In conclusion, these findings uncover novel circuit mechanisms of pBLA in regulating epileptic seizures in TLE and have the potential to lead to the development of more precise and effective interventions targeting neural circuits for the treatment of TLE.

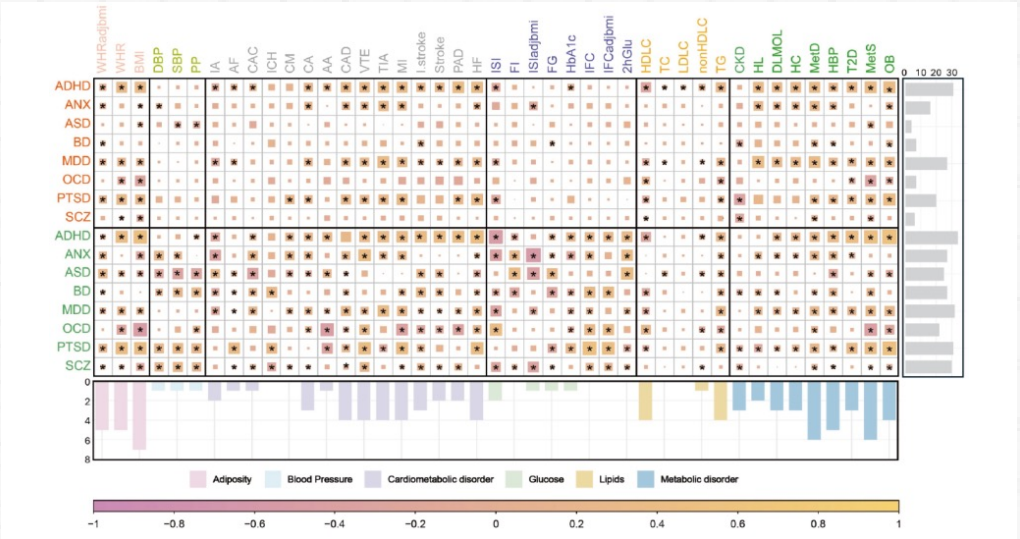
Sun YH#, Hu BW, Tan LH, Lin L, Cao SX, Wu TX, Wang H, Yu B, Wang Q, Lian H, Chen J*, Li XM*. Posterior basolateral amygdala is a critical amygdaloid area for temporal lobe epilepsy. ***Advanced Science***. 2024 Oct 30:e2407525. doi: 10.1002/advs.202407525.

XIAO-MING LI'S RESEARCH GROUP

The group focuses on the pathogenesis and clinical translation of psychiatric disorders such as anxiety and depression as driven by abnormal fear expression. The team aims to identify objective diagnostic biomarkers and new therapeutic targets to provide effective and precise treatment strategies for such conditions.

Unravelling the psycho-metabolic nexus:

Shared genetic architecture and bidirectional clinical risks within the psycho-metabolic nexus



Genetic correlation in psycho-metabolic nexus

Increasing evidence suggests that there is a complex interplay between psychiatric disorders and metabolic dysregulations. However, most research has been limited to specific disorder/dysregulation pairings, leaving a significant gap in our understanding of the broader psycho-metabolic nexus.

The research team led by Prof. **Shaohua Hu** has recently published an article entitled *"Shared genetic architecture and bidirectional clinical risks within the psycho-metabolic nexus"* in ***eBioMedicine*** on Dec 27, 2024. The study highlights the intertwined genetic and clinical relationships between psychiatric disorders and metabolic dysregulations, emphasizing the need for integrated approaches in diagnosis and treatment.

Their study leveraged large-scale cohort data and genome-wide association study (GWAS) summary statistics, covered 8 common psychiatric disorders, and included 43 metabolic aspects (19 metabolic traits, 9 metabolic disorders, and 15 cardiometabolic disorders). Based on GWAS data, this study introduced a comprehensive analytical strategy to identify shared genetic bases sequentially ranging from key genetic correlation regions to local pleiotropy and pleiotropic genes. Finally, this study developed polygenic risk score (PRS) models to translate these findings into clinical applications.

Based upon a cohort of 310,848 participants from the UK Biobank, this study identified significant bidirectional clinical risks between psychiatric disorders and metabolic dysregulations. Genetic correlation analysis confirmed 104 robust trait pairs, revealing 1,088 key genomic regions including critical hotspots such as chr3: 47588462-50387742. Cross-trait meta-analysis uncovered 388 pleiotropic single nucleotide variants (SNVs) and 126 shared causal variants. Among these variants, 45 novel SNVs were associated with psychiatric disorders and 75 novel SNVs were associated with metabolic traits, shedding light on new targets to elucidate the mechanism of comorbidity. Additionally, this study uncovered key pleiotropic genes, such as *RBM6, APEH, ARIH2, HYAL3, MST1, P4HTM, RNF123, UBA7,* and *WDR6*, which play critical roles in gene regulation and metabolic processes. These genes were identified to be those primarily associated with the hyaluronan metabolic process and cellular stress response pathways. For their phenotypic associations, these genes were associated with a wide range of phenotypes including brain morphology, psychiatric disorders, metabolic profiles, autoimmune conditions (e.g., inflammatory bowel disease), and behavioural traits (e.g., cognition, sleep, and alcohol consumption).

Building on genetic correlations between psychiatric disorders and metabolic traits, this study further highlighted new therapeutic targets including HDAC and mTOR inhibitors, for managing the comorbidity of psychiatric disorders with metabolic disorders. Clinically, by integrating clinical risk results with genetic associations, the team focused on 4 psychiatric disorders (MDD, BD, SCZ, and ANX) and 3 metabolic dysregulations (BMI, T2D, and CAD) as either exposure or outcome to construct 24 PRS model profiles. When psychiatric and metabolic genetic information was integrated, these PRS models demonstrated enhanced predictive power.

The study highlights the intertwined genetic and clinical relationships between psychiatric disorders and metabolic dysregulations, emphasising the need for integrated approaches in diagnosis and treatment.

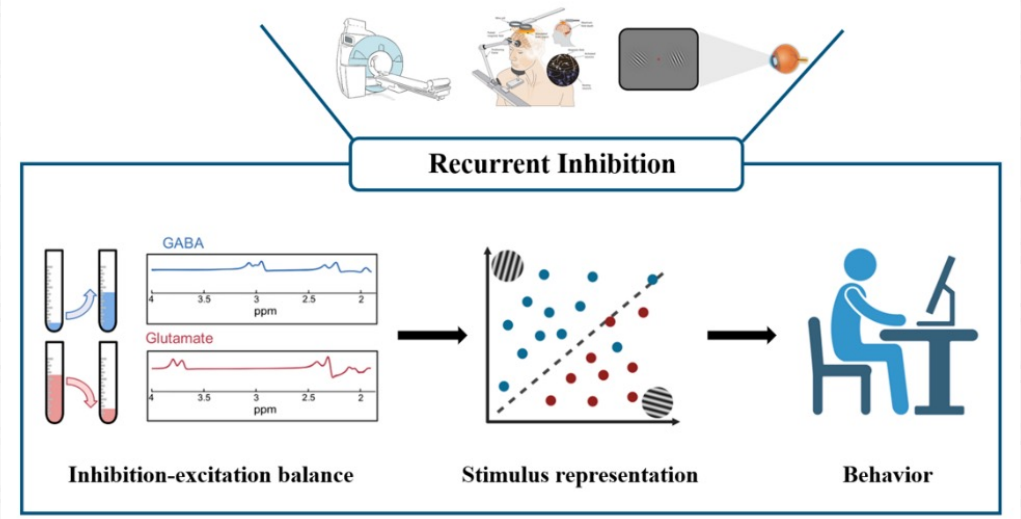
Guo X#, Feng Y#, Ji X#, Jia N#, Maimaiti A, Lai J, Wang Z*, Yang S*, Hu S*, 2025. Shared genetic architecture and bidirectional clinical risks within the psycho-metabolic nexus. ***eBioMedicine*** 111, 105530. https://doi.org/10.1016/j.ebiom.2024.105530

SHAOHUA HU'S RESEARCH GROUP

The research team of Shaohua Hu focuses on the field of biological and clinical psychiatry. They have long been committed to researching the pathogenesis, biomarkers, and emerging diagnostic and therapeutic methodologies of affective disorders, especially bipolar disorder and depression. The team is also devoted to clinical transformation of findings from pre-clinical research in order to provide innovative scientific evidence for precise psychiatry.

Recurrent inhibition for perceptual plasticity

Recurrent inhibition refines mental templates to optimize perceptual decisions



Recurrent inhibition: an integrative brain plasticity mechanism for improving perceptual decisions
GABAergic inhibition drives improved perceptual decisions by strengthening task-relevant representations through recurrent processing in visual cortex

The idea that the human brain solves complex tasks by forming mental templates as internal representations of key information relevant for behaviour, has intrigued psychologists and neuroscientists since such ideas were presented by the influential American philosopher William James. Training is thought to help the brain refine these templates, thereby enhancing perceptual decision-making processes. However, exactly how the brain achieves this remains debated. We still lack a comprehensive account of the experience-dependent plasticity mechanisms that support adaptive decision-making.

On July 31, 2024, **Ke Jia** and his research group published a research article in ***Science Advances***, entitled *"Recurrent inhibition refines mental templates to optimize perceptual decisions"*. This research introduces the recurrent inhibition of an integrative brain plasticity mechanism for improving perceptual decisions. The team capitalized on state-of-the-art ultra-high-field (7T) MRI to introduce a multimodal brain imaging approach, combining fMRI at submillimeter resolution with magnetic resonance spectroscopy (MRS) to investigate interactions between fine-scale functional and neurochemical plasticity mechanisms. Participants were trained on an orientation discrimination task for five consecutive days with their performance tested before and after training both in and outside the 7T scanner. Researchers leveraged the submillimetre resolution of 7T laminar fMRI to interrogate plasticity mechanisms across cortical depths that are known to be associated with dissociable neural computations. Their findings showed that training alters orientation-specific representations in superficial (rather than middle or deeper) V1 layers by enhancing the representation distance (i.e., increasing discriminability of trained vs. untrained representations) rather than by reducing representation variance for the trained orientation. In this way, they were able to provide evidence for recurrent experience-dependent plasticity. The team proposed that these refined mental templates represent familiar orientations in a fine-tuned manner and relate to improved perceptual discrimination.

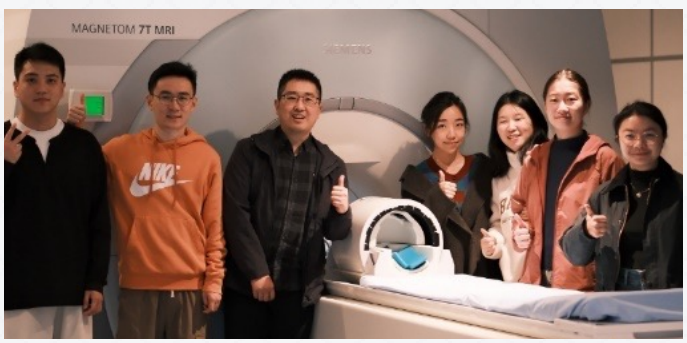
Furthermore, quantification by MRS confirmed increased GABAergic inhibition following training in the early visual cortex, correlating with behavioral enhancements. Modelling neurochemical and functional plasticity interactions revealed that training alters GABAergic inhibition in the visual cortex that drives improved perceptual judgments by strengthening orientation-specific representations (i.e., discriminability of the trained orientation as indicated by representation distance) in superficial V1 layers.

Collectively, these findings provide compelling evidence for a recurrent inhibitory plasticity mechanism for perceptual learning. Combining multimodal UHF brain imaging with information-based analysis, this study underscores the pivotal role of recurrent inhibition in refining information processing towards optimized perceptual decisions. Training refines mental templates by fine-tuning the representation of task diagnostic features (i.e., trained orientation), suppressing similar orientations across cortical columns via horizontal connections in superficial layers of the primary visual cortex. Uncovering these multimodal plasticity mechanisms at the intersection of neurochemical and functional signals provides novel insight into bridging a knowledge gap between animal and human brain circuits that support human learning and adaptive behavior.

Jia K[#]*, Wang MX[#], Steinwurzel C, Ziminski JJ, Xi Y, Emir U, Kourtzi Z*. Recurrent inhibition refines mental templates to optimize perceptual decisions. ***Science Advances***. 2024 10 (31), eado7378.

KE JIA'S RESEARCH GROUP

Utilizing a multidisciplinary approach that integrates psychophysics, computational modelling, ultra-high field fMRI, and TMS, Ke Jia's research group investigates how training shapes our perception, decision-making, and working memory systems.



What are the specific phenotypic differences between the two mechanisms of learning that lead to increased neural representation distances and decreased variability? While experimental results have provided supportive evidence for the first hypothesis, were there any related experiments conducted for the hypothesis of decreased variability?

Ke Jia: The specific differences between learning-induced increases in neural representation distances or decreases in variability can be explored by conducting principal component analysis on the responses of different voxels in the primary visual cortex to three orientations of visual stimuli across different trials and projecting them into high-dimensional space. If learning causes an increase in representational distances between different orientations of stimuli, the Mahalanobis distance between the reaction distributions of different orientations in high-dimensional space will increase. However, if learning leads to a decrease in neural activity variability, a reduction in the variance of the reaction distributions to different orientations of stimuli will be observed. The results of this experiment support the hypothesis of increased representational distances, where no reduction in the variance of reaction distributions to different orientations of stimuli was found.

How does ultra-high field magnetic resonance spectroscopic imaging (MRS) technology recognize the release of different neurotransmitters? What role does the inhibitory-excitatory balance play in the learning process?

Ke Jia: MRS technology identifies the concentration of different neurotransmitters in specific brain regions based on differences in electron cloud distribution around hydrogen nuclei in various chemical substances. This leads to varying degrees of shielding of the hydrogen nuclei and, consequently, to differences in resonance frequencies (i.e., chemical shifts). In this experiment, we used MRS to measure the changes in the content of the inhibitory neurotransmitter (GABA) and excitatory neurotransmitter (Glutamate) in the early visual cortex before and after learning. We found that perceptual training mainly increased the concentration of GABA in the perceptual cortex, while the concentration of Glutamate remained unchanged. Combined with functional MRI results, it is speculated that learning may change the concentration of GABA in the perceptual cortex, affecting its tuning curve for different orientations of stimuli, enhancing the selectivity of responses to different orientations of stimuli, and thereby improving individual performances in discrimination tasks.

The recording of neural signals has made significant progress in terms of temporal and spatial precision. This has supported computational methods facilitating fine-grained encoding in information processing. However, current neural manipulation techniques can only manipulate the activation or inhibition of groups of neurons relatively coarsely. This seems to pose a challenge to the causal validation of functional gain or loss. Will neural manipulation and neural encoding recording continue to develop separately, or will they eventually verify and promote each other as they develop?

Ke Jia: In the field of neuroscience, there are various recording technologies operating at different spatial scales. These range from single-cell recordings to local field potentials, optical imaging, and magnetic resonance imaging. There are also corresponding control technologies operating at similar spatial scales including optogenetics, transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). The emergence of these novel recording and control technologies is highly likely to foster mutual advancement, thereby deepening our understanding of the neural mechanisms underlying various cognitive processes.

It seems that the current decoding of neural encoding in the human brain still uses machine learning algorithms. Does the proposal of more neural encoding methods help improve artificial intelligence algorithms? In what way will the information processing mechanisms of the human brain participate in the enhancement of machine information processing capabilities?

Ke Jia: I do not have an in-depth understanding of the field of artificial intelligence, but I believe that the decoding of human brain neural encoding mechanisms can promote the development of the artificial intelligence field in the following ways. First, the human brain has extremely low energy consumption, only tens of watts, and understanding its neural encoding mechanisms can help artificial intelligence save energy. Second, although many current deep learning networks perform excellently in image recognition, they have weak resistance to interference. The exploration of human brain neural encoding mechanisms is expected to lead to enhancements in the resistance to interference for deep learning networks. Third, there is still controversy about whether deep learning networks or large language models can achieve general artificial intelligence. Understanding the neural encoding mechanisms of the human brain may therefore provide assistance in the development of general artificial intelligence.

How is 7T achieved, what are the special site and technical requirements? How is the trade-off made between signal-to-noise ratio and spatial resolution? How is the difference in spatial resolution between MRS and fMRI bridged?

Ke Jia: Ultra-high field (7T) fMRI, as a non-invasive magnetic resonance technology, is based on the principle that when neuronal activity increases in specific brain areas, local blood flow rises, and the proportion of deoxygenated hemoglobin in the blood decreases. Since deoxygenated hemoglobin is a paramagnetic substance, it causes magnetic field inhomogeneity and accelerates the dephasing of hydrogen nuclei, leading to a weakening of T2-weighted image signals. Conversely, a decrease in the proportion of deoxygenated hemoglobin will enhance the strength of T2-weighted image signals, thus establishing a correlation between neural activity and magnetic resonance signal intensity.

Under specific experimental effect sizes, the higher the spatial resolution, the stronger the required signal-to-noise ratio or the more experimental trials needed. However, head movement of individuals during magnetic resonance significantly interferes with signal signal-to-noise ratio, so the number of experimental trials is generally fixed. The signal-to-noise ratio of magnetic

resonance technology mainly depends on the strength of the static magnetic field. Traditional 3T magnetic resonance imaging technology has a spatial resolution of about 8 - 27 mm^3, whereas 7T ultra-high field magnetic resonance can reach 0.1 - 0.5 mm^3, and the most advanced 11.7T or 14T magnetic resonance can achieve a spatial resolution of 0.01 - 0.1 mm^3.

There is a significant difference in spatial resolution between MRS and fMRI. To establish a relationship between the two, the following three methods were used: First, the relationship between inter-individual MRS signal variability and fMRI signal variability was calculated. Results showed that the greater the increase in GABA for the subjects, the more significant the enhancement of selectivity in the sensory cortex's response to stimuli of different orientations, thereby establishing a correlation between them. Second, using tDCS technology to influence the GABA concentration in the perceptual cortex on a macroscopic scale, it was found that changes in GABA concentration do indeed affect the selectivity of individual perceptual cortex responses to stimuli of different orientations. Third, a neural network model was constructed and trained to perform the same visual tasks. In this it was found that there is a correlation between inhibitory neural activity within the network and the network's selectivity in response to the stimuli of different orientations.

BBMI 2024

Research Progress

>20 Approved **RESEARCH PROJECTS**

>15 **NATIONAL NATURAL SCIENCE FOUNDATION PROJECTS**

3 Zhejiang Provincial Science and Technology Department ***PIONEER & LEADING GOOSE*** **R&D KEY PROJECTS**

38 **GRANTED PATENTS**

>160 Published **ACADEMIC PAPERS**

>50 Published **HIGH-LEVEL PAPERS**

Awards and Honors BBMI 2024

Elsevier 2023 Highly Cited Scholars in China

Hailan Hu
Biology

Shumin Duan
Basic Medicine

Tao Li
Clinical Medicine

National Natural Science Award

2nd Prize

Hailan Hu Team

"Neural Mechanisms of Depression Induced by Negative Emotions and Social Competition"

Zhejiang Provincial Natural Science Award

2

1st Prize

Yan Zhang Team

"Structure and Function of G Protein-Coupled Receptor Signal Transduction"

3rd Prize

Lijun Kang Team

"Physiological and Pathological Mechanisms of the Perception of Environmental Cues"

Zhejiang University 2023 "Top 10 Academic Advances"

3

Hailan Hu Team

"Neural Mechanisms of Depression Induced by Competitive Defeat and the Sustained Antidepressant Effects of Ketamine"

Ge Bai Team

"Abnormal Stress Granules as a Key Mechanism in Peripheral Neuropathy"

Yan Zhang Team

"Perception Mechanisms of Carbon-Carbon Double Bonds and Cannabinoid Molecules"

Asia Pacific APNNS Award

Huajin Tang
Asia Pacific Neural Network Society Outstanding Achievement Award

National Advances in Optics Award

Hongtao Lin
Top 10 Advances in Optics in China for 2023 (Applied Research Category)

Zhejiang University Yongping Teaching Award

Aimin Bao
Nominated for the 10th Yongping Teaching Contribution Award at Zhejiang University

Zhejiang University ZHU Kezhen Scholarship

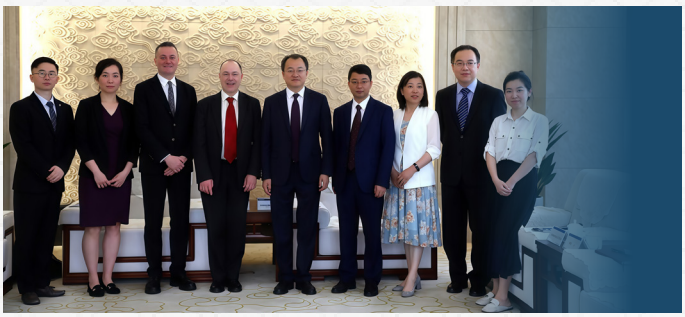
Yuying Liao
PhD student of the 2020 cohort awarded the 2023-2024 Graduate ZHU Kezhen Scholarship

Platform Construction

We have strengthened collaboration and communication with the affiliated hospitals of the School of Medicine. Together, we successfully obtained approval for five key laboratories from Zhejiang Province. In May, The Affiliated Hospital of the school of Brain Science and Brain Medicine, Zhejiang University was inaugurated. The goal of the institute is to explore a new model for the integration of basic research, clinical research, translational research, and industrial development in the brain science and brain medicine.

The Affiliated Hospital of the School of Brain Science and Brain Medicine, Zhejiang University

International Exchange



In May, DU Jiangfeng, President of Zhejiang University, met with a distinguished delegation from the University of Southampton, led by President and Vice-Chancellor Mark Smith and Vice-President International and Engagement Andrew Atherton. The delegation also toured the School of Brain Science and Brain Medicine's laboratories, gaining a more insightful understanding of Zhejiang university's cutting-edge technological prowess and scientific advancements in related fields.

Since the inception of a cooperation memorandum in 2013, the two universities have enjoyed robust collaborations in the fields of humanities, marine sciences, and medicine. We looked forward to honing in on specific areas of cooperation and expanding education and research collaboration in more fields such as brain medicine, green marine science, and computer science.

In November, Dean Diana Eccles and Vice Dean Ruihua Hou of the University of Southampton School of Medicine visited School of Brain Science and Brain Medicine. Both sides conducted further in-depth discussions on the institutional mechanisms for international cooperation and plans for future collaborative efforts.


Ronggui “Cory” Hu

New Faculty Member

Ronggui “Cory” Hu joined the BBMI center of ZJU as a distinguished professor in 2024. He primarily focuses on the mechanistic and translational study of protein homeostasis and human diseases, including but not limited to ASD (autism spectrum disorders) and cancer. Along the way, he and his team have made significant contribution to understanding of the etiology of ASD by unraveling the key roles of dyregulated retinoic acid signaling in ASD subtypes of distinct genetic and environmental associations. Substantial efforts of the team are now being dedicated to targeted intervention into the disorders. Through mechanism-based study, they are innovating and applying multiple synthetic biology approaches to probing into biological processes and providing novel tools of therapeutic potential as well.


Zhihua Gao

Talent Program

Zhihua Gao, selected for the National Talent Program in 2024, is interested in how the neuroendocrine and neural-immune network controls basic brain functions and how it is implicated in brain diseases. Her work aims to characterize the fundamental mechanisms underlying the maintenance of brain homeostasis and identify potential targets involved in homeostatic dysregulation in brain diseases.

Donations

BBMI 2024

We are deeply grateful to all our sponsors for their generous support. This support has not only created a more focused and conducive research environment for the center to explore the "core" issues in the field of brain science but also greatly inspired faculty and students to engage in deeper brain science research.

These funds will be used to reward the faculty and students from ZJU who have made significant contributions in the areas of brain science research, clinical practice, translational outcomes, and social services. Additionally, some of the funds will be specifically allocated to support academic exchanges, publicity, and promotional activities in the field of brain science.

Hangzhou Bai Mai Xing Technology Co., Ltd.

20,000 RMB

Baiaogu Biotechnology (Hangzhou) Co., Ltd

20,000 RMB

Shenzhen Reward Life Technology Co., Ltd.

10,000 RMB

Shanghai Qing Sheng Biotechnology Co., Ltd.

10,000 RMB

Donation Contact

brains@zju.edu.cn

The BBMI Academic Seminars

2024 Second Half

Robert FROEMKE

New York University

June 25th, 2024

Love, death, and oxytocin: the challenges of mouse maternal care

Luyang WANG

University of Toronto

September 13th, 2024

Targeting nonselective cation channels to mitigate ischemic brain injury

Zirlinger MARIELA

Neuron

September 25th, 2024

A behind-the-scenes look at the Peer-Review process: Publishing with *Neuron* and *Cell Press*

Yingxi LIN

UT Southwestern Medical Center

September 25th, 2024

Cellular memories in active neuronal ensembles

Wencheng XIONG

Case Western Reserve University

October 30th, 2024

How does drinking rapidly quench thirst?

Peter STERN

Science

November 12th, 2024

The manuscript selection process at *SCIENCE*

For neuroscientist Hailan Hu, embracing new challenges is key to both personal and professional growth

Hailan Hu

Dr. Hu, PhD, of the Zhejiang University School of Medicine was selected as one of the ***Cell Press*** 50 Scientists that Inspire for her work in understanding emotions, social behaviors, and psychiatric diseases from a molecular genetic standpoint.

Dr. Hu is a professor and dean of the School of Brain Science and Brain Medicine at Zhejiang University. She has also held positions at the Chinese Academy of Sciences as a principal investigator and at the University of California San Francisco as a postgraduate researcher. She has received many awards, including the IBRO-Kemali Prize, L'Oreal-UNESCO Women in Science International Award, and New Cornerstone Investigator Award.

Dr. Hu's education spans multiple disciplines, countries, and states, including a BS in Biochemistry and Molecular Biology from Beijing University and a PhD in Neuroscience from the University of California, Berkeley. Her postdoctoral training included work at the Cold Spring Harbor Laboratory in New York and the University of California, San Diego.

In her lab, Dr. Hu and her team explore the neural mechanisms underlying social behaviors and psychiatric diseases. In this Q&A, she encourages aspiring scientists to explore different disciplines early in their careers and opens up about the challenges of balancing research and administrative responsibilities as a scientist.

As part of the celebrations for our 50th anniversary, *Cell Press* is honored to feature 50 notable scientists who inspire us.

Editors at each of our journals across the sciences have nominated scientists whose research and careers drive innovation, cross boundaries, and inspire the leaders of the future.

01

What does innovation in science look like to you?

Hailan Hu: To me, innovation is not just about inventing something entirely new. It is about connecting existing, seemingly unrelated dots to unravel mysteries, challenge existing paradigms, and generate something truly novel. It requires curiosity, intuition, and analytical rigor, and it often involves blending insights from different disciplines.

02

What inspired you to become a scientist?

Hailan Hu: For my generation in China, when we were kids, almost everyone wanted to grow up to become a scientist or a writer, as they were portrayed as the most glorious and exciting careers. As I progressed through school, I found myself doing much better in math and physics than in literature courses. So it felt like a logical choice to pursue a science-related major.

Along the way, I was fortunate to encounter exceptionally supportive and inspiring teachers and mentors, like Corey Goodman and Roberto Malinow, who nurtured my interests. They continue to motivate me at every stage of my career.

03

Tell us about a moment of discovery that has been a highlight of your career.

Hailan Hu: One such moment occurred several years ago when two exceptionally talented postdoctoral researchers in my lab were independently conducting research related to depression. One discovered a regional effect of a drug in antidepressant behavior, while the other identified a depression-related firing pattern in neuronal cells.

Initially, we didn't connect these findings. But one day, while I was sitting in a conference, a speaker mentioned a published result from his lab—it was like a bolt of lightning struck. His work enlightened me that there could be an immediate mechanistic link that connects our team's two results. Right away, I texted people in the lab to plan an experiment testing this connection.

When the results panned out, showing that this link did in fact exist, we were all thrilled. Our findings led to the discovery of a new conceptual framework to explain ketamine's antidepressant effects. Such experience underscored the beauty of scientific discovery, where seemingly disparate findings can come together in a most unpredictable way and coalesce into a beautiful and coherent new understanding.

04

Are there barriers or hurdles you face in your career? How do you navigate them?

Hailan Hu: Currently, balancing research and administrative responsibilities as a school dean and center director is a major challenge. My administrative role requires me to serve the community, secure resources, and foster talent growth, whereas my true passion lies in conducting research and mentoring students in the lab. To deal with this challenge, maintaining open communication and collaboration within my team and with external partners has been instrumental. Learning to delegate responsibilities to capable team members has also proven invaluable.

05

What are you most excited about in your field right now?

Hailan Hu: I'm particularly enthusiastic about current research into the mechanisms of rapid-acting psychiatric drugs like ketamine and psychedelics. These studies represent more than just conventional pharmacological research—they offer direct pathways to delve into the fundamental brain mechanisms underlying psychiatric disorders.

Psychiatric disorders have traditionally been challenging to understand due to their slow progression, complex symptoms, and multifaceted genetic origins. However, rapid-acting drugs provide a unique opportunity—a shortcut, if you will—to delve into the core mechanisms of these diseases. Their swift onset and potent effects allow researchers to bypass secondary effects and directly target the primary factors involved in a disease's cause and development.

Understanding the primary molecular targets of these drugs, alongside insights gained from localized drug application and circuit manipulation studies, promises to illuminate new avenues for diagnosis, prevention, and treatment strategies for mental disorders. This reverse translational approach holds immense promise for transforming our understanding and management of psychiatric conditions.

06

Do you have words of wisdom for students thinking about science?

Hailan Hu: I would encourage students considering a career in science to step outside their comfort zones, embrace a variety of experiences, and explore different disciplines and perspectives early in their careers. Accumulating varied experiences early on is like connecting different "dots." Eventually, these diverse experiences can coalesce into sources of creativity and innovation, enabling novel connections and breakthroughs in scientific inquiry.

In my own journey from graduate school to my postdoctoral lab, I transitioned from molecular genetics to electrophysiology and behavior. At first, it was really challenging to start from scratch in a new field. But despite the initial difficulties, this transition has proven to be one of the most rewarding and beneficial decisions of my career. In hindsight, my multidisciplinary scientific training has uniquely equipped me to approach system neuroscience questions from a molecular genetic standpoint—a perspective that has allowed me to shape a distinctive niche for my work.

So, for any aspiring scientist, I would like to emphasize the importance of being open to new challenges, seize opportunities to diversify one's skill set, and view each new experience—no matter how daunting—as a valuable step toward personal and professional growth.

What do you think the next 50 years will look like for your field?

07

What changes would you like to see?

Hailan Hu: Looking ahead 50 years, I envision a transformative era for neuroscience and the broader field of medicine, akin to the advancements seen in cancer treatment over recent decades. Cancers that were once considered incurable have now become manageable chronic conditions through precision medicine, and I believe we are on the cusp of achieving similar breakthroughs for brain disorders.

Neuroscientists are making remarkable strides in understanding the mechanistic underpinnings and brain targets of diseases like Alzheimer's, Parkinson's, depression, schizophrenia, and autism. These insights are paving the way for the development of new drugs and innovative treatment strategies. In the next half-century, I anticipate that what are currently viewed as debilitating and devastating brain disorders can be effectively treated or even cured.

Brain Navigation

The Application and Development of Brain Imaging

Prof. Dong Li

School of Life Sciences,
Tsinghua University.

Engaged in the development of optical microscopic imaging technology and its application in life science research. Has a particular focus on developing super-resolution fluorescence microscopy imaging technology suitable for in *vivo*, high-speed, long-term, and low-damage applications.

Prof. Kai Wang

Center for Excellence in Brain Science and Intelligence Technology,
Chinese Academy of Sciences.

Has developed a range of new technologies, including adaptive optics microscopy, lattice light-sheet microscopy, light-field microscopy, and *in vivo* super-resolution imaging microscopy.

Prof. Guo Hua Shi

Distinguished Core Researcher at the Suzhou Institute of Biomedical Engineering and Technology,
Chinese Academy of Sciences.

Committed to the research of *in vivo* optical imaging and detection methods. As the chief scientist, provides stable support for young scientist teams in basic research fields and major projects such as the National Major Scientific Instrument Development Special Project.

Prof. Ke Si

BBMI,
the School of Brain Science and Brain Medicine,
Zhejiang University.

Dedicated to the structural and functional analysis of neural networks. Develops advanced microscopic imaging techniques to study information communication and regulatory mechanisms between neural networks, transparent brain technology, and three-dimensional imaging.

01 What significant role does brain functional imaging play in current neuroscience research? What distinctive contributions does this technology offer in unveiling the cerebral information processing mechanisms and deciphering the operational patterns of neural circuits?

Kai Wang: Brain functional imaging stands as a pivotal tool in neuroscience research, spanning applications from macroscopic functional magnetic resonance imaging (fMRI) to microscopic optical microscopy. These advanced technologies enable real-time observation of dynamic neural circuit changes and facilitate the mapping of the brain's overall activity patterns. Their unparalleled and indispensable nature in elucidating neural mechanisms has garnered widespread recognition.

Dong Li: Brain functional imaging is actually a complex technical system that covers scales from whole-brain functional MRI to optical calcium imaging, voltage imaging, and so on, from macroscopic to mesoscopic to microscopic scales. However, there is currently a lack of technology that can seamlessly integrate different spatial and temporal scales. Exploring the relationship between neural activity and behavior, especially on a large spatial scale, remains a frontier challenge.

Guohua Shi: The future direction may include more advanced technology applications, such as magnetoencephalography (MEG). Compared to traditional fMRI, MEG has advantages in sensitivity and signal capture speed. In the future, it is expected to be combined with structural MRI or CT and other technologies for disease localization analysis and real-time reaction research.

02 In deep imaging, the scattering of light in complex brain tissue and associated lack of clarity is a major challenge. What new technologies can help overcome this problem?

Kai Wang: Recent brain transparency technologies provide new solutions for deep imaging. For example, one research team at Stanford University has significantly reduced light scattering by enhancing tissue transparency through chemical methods. This approach demonstrates the potential for *in vivo* tissue transparency, providing new directions for the further development of deep imaging.

Dong Li: Adaptive optics (AO) technology also provides a key to enhance the resolution of deep imaging. By correcting wavefront distortions, AO can improve imaging results. However, if transparency technology can be more maturely applied to brain tissue, it will surely become a powerful bridge between deep imaging and modern optical technologies.

Guohua Shi: Another direction worth noting is imaging technology for turbid tissues, which does not require transparency treatment but can still detect signals in tissues about 10 millimeters deep. If this technology can break through theoretical bottlenecks, it will achieve non-destructive imaging of deep brain tissue, providing greater flexibility for basic research.

Roundtable Forum

03 With the development of imaging technology, the surge in data volume and increased processing difficulty, can artificial intelligence (AI) and deep learning effectively address these challenges?

Kai Wang: AI has shown a lot of promise in pulling out neural activity data, classifying behaviors, and aligning data across different modalities. However, future development needs to address the issue of data standardization to ensure collaborative analysis across different modalities.

Dong Li: The biggest challenge right now is standardizing data processing. There are differences in data processing methods between laboratories, and this inconsistency poses obstacles to the promotion of AI methods. Therefore, it is necessary to establish unified standards across the industry to promote the universal application of AI.

Guohua Shi: Firstly, AI is undoubtedly a direction for future development, especially with great potential in assisting classification, segmentation, and data analysis. However, AI is essentially a statistical tool that can only help process data and cannot solve all problems independently, especially in the fields of brain science and medicine. A major issue is the standardization and unification of models. Although AI can achieve excellent results on specific datasets, the effectiveness may not be guaranteed when applied to other datasets. Therefore, establishing universal, unified standards and models remains a significant challenge for the application of AI in these fields. Particularly in brain science, AI methods may perform well on certain specific datasets, but ensuring that these methods can be widely applicable and interpretable is an urgent problem to be solved. Another issue is data standardization. In different laboratories, data processing methods vary. Sometimes the data shared is not even the most original data. This inconsistency further complicates the difficulty of establishing unified standards and universal models. Therefore, while AI offers many possibilities in data analysis, achieving widespread application and general acceptance of standardized processes within the industry is unlikely to occur quickly or easily.

Ke Si: The challenges of data analysis reflect the current necessity for close collaboration in interdisciplinary fields, especially between biology and data science. From animal behavior modeling to brain functional imaging, the increasing volume of data has made issues of data collection, storage, and analysis far more prominent. Particularly, how to effectively compress and process this massive data has seen some progress with deep learning methods. The core issue remains how to establish standards to ensure the applicability and accuracy of models, especially for specific data types. Moreover, biologists typically focus on key points or core data when analyzing data, rather than getting bogged down by large amounts of raw data. This necessitates close collaboration between data scientists and neuroscientists, where mutual knowledge complementarity is crucial. Data scientists may lack in-depth understanding of the biological field, while biologists need advanced analytical methods to extract deeper information from data. Therefore, interdisciplinary collaboration will be key to advancing this field.

04 Promoting interdisciplinary collaboration in brain science is one of the important missions of the BBMI Center. How do the experts view the significance and prospects of this collaborative model?

Kai Wang: Interdisciplinary collaboration is an inevitable trend in promoting scientific development. The complexity of brain science requires researchers to integrate multiple perspectives from technology, theory, and application to jointly advance innovation.

Dong Li: Every aspect of brain science research, from data collection to analysis and technical application, requires cross-field collaboration. Only by integrating the strengths of multiple disciplines can we comprehensively uncover the mysteries of the brain.

Guohua Shi: Interdisciplinary collaboration involves not only the integration of technology and biology but also the deep participation of multiple fields such as medicine and engineering. Through the fusion of these fields, we can develop more practical research tools and promote progress in both basic and clinical research.

Ke Si: Interdisciplinary research is an inevitable trend in scientific development, but effectively promoting this collaboration still faces many challenges. First, researchers need to break down disciplinary boundaries and actively step out of their comfort zones. For example, researchers in neuroscience need to learn the principles of optoelectronic technology, while researchers in optoelectronics should pay attention to the practical needs of neurobiology to better promote scientific progress. Secondly, the evaluation system and mechanisms need to be adjusted. Currently, some disciplines have overly stringent requirements for research outcomes, making it difficult to adapt to the characteristics of interdisciplinary research. Setting up more flexible evaluation systems that support long-term, meaningful research is really important. Additionally, interdisciplinary research demands high resources and has high trial-and-error costs, thus requiring support involving research funding, equipment, and time. Although interdisciplinary research places higher demands on researchers' psychological resilience, its outcomes are more innovative and competitive in the job market, which is precisely its appeal.

Brain functional imaging and precision neural regulation: From basic research to clinical application

Interview with Professor Wei Deng

What are the main current clinical applications of brain functional imaging technologies, and what problems do they primarily address?

Wei Deng: Mechanistically, current brain functional imaging techniques primarily provide an indirect reflection of local brain activity through blood oxygen imaging and radioactive tracer imaging. The former includes functional Magnetic Resonance Imaging (fMRI) and functional Near-Infrared Spectroscopy (fNIRS). In these, when a brain region becomes more active, the proportion of oxygenated hemoglobin increases and changes in its magnetization and light absorption characteristics can then be detected. Radioactive tracer imaging, meanwhile, requires the use of radioactive tracers to track changes in the metabolism of substances such as glucose. These imaging tools generally have high spatial resolution but lower temporal resolution. Additionally, there are neuro-electrophysiological tools that reflect brain function, such as high-density electroencephalography (EEG) and magnetoencephalography (MEG). These tools provide very high temporal resolution, down to the millisecond level, but have lower spatial resolution.

Currently, these technologies are primarily applied in two main areas in clinical practice. On one hand, they are used for the diagnosis and assessment of functional brain disorders. In clinical practice, the same diagnosis may present with different symptoms, and similar symptoms may be attributed to different diseases. In such cases, identifying whether the same brain networks are damaged and the extent of the damage can provide new diagnostic criteria and frameworks. This aligns with the Research Domain Criteria (RDoC) proposed in the U.S. for precision medicine in mental disorders, which advocates integrating scientific evidence and biomarkers from multiple biological fields to seek objective characterization of the symptoms or phenotypes being studied. On the other hand, these technologies offer insights into disease mechanisms. At present, the etiologies of most psychiatric disorders are unclear, and functional imaging findings indicate that cognitive deficits and complex symptoms often cannot be attributed solely to a single dysfunctional brain region. Basic and clinical research in both animal models and humans have demonstrated that functional impairment involves multiple areas within particular circuits or even across the entire brain functional networks.

What are the characteristics of brain functional imaging in patients with depression? How can brain functional imaging assist in the diagnosis and treatment of depression?

Wei Deng: A single symptom often lacks practical diagnostic value; rather, it is the grouping of multiple symptoms that share common patterns of disease progression—known as a symptom constellation or syndrome—that serves as an important clinical basis for diagnosing psychiatric conditions. Within such a syndrome, there can be different layers of symptoms, including core symptoms, accompanying symptoms, and additional symptoms, all of which together form the rich clinical features of the disease.

Functional imaging can distinguish healthy individuals from patients with psychiatric disorders based on identifiable brain imaging characteristics. Research shows that specific psychiatric symptoms correlate, to some extent, with changes in certain brain circuits. However, functional neuroimaging findings are often difficult to replicate, and the high heterogeneity of psychiatric disorders further complicates the task of pinpointing which specific disease is present based on imaging changes alone. Because syndromes are composed of relatively stable combinations of symptoms, it is worth considering whether their corresponding brain network imaging patterns might have greater value for auxiliary diagnosis. When we accumulate sufficient data—together with essential clinical annotations—it may become possible to redefine psychiatric diagnoses based on brain functional imaging and other objective results. This "cross-diagnostic" research approach is particularly valuable in moving the field forward.

Given the rapid progression and high relapse rates of depression, current neuroregulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), require precise modulation of key brain regions. Brain functional imaging can provide intuitive guidance for clinicians. For example, our research found that the amygdala shows abnormal hyperactivity in both depression and anxiety patients, and where depression patients exhibit characteristic overactivity in the subgenual anterior cingulate cortex (sgACC). However, because these regions lie deep within the brain, regulating them involves challenges of energy dissipation, making direct and precise stimulation difficult.

Brain network studies help reveal the inter-regulatory relationships between brain regions. For instance, the left dorsolateral prefrontal cortex (dlPFC) is responsible for

positive emotions; the higher its activity, the more energetic and positive a person feels, while the right dlPFC is associated with negative emotions. Further analyses of functional connectivity show that abnormal activity in the dlPFC and sgACC often form a "seesaw" (negative correlation) relationship. Building on these findings, in actual neuroregulation procedures, clinicians can tailor interventions to the patient's specific condition, using precise navigational strategies to "compensation for deficiencies and reduction of excess." For instance, in cases of depressive syndrome, excitatory stimulation of the left dlPFC can indirectly suppress overactivity in the sgACC, and/or inhibitory stimulation of the right dlPFC can be used to restore balance between the two hemispheres.

Your research focuses on the brain functional characteristics of depression in different populations (such as postpartum depression, adolescent depression, etc.). What implications does this have for the treatment of psychiatric disorders in specific populations?

Wei Deng: This line of research is typically referred to as neuroregulation studies in special populations. Such groups differ markedly from the average adult population. For instance, patients with postpartum depression undergo significant changes in lifestyle and hormone levels, leading to distinct patterns of brain function. These patients often experience disruptions in circadian rhythms and display abnormal hyperactivity in regions related to maternal behavior and attachment, such as the orbitofrontal cortex and anterior cingulate cortex. Additionally, the lateral habenula shows a notably higher incidence of abnormality. Drawing on these features and related basic research findings, we have combined transcranial modulation with chronobiological interventions—such as light therapy—to achieve promising therapeutic outcomes.

In adolescent depression, medications may be less effective than in adults and can carry more severe side effects. As a result, neuroregulation therapies—which can act quickly, deliver clear benefits, and cause fewer adverse reactions—are gaining traction. Meanwhile, the incidence of adolescent psychiatric disorders has risen markedly in recent years, accompanied by a rapid increase in outpatient visits. In response to these trends, we have increasingly employed functional near-infrared spectroscopy (fNIRS) for brain function assessment as part of an accelerated treatment strategy. Its rapid assessment capability, coupled with good patient compliance, forms a "detection-treatment-feedback-continuous optimization" process that drives progress in adolescent depression diagnosis and treatment.

How has the development of artificial intelligence technology in recent years contributed to the data analysis of brain functional imaging, and what is its significance for advancing the application of brain functional imaging?

Wei Deng: When I was a graduate student, data analysis was indeed a major challenge due to the vast amount of brain functional imaging data, all of which had to be analyzed manually. With the advancement of technology, some preliminary automation in data analysis had been achieved, but there was still a gap before it could be used in clinical reports. Over more recent years, with the development of computer vision technology, our image processing has largely become automated.

In one of our longitudinal collaborative projects, we use algorithms to recommend stimulation sites, input them into a neural navigation system, and utilize an infrared camera to guide the TMS coil to precisely stimulate target areas in the human brain, while also assessing the accuracy and effectiveness of these stimulation points. Additionally, AI-based structural imaging can apply image segmentation techniques to precisely partition brain functional images—for example, to achieve fine-grained localization of hippocampal subfields—and can also compute the asymmetry between the left and right hemispheres, providing new perspectives for data analysis in brain functional imaging.

Nevertheless, new challenges remain. For magnetoencephalography (MEG) data analysis, event-related field (ERF) analysis and source localization require complex manual calculations and processing. Even for experienced analysts, it can take at least four hours to complete a single analysis report. We look forward to AI technology helping us analyze MEG data more quickly and accurately in the future.

What are the current development trends in brain functional imaging equipment? What progress has China made in the research and development of brain functional imaging devices?

Wei Deng: The development of brain functional imaging equipment can generally be categorized into three major trends. First is portability. For example, compared to traditional fixed devices, wireless head-mounted devices require less patient cooperation, making data collection possible under conditions of high ecological validity—a tremendous convenience for patients with psychiatric disorders. Second is increasing scanning speed. The iteration of equipment and the introduction of synchronous scanning technology mean faster scanning times, thereby shortening the patient's required cooperation and allowing the collection of larger amounts of data in a shorter period, with reduced tissue distortion and clearer resulting images. Finally, there is increased accessibility. In recent years, domestic equipment has made significant breakthroughs in market share and technological competitiveness. For instance, Shanghai United Imaging Healthcare Co., Ltd. has gradually broken the foreign monopoly on MRI equipment, while Danyang Huichuang Medical Equipment Co., Ltd. has become a leader in the functional near-infrared imaging industry. Through technical innovation and cost controls, these companies have greatly lowered the procurement and operating costs of brain functional imaging equipment, making them accessible to a greater number of hospitals and research institutions.

What processes do brain functional imaging devices go through from laboratory and enterprise development to clinical application? Are there any policy frameworks supporting the rapid translation of these devices?

Wei Deng: Generally, brain functional imaging devices used in clinical practice must undergo the medical device registration and approval process, which can be quite cumbersome. However, devices that have not yet obtained the necessary qualifications can still undergo clinical trials at designated medical device clinical trial institutions that meet the required conditions and are properly registered. Both the national and local governments have made significant efforts to promote the translation of brain functional imaging devices. At the national level, with the support of the Ministry of Science and Technology's "Science and Technology Innovation 2030 — Brain Science and Brain-like Research" major project, we have established the Zhejiang University Brain-Machine Regulation Clinical Translation Research Center (Mental Health Subcenter). Through these open platforms and the construction of research-oriented wards, we are now able to conduct a variety of clinical experiments and studies, including IITs (investigator-initiated trials) and pre-registration clinical evaluations. Zhejiang Province and Hangzhou City have also placed great emphasis on the development of the biomedical industry. As early as 2021, a series of industrial policies have been introduced to support the research and development of related equipment. Our hospital has also actively responded, supporting R&D institutions and local biomedical enterprises in conducting clinical trials on these platforms. In the future, I hope that clinical doctors will be more involved in the early-stage development of these devices to help them better transition into clinical practice, thereby strengthening the connection between academia, research, industry, and application in the brain functional imaging field.

Within the BBMI Center and the National Key Laboratory of Brain-Machine Intelligence, what interdisciplinary collaborations have you currently undertaken, and what are your expectations for future medical-engineering integration and clinical-basic research collaboration?

Wei Deng: Over recent years, communication with individuals from other disciplines has indeed increased. On a personal level, these exchanges help address the shortfalls in exploring deeper mechanisms that purely clinical research cannot overcome. We have also collaborated with basic researchers on several scientific projects. Zhejiang University has strong capabilities in brain science research, and Hangzhou Seventh People's Hospital has made significant progress in recent years. I hope that in the future, we can strengthen collaboration with basic research on specific scientific projects, bridging animal research with clinical practice, while also bringing clinical issues into the laboratory. Through this "bidirectional" approach between basic and clinical research, we aim to solve clinical problems and better benefit patients.

Prof. Wei Deng

Director of the Brain-Machine Joint Diagnosis and Treatment Center at Zhejiang University School of Medicine Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Executive Director of the Zhejiang Provincial Clinical Medicine Research Center for Psychiatric and Psychological Diseases.

His primary research areas include:

1. Digital health in psychiatry and the application of specialized large models.
2. Neuroplasticity, cognitive function correction, and cognitive enhancement.
3. Cross-temporal brain function assessment based on multimodal representations (imaging, electrophysiology, eye movement, wearable devices, etc.).
4. Precision, multimodal neural regulation and mechanism research.
5. Brain-machine interaction and closed-loop neural feedback.
6. Biological rhythms, chronobiology, and sleep regulation.

Development of diffusion magnetic resonance imaging technology and its clinical translation

Interview with Professor Dan Wu

Could you briefly introduce the basic principles of Diffusion Magnetic Resonance Imaging (dMRI) and its clinical significance?

Wu Dan: Diffusion Magnetic Resonance Imaging (dMRI) is a technique based on the diffusion of water molecules, which allows for the detection of changes in the microstructure of biological tissues. It is widely used in neuroscience and clinical diagnostics. In the field of neuroscience, dMRI is primarily used for neural fiber tractography and brain network construction, aiming to reveal the relationship between neural connections and brain function. In clinical diagnostics, dMRI is applied in the early detection, pathological grading, and molecular subtyping of diseases such as stroke and brain tumors. Current research focuses on improving the spatial resolution and imaging speed of dMRI, and developing biophysical models to non-invasively probe cellular microstructures. Ultimately the goal is to provide more precise and efficient technical support for both basic research and clinical applications.

Your work focuses on improving the speed and resolution of Diffusion Magnetic Resonance Imaging (dMRI). What areas are you mainly working on?

Wu Dan: Our research adopts a comprehensive approach across hardware, acquisition strategies, and post-processing methods to improve the resolution and accuracy of diffusion MRI. In terms of hardware, we have developed an ultra-high-gradient MRI system specifically designed for brain imaging, aimed at enhancing gradient field strength to improve imaging resolution and the accuracy of microstructural reconstruction. Regarding acquisition strategies, we have designed 3D diffusion MRI pulse sequences with advanced navigator strategies, significantly improving the signal-to-noise ratio and resolution of the images. For post-processing, we combine cutting-edge technologies such as artificial intelligence and apply super-resolution imaging techniques to further enhance image quality. With these efforts, we are able to achieve a balance between spatial resolution, signal-to-noise ratio, and contrast to meet the diverse needs of research or clinical applications.

You mentioned that pulse sequence design is a key part of the technology. In clinical practice, do the development and promotion of these new methods face any challenges?

Wu Dan: Our research benefits greatly from the highly interdisciplinary field of biomedical engineering. Since returning to China in 2018, I have established strong collaborations with clinical teams in China, and we have successfully driven multiple studies, particularly making significant progress in the oncology field. The microstructural imaging technology we developed enables non-invasive extraction of pathology-related biomarkers, demonstrating its advantages in brain gliomas, prostate cancer, and breast cancer research. It has already proven its clinical values pathological grading, molecular subtyping, and chemotherapy evaluation in prostate cancer, breast cancer, and brain gliomas. In the field of neurological diseases, our technology has shown high sensitivity in early Alzheimer's disease research, allowing for the detection of changes in brain cell density and revealing increased transmembrane water transport related to amyloid beta (Aβ) protein deposition and astrocyte activation. We have also made progress in studying brain diseases such as stroke and epilepsy. Currently, the technology is being used in over 60 hospitals worldwide and has been implemented in collaboration with major MRI manufacturers, such as United-Imaging, Siemens, Philips, and General Electric, making it possible to apply this technology to existing devices.

With the improvement in resolution and scanning speed, is it possible in the future to complete a full-body health assessment through both Diffusion MRI and blood tests?

Wu Dan: Currently, while some high-end health checkup centers offer full-body MRI scans, there are still many challenges in the technical application. Firstly, full-body MRI scans are time-consuming, and the limited field-of-view of the equipment often requires multiple stages to cover the entire body. Second, even in high-end health checkup institutions, the availability and scan efficiency of the equipment are still limited, and full-body scanning is not widely used, especially in general medical institutions. Therefore, despite the high diagnostic accuracy of MRI, its expensive cost and equipment requirements make it unsuitable as a routine screening tool.

With the introduction of artificial intelligence technologies, it is expected that in the future, the scan process can be accelerated, data processing algorithms optimized, and machine learning techniques applied to improve the efficiency and accuracy of full-body scans, thus supporting early disease screening. However, technological advancements still require time, and the goal of achieving full-body health assessment will need to be realized gradually based on data accumulation and technical refinement.

Your recent work has made significant progress in imaging research on fetal brain development. Could you discuss the technological breakthroughs and research findings in this field?

Wu Dan: The fetus is in a state of motion within the mother's body, and the fetal brain structure differs greatly from that of an adult. This presents significant technical challenges for fetal brain functional imaging. We optimized in both the front-end data acquisition and back-end processing techniques. Ultimately, we established a normative model for normal fetal brain development, accurately characterizing the spatiotemporal development trajectory of the fetal brain. For instance, using T2 structural imaging, we revealed cortical morphology in different brain regions, including cortical thickness, curvature, and cortical volume expansion rate. Our research found that key milestones in fetal brain development occur between 30 to 32 weeks of gestation, during which the developmental speed of different brain regions accelerates, particularly the process of pre-myelination in white matter fiber tracts, which lays the foundation for the onset of myelination. This spatiotemporal atlas not only enabled track changes in the fetal brain at different stages of development and but also set normative baseline for detecting fetal brain disorders. We further explored the impact of conditions such as fetal growth restriction and congenital heart disease on fetal brain development. We identified some abnormal developmental patterns, which could serve as potential bases for early diagnosis.

When translating your research findings into clinical applications, what do you consider to be the key steps? What are the current difficulties and challenges, and what role have you played in this process?

Wu Dan: The key steps in translating technology into clinical applications include performing multi-center trials to validate the effectiveness of new imaging biomarkers, and then incorporating these biomarkers into disease diagnostic guidelines to establish them as standard practices. Next, it is essential to collaborate with equipment manufacturers to integrate our imaging sequences into clinical devices, addressing online data processing issues to ensure that the technology can operate on the devices and provide quantitative evaluation results. Currently, data processing and post-processing reconstruction remain the primary challenges, especially in generating real-time microstructural maps. We are working with equipment manufacturers to develop online post-processing and training hospital staff for data handling. One of the challenges lies in sharing the intellectual property between manufactures and researchers. Additionally, gaining acceptance from clinicians to a new technique is another challenge. We need to demonstrate the clinical value of the new technology, despite considerations like acquisition time and additional efforts required.

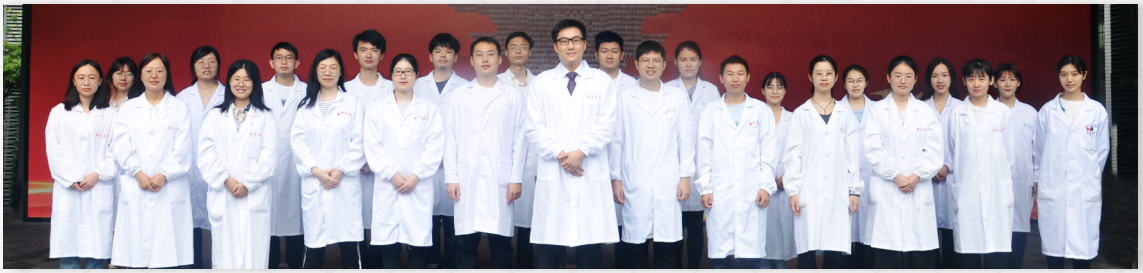
What are your expectations or suggestions for an interdisciplinary collaboration platform in the MOE Frontier Science Center for Brain Science and Brain-machine Integration (BBMI)?

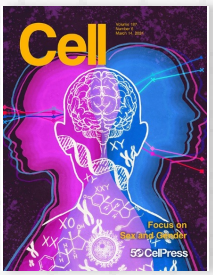
Wu Dan: I believe the BBMI has immense potential. One model worth emulating is encouraging cross-disciplinary collaboration through seed funding for faculty teams. Although the initial outcomes may not be clearly defined, this mechanism can effectively promote gradual collaboration. The advantage of the BBMI is that it brings together basic research, technical teams, and clinical resources, enabling cooperation across different disciplines. I suggest that the BBMI focus on specific topics, fostering full-chain collaboration from basic research to technology development and clinical application, in areas such as brain development, autism, and Alzheimer's disease. Through this kind of collaborative platform, interaction and cooperation between different teams can be promoted, forming a multi-party collaborative mechanism that facilitates the translation and application of research findings.

Prof. Dan Wu

Professor of the Department of Biomedical Engineering, Colleage of Biomedical Engineering and Instrumental Science, Zhejiang University.

Her main research areas include the development of magnetic resonance imaging sequences and medical image analysis methods. She has made several original contributions, particularly in high-resolution imaging sequences, diffusion magnetic resonance-based microstructure mapping, and fetal and infant brain imaging.

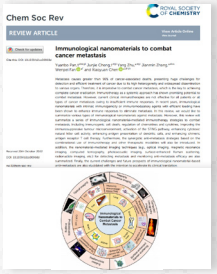




Prof. Yan Zhang's Research group

Structure-based design of non-hypertrophic apelin receptor modulator. Wang W#, Ji S#, Zhang W#, Zhang J#, Cai C#, Hu R#, Zang S, Miao L, Xu H, Chen L, Yang Z, Guo J, Qin J, Shen D, Liang P, Zhang Y*, Zhang Y*. ***Cell***. 2024 Mar 14;187(6):1460-1475.e20.

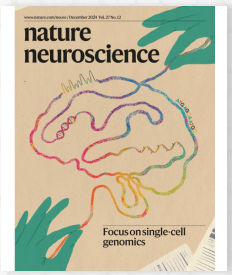
This study reports the molecular basis for binding and activation of the APLNR-Gi1 complex by apelin and biased agonists, reveals the "twin hotspots" in APLNR as key determinants for signaling bias, and further designs and generates exclusive G-protein-biased agonists WN353 and WN561. Pathophysiological experiments have provided evidence that WN561 demonstrates superior therapeutic effects against cardiac hypertrophy and reduced adverse effects compared with the established APLNR agonists. In summary, our designed APLNR modulator may facilitate the development of next-generation cardiovascular medications.



Prof. Jianming Zhang's Research group

Immunological nanomaterials to combat cancer metastasis. Pan Y#, Cheng J#, Zhu Y, Zhang J*, Fan W*, Chen X*. ***Chemical Society Reviews.*** 2024, 53, 6399-6444.

In this review, we would like to summarize various types of immunological nanomaterials against metastasis. Moreover, this review will summarize a series of immunological nanomaterial-mediated immunotherapy strategies to combat metastasis Furthermore, the synergistic anti-metastasis strategies based on the combinational use of immunotherapy and other therapeutic modalities will also be introduced. Finally, the current challenges and future prospects of immunological nanomaterial-based anti-metastasis are also elucidated with the intention to accelerate its clinical translation.



Prof. Jing Wang & Researcher Jiaming Hu's Research group

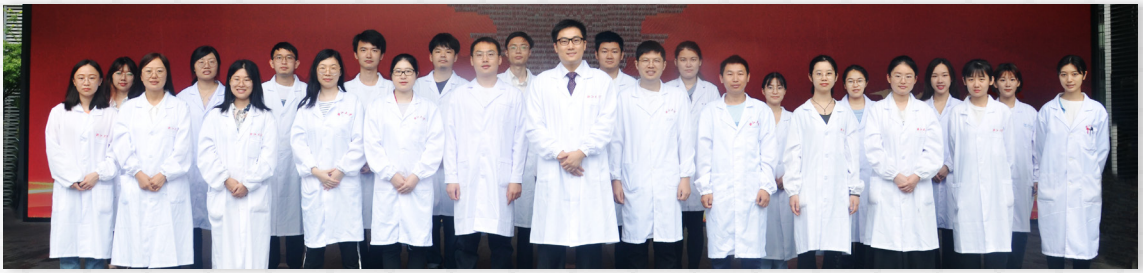
Multiple Loci for Foveolar Vision in Macaque Monkey. Qian M#, Wang J#, Gao Y#, Chen M, Liu Y, Zhou D, Lu H, Zhang X*, Hu J*, Roe A*. ***Nature Neuroscience.*** 2024 Dec 05. doi: 10.1038/s41593-024-01810-4.

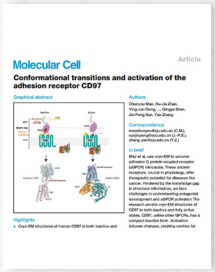
This study shows that in the ventral pathway (visual areas V1–V4 and the posterior inferior temporal cortex), viewing of a small foveolar spot elicits a ring of multiple (eight) foveolar representations per hemisphere. This ring surrounds an area called the 'foveolar core', which is populated by millimeter-scale functional domains sensitive to fine stimuli and high spatial frequencies, consistent with foveolar visual acuity, color and achromatic information and motion. Thus, this elaborate rerepresentation of central vision coupled with a previously unknown foveolar core area signifies a cortical specialization for primate foveation behaviors.

Prof. Shaohua Hu's Research group

Single-cell transcriptomic atlas reveals immune and metabolism perturbation of depression in the pathogenesis of breast cancer. Wu L#, Liu J#, Geng Y#, Fang J#, Gao X, Lai J, Yao M, Lu S, Yin W, Fu P*, Chen W*, Hu S*. ***Cancer Communications.*** 2024;44(11):1311-1315.

This study offers preliminary insights regarding the impacts of comorbid depression history in patients with breast cancer. We suggest a potential association between depression history and a poorer prognosis in breast cancer, characterized by a decrease in specific epithelial cells and impaired immune regulation signals within primary tumors. Furthermore, we propose potential alterations in the metabolic status of breast tumor cells in patients with depression.

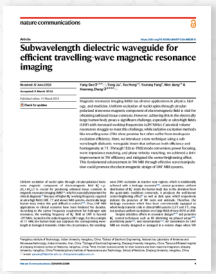




Prof. Yan Zhang's Research group

Conformational transitions and activation of the adhesion receptor CD97. Mao C#*, Zhao R#, Dong Y#, Gao M#, Chen L#, Zhang C#, Xiao P#, Guo J, Qin J, Shen D, Ji S, Zang S, Zhang H, Wang W, Shen Q, Sun J*, Zhang Y*. ***Molecular Cell.*** 2024 Feb 1;84(3):570-583.e7.

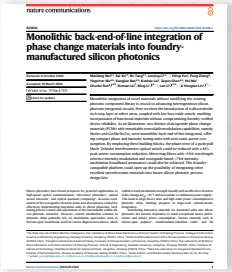
This study reported the cryo-electron microscopic structure of a typical aGPCR CD97, which plays a key role in the immune system, in the fully active state of inactive carrier and G13 binding. Combined with cell function experiments and molecular dynamics simulations, the structural changes and activation mechanisms of CD97 during the process of sensing mechanical forces were identified. This is the first time in the world to reveal the electron microscope structure of the non-activated state of adherent GPCRS, and also provides key information for future drug discovery.



Researcher Xiaotong Zhang's Research group

Subwavelength Dielectric Waveguide for Efficient Travelling-Wave Magnetic Resonance Imaging. Gao Y*, Liu T, Hong T, Fang Y, Jiang W, Zhang X*. ***Nature Communications.*** 2024 Mar 14;15(1):2298.

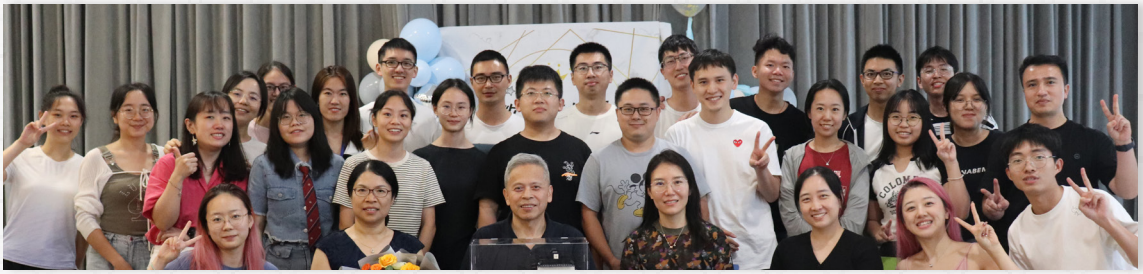
In MRI, uniform excitation of nuclei spins through circular polarized transverse magnetic component of electromagnetic field is vital for obtaining unbiased tissue contrasts. However, achieving this in the electrically large human body poses a significant challenge, especially at ultra-high fields (UHF) with increased working frequencies (≥297 MHz). Here, we introduced a new technique using a subwavelength dielectric waveguide insert that enhances both efficiency and homogeneity at 7T. Through TE11-to-TM11 mode conversion, power focusing, wave impedance matching, and phase velocity matching, we achieved a 114% improvement in travelling-wave (TW) efficiency and mitigated the center-brightening effect.



Reasercher Hongtao Lin's Research group

Monolithic back-end-of-line integration of phase change materials into foundry-manufactured silicon photonics. Wei M[#], Xu K[#], Tang B[#], Li J*, Yun Y, Zhang P, Wu Y, Bao K, Lei K, Chen Z, Ma H, Sun C, Liu R, Li M*, Li L*, Lin H*. ***Nature Communications.*** 2024 Mar 30; 15: 2786.

In this study, we developed a monolithic back-end-of-line integration, enabling incorporation of functional materials without compromising foundry-verified device reliability. As an illustration, two distinct chalcogenide phase change materials (PCMs) with remarkable nonvolatile modulation capabilities were monolithic back-end-of-line integrated, offering compact phase and intensity tuning units with zero-static power consumption. This foundry-compatible platform could open up the possibility of integrating other excellent optoelectronic materials into future silicon photonic process design kits.



Prof. Shumin Duan & Prof. Yanqin Yu's Research group

Adenosine-Dependent Arousal Induced by Astrocytes in a Brainstem Circuit. Zhu Y[#], Ma J[#], Li Y[#], Gu M, Feng X, Shao Y, Tan L, Lou H, Sun L, Liu Y, Zeng L, Qiu Z, Li X, Duan S*, Yu Y*. ***Advanced Science***. 2024 Nov 4:e2407706.

This study is the first to uncover the unique role of astrocytes in the brainstem parafacial zone (PZ) in promoting and maintaining wakefulness through extracellular adenosine signaling via A1 receptors. PZ astrocyte activation induced arousal by suppressing the GABA release from the PZGABA neurons, which promote NREM sleep and project to the parabrachial nucleus. This work sheds light on the underlying mechanisms at the neural circuit level, offering new insights into the physiological role of astrocytes in sleep-wake regulation and their impact on sleep-wake circuits.

Prof. Jiangtao Guo's Research group

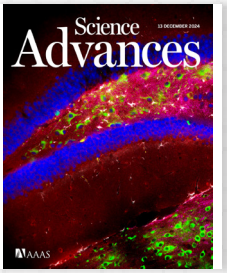
A small-molecule activation mechanism that directly opens the KCNQ2 channel. Zhang S#, Ma D#, Wang K#, Li Y#, Yang Z, Li X, Li J, He J, Mei L, Ye Y, Chen Z, Shen J, Hou P, Guo J*, Zhang Q*, Yang H*. ***Nature Chemical Biology.*** 2024 Jul;20(7):847-856.

This study reports a novel small molecule agonist, Ebio1, which increases the conductance of the KCNQ2 channel. By utilizing techniques such as cryo-electron microscopy, mutagenesis, molecular modeling, and small molecule derivative probes, the study unveiled a new regulatory mechanism by which Ebio1 directly opens the pore region. The findings provide a template for identifying and elucidating the mechanisms of channel-selective chemical tools and exploring their functions for developing new therapeutic drugs.

Prof. Ping Wang's Research group

Multimodal spatiotemporal monitoring of basal stem cell-derived organoids reveals progression of olfactory dysfunction in Alzheimer's disease.Liu M, Jiang N, Qin C, Xue Y, Wu J, Qiu Y, Yuan Q, Chen C, Huang L, Zhuang L*, Wang P*. ***Biosensors and Bioelectronics.*** 2024 Feb 15; 246: 115832.

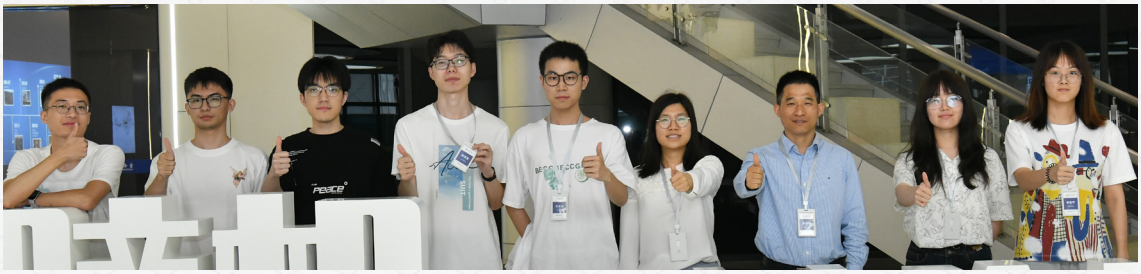
This study combines impedance biosensors and live imaging for real-time analysis of olfactory epithelium (OE) organoid morphology and physiology during Alzheimer's disease (AD) progression. Impedance measurements showed lower proliferation in organoids from APP/PS1 transgenic mice compared to wild-type mice. Live imaging revealed abnormal protein aggregation, including amyloid plaques and neurofibrillary tangles, increasing with disease progression. This multimodal bioelectrical and imaging platform offers new insights into the mechanisms of olfactory dysfunction and potential early diagnosis and treatment of neurodegenerative diseases.



Researcher Hyeon Jeong Lee's Research group

INSPIRE: Single-Beam Probed Complementary Vibrational Bioimaging. Fu P#, Zhang Y#, Wang S, Ye X, Wu Y, Yu M*, Zhu S, Lee H*, Zhang D*. ***Science Advances.*** 2024. 2024 Dec 11.Vol 10, Issue 50. doi: 10.1126/sciadv.adm7687

This study presents INSPIRE (Single-Beam Probed Complementary Vibrational Bioimaging), a novel bioimaging technique that, for the first time, enables simultaneous detection of high-resolution, high-sensitivity infrared and Raman vibrational spectra on a single microscopic platform. By addressing a longstanding challenge in biomedical optics, INSPIRE opens new avenue for applications in biomedical research, materials science, and pharmaceutical development.




SPAIC: A Spike-based Artificial Intelligence Computing Framework

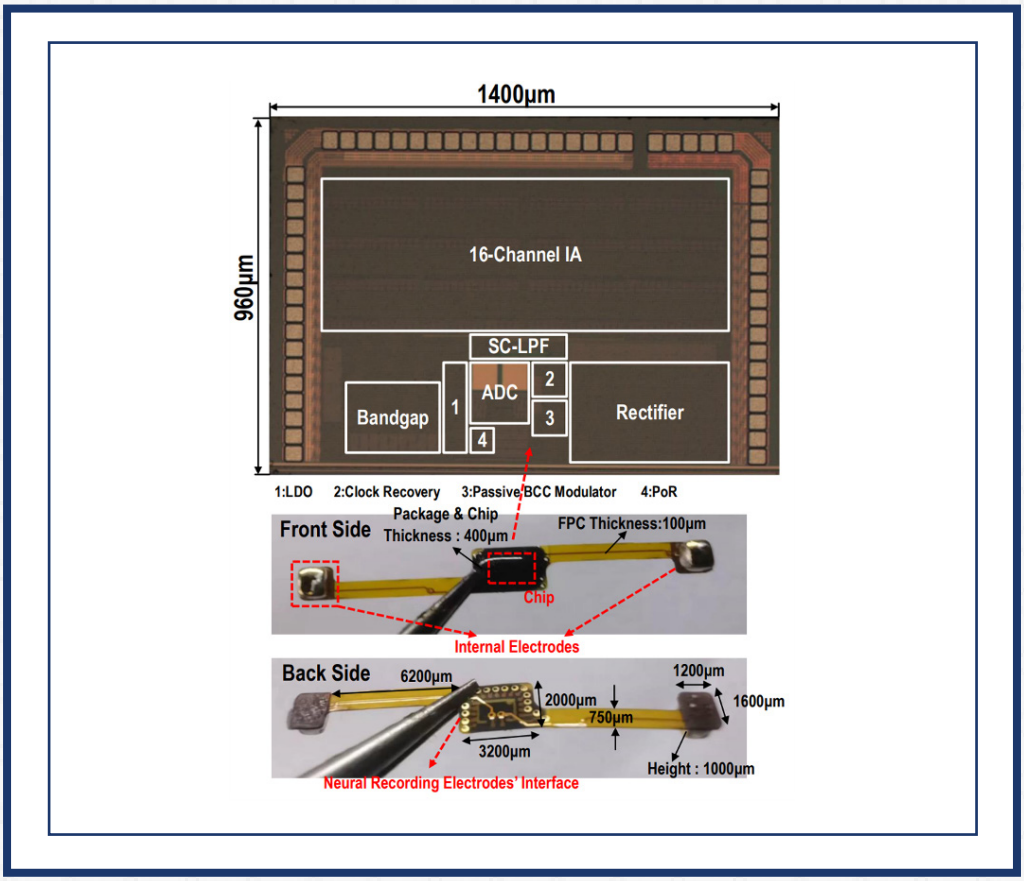
Prof. Huajin Tang's Research group

SPAIC: a spike-based artificial intelligence computing framework. Hong C, Yuan M, Zhang M, Wang X, Zhang C, Wang J, Pan G, Tang H*. ***IEEE Computational Intelligence Magazine.*** 2024;19(1):51-65.

In this work, we present a Python-based spiking neural network (SNN) simulation and training framework, named SPAIC, that aims to support brain-inspired model and algorithm research integrated with features from both deep learning and neuroscience. To integrate different methodologies from multiple disciplines and balance flexibility and efficiency, SPAIC is designed with a neuroscience-style frontend and a deep learning-based backend. Various types of examples are provided to demonstrate the wide usability of the framework, including neural circuit simulation, deep SNN learning and neuromorphic applications. As a user-friendly, flexible, and high-performance software tool, it will help accelerate the rapid growth and wide applicability of neuromorphic computing methodologies.

Battery–Free Fully–Implanted BMI Chip & Prototype Based on Passive Body Channel Communication

Wireless implanted devices are widely adopted for long-term neural-recording applications, where the cable-induced infection risk can be avoided. Battery-free communication based on wireless power transfer (WPT) can eliminate the battery to reduce the size of a wireless implant, realizing minimally invasive surgery. However, conventional battery-free implants suffer from a short communication range, such as inductive coupling, near-infrared (NIR) transmission, and active body-channel communication (BCC), which cannot apply to deep brain zones. Ultrasonic power transfer and communication benefit from a low channel loss, but the low carrier frequency leads to a low data rate, which is not able to transfer full-span neural signals such as spikes and multichannel signals. In this work, a galvanically-switching passive-BCC technique is proposed for neural implants, to extend the effective range of both power transfer and wireless communication. The brain tissue is utilized to form a galvanic loop for power delivery, while the neural-recording data switch the loop current to conduct passive BCC. The proposed technique is implemented in a neural recording chip fabricated in a 55nm CMOS process. Through-tissue measurement shows that the chip realizes a battery-free communication range of 5.5cm, with a bit-error rate (BER) of 4.4×10^{-6}. In the in-vivo demonstration, a $5.9mm^3$ flexible prototype with the proposed chip inside is fully implanted into a Sprague–Dawley rat, where the neural signals are read battery-free through the passive-BCC technique.



Prof. Wanjun Guo

The Zhejiang Province "Leading Earth Goose" Program

▼ **Study on new regulation techniques and comprehensive diagnosis and treatment strategies for major brain diseases - Study on new regulation techniques and comprehensive diagnosis and treatment strategies for depressive disorders**

Depression disorder has been widely recognized as the main cause of inevitable suffering and premature death, with its high prevalence rate, unclear mechanism, insufficient confirmability of biological markers, and low cure rate of simple drug therapy. It is urgent to further explore comprehensive diagnosis and treatment strategies and technical systems to improve the treatment effect of depression on the basis of conventional drug therapy, such as combined non-drug therapy. Psychotherapy (such as mindfulness intervention) and non-invasive neuroregulatory techniques.

This project will be based on the highly integrated device system successfully developed by the applicant team in the early stage, which can collect EEG and heart rate variation signals during VR-MBI treatment, and use the research evidence of various physiological electrical signals such as EEG, eye movement, heart rate variation and neuroimage monitoring of patients with depression to develop an adaptive closed-loop neural regulation algorithm with multi-modal information fusion. A real-time adaptive closed-loop tDCS regulatory system for depressive disorder VR-MBI integrating multi-modal information acquisition, decoding feedback, and comprehensive treatment functions was formed, and a large sample, multi-center MDD and PSD specific disease cohort was established, and the design strategy of randomized controlled trial combined with sequential treatment self-control was adopted. The efficacy and clinical application value of the two sets of comprehensive diagnosis and treatment schemes developed based on this project were evaluated, and the regulation system verified and optimized by clinical research was promoted and applied in clinical practice.

Prof. Hongtao Lin

The Zhejiang Province "Leading Earth Goose+X" Program

▼ **12-inch CMOS-compatible silicon photonic fabrication technology**

With the rapid advancement of big data and artificial intelligence, coupled with the onset of the post-Moore's Law era, silicon photonics has entered a critical phase of development. However, there remains a significant gap between China's CMOS-based silicon photonics technology and international standards. This project will leverage the province's 55 nm node CMOS advanced process development line to establish 12-inch CMOS-compatible silicon photonic integrated chip fabrication technologies. By fostering collaboration among leading domestic "industry-university-research" institutions specializing in information photonics and semiconductor processes, the project will focus on developing 3D silicon photonic active integration technologies compatible with the 55 nm CMOS node. Additionally, a silicon photonic device library (PDK) based on optical proximity correction (OPC) for curved optics will be created. The project will also address the development of 12-inch silicon photonic wafer packaging and testing techniques, high-performance mode converters, and external cavity lasers, with accompanying application demonstrations. The ultimate goal is to achieve breakthroughs in 12-inch silicon photonic process technologies and PDK development, establish a pilot-scale R&D platform, and provide wafer-scale services for silicon photonics, thereby accelerating China's advancement toward achieving global leadership in silicon photonics technology.

Prof. Dan Wu

United Key Project of of National Natural Science Foundation

▼ Ultra-high gradient brain-only MRI system for high spatiotemporal resolution neuroimaging.

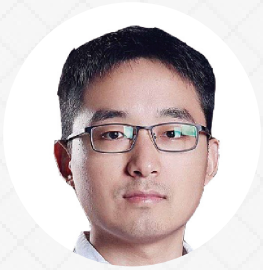
Magnetic resonance imaging (MRI) provides an important tool for neuroscience research. However, existing MRI techniques are mostly limited to the macroscopic scale, making it difficult to characterize the fine structure of the brain at the mesoscopic scale, let alone detect microscopic structural information. One of the key factors is that existing MRI gradient performance cannot support breakthroughs in imaging scale. In theory, high gradient field strength and slew rate can effectively improve imaging resolution and accuracy of microstructure reconstruction, but the development of high-gradient system faces many technical challenges such as bioelectromagnetic effects, noise effects, and eddy current effects, making it difficult to be used in neuroscience resesarch. This project proposes the design of a brain-only gradient system. We aim to overcome the above technical challenges through the development of key hardware components and imaging techniques, and built MRI system with the highest gradient field strength in the world (gradient field strength ≥ 650mT/m, slew rate ≥ 600T/m/s) targeted for neuroimaging of large animals. At the hardware component level, we plan to use bioelectromagnetic simulation, noise modeling, eddy current control and other methods to significantly reduce bioelectromagnetic effects and achieve a safe, silent, and stable gradient system; at the imaging technique level, we will make full use of high gradient performance to develop high-resolution fast imaging sequence and microstructure imaging models to achieve submillimeter high-resolution imaging and brain microstructure reconstruction. We expected to complete a set of brain-only MRI prototypes that support the development of cutting-edge neuroscience.

Prof. Chong Liu

National Natural Science Foundation

▼ Neuronal and immuno-microenvironment regulation and visualization in the initiation and early progression of malignant glioma

High-grade glioma is one of the most malignant cancers, and the molecular and cellular mechanisms of its initiation and early progression are largely unknown. It has been shown that neurons and immune cells constitute two important microenvironmental units of glioma. Both units have profound effects on many aspects of glioma pathology, such as the evolution roadmap of tumor initiation, the ultimate pathologic phenotype of end-stage tumors, prognosis and the choice of therapeutic paradigm. However, it is largely unknown how neuronal and immuno-microenvironment interacts with the tumor cell of origin, and regulates the latter's malignant transformation, the evolutionary roadmap of initiation and early progression, and the ultimate pathological phenotypes. To address this fundamental theorical question, in this projection, we propose to develop a series of unique geneticlineage-tracing mouse glioma models, in combining with a panel of cutting-edge visualization methods tailored for studying tumor-microenvironment interactions. By performing cross-species comparative studies on whole brain samples from phenotypically normal people and glioma patients, we aim to depict the high-resolution temporospatial roadmap of glioma initiation and early progression, as well as the dynamic interaction patterns of glioma cells with neuronal and immune-microenvironment, to reveal the generalizable principle of glioma ecosystem. Finally, we aim to construct a panoramic integrated association map of gliomagenesis based on traditional pathology, lineage tracing, multi-omics analysis, tissue clearing and nuclear magnetic imaging. The results will provide a theoretical framework and the experimental, mdoel and technique supports for the prevention, early diagnosis and targeted therapy of glioma.



Prof. Yi Zhang

National Key Research and Development Project of China

▼ **Early Screening and Optimization of the Diagnostic and Treatment Strategy for Neonatal Hypoxic-Ischemic Encephalopathy**

Hypoxic-Ischemic Encephalopathy (HIE) is an important cause of acute neonatal death and neurological sequelae. Although the treatment level of newborns continues to improve, HIE still affects about 2 million newborns around the world every year, and the incidence of HIE in China is about 1%, higher than that in developed countries, and 25% of children have serious neurodevelopmental disorders. Aiming at this domestic and foreign research key and difficult problem, this project aims to build China's HIE early screening and precision diagnosis and treatment system, optimize long-term management plans, and improve the quality of life of children.

Prof. Dan Wu

Major Scientific Instrument Development Project of National Natural Science Foundation

▼ **Development of MR microstructural imaging markers for prostate cancer diagnosis and investigation of the associated molecular mechanisms**

Prostate cancer (PCa) is the second most common malignant tumor in men, and magnetic resonance imaging (MRI) is the main non-invasive tool for early diagnosis and progression monitoring of PCa. However, conventional MRI typically reflects the macroscopic characteristics of cancer and is not accurate enough for diagnosis of PCa. Therefore, it is urgent to develop new markers that specifically reflect tumor pathology and function. In addition, the underlying molecular mechanisms of existing imaging markers are unclear, making it difficult to clearly characterize the occurrence and development process of PCa. To this end, this project aims to develop a new MR microstructural imaging technique to characterize the pathological microstructure and metabolic functions of PCa in a non-invasively, in situ, comprehensive manner. We will also investigate the molecular mechanisms of the proposed microstructural markers using spatial transcriptome. On the one hand, we propose to probe microstructural morphology and transmembrane water exchange (reflecting metabolic function) based on the full diffusion-time spectral of water diffusion to achieve simultaneous imaging of pathological microstructure and metabolic function. On the other hand, we will develop an image-transcriptome spatial correlation method, through the alignment and fusion of microstructural markers and spatial transcriptome, to elucidate the genetic substrates of the imaging phenotypes. Finally, we will establish an intelligent diagnostic system using multi-modal MRI to improve pathological grading and active surveillance of PCa. Through the innovation of microstructural markers and investigation on their molecular mechanisms, the project aims to facilitate the precise diagnosis and personalized treatment of major malignant tumors including PCa.

Prof. Jianhong Luo

Key R&D Program of Zhejiang Province

▼ Mechanisms and regulation of brain network for social deficits and affective disorders

Social and emotional well-being are fundamental to human adaptability and self-development. Functional brain imaging studies have shown that such complex behaviors are associated with the coordination of brain-wide networks. However, due to limitations in technology, the neurobiological mechanism underlying the brain network of social and emotional function, as well as their dysfunction, remain poorly understood. This also hinders the development of novel regulatory technologies. Therefore, there is an urgent need to explore new approaches for real-time recording and analysis of dynamic brain-wide network activity under specific behavioral paradigms. This would clarify the mechanisms of multi-regional brain coordination and underlying neural circuit function in social and emotional regulation, identify brain network abnormalities in related pathological states, and facilitate the development of neuroregulatory technologies. This project aims to leverage the interdisciplinary strengths of a team combining medicine, engineering, and information sciences to develop methods for recording local field potentials and fiber photometry across multiple brain regions on a whole-brain scale. Using mouse models of social deficits and emotional disorders, the project will decode the dynamic brain network encoding specific behavioral events. Through optogenetic and chemogenetic manipulations, it seeks to elucidate the relationship between underlying neural circuit activity, dynamic brain networks and behavior, and explore intervention methods based on abnormality of dynamic brain network. Through this project we aim to achieve novel discoveries in basic neuroscience, breakthroughs in dynamic brain network recording and analysis techniques, and new advancements in neuromodulatory intervention of social deficits and emotional disorders.

Prof. Yudong Zhou

Key Project of National Natural Science Foundation

▼ Metabolic inflammation in the paraventricular nucleus of the thalamus controls compulsive eating behavior

An important way for the central nervous system to respond to risk factors is through the activation of relevant immune pathways to produce structural and functional adaptive changes. The brain can mount an effective immune response not only against infection and injury, but also against some non-infectious factors. For example, excessive intake of high-energy, fat-rich diets can induce metabolic inflammation in the hypothalamus, manifested by the activation of hypothalamic glial cells and inflammatory pathways, and have a significant impact on energy homeostasis, leading to various metabolic diseases including obesity. Based on our discovery that activation of microglia in the anterior paraventricular nucleus of the thalamus (aPVT) mediates the compulsive eating behavior induced by a high-fat diet, we plan to further study the role and mechanism of metabolic inflammation in the reward center in regulating feeding motivation. By elucidating 1) how long-chain saturated fatty acids enter aPVT to promote microglial activation, 2) how activated microglia regulate aPVT neuronal activity through key inflammatory factors, and 3) metabolic inflammation remodels the reward circuitry to regulate food intake, we propose to systematically analyze the entire process of central feeding and reward circuits integrating the body's nutritional information through various projection pathways and signaling molecules to regulate feeding and maintain the body's energy homeostasis. This project is of great significance for in-depth understanding of the role of neuroimmune signals in reward centers in the regulation of energy metabolism caused by excessive intake of lipid molecules, and lays the foundation for understanding the pathogenesis of metabolic diseases and developing targeted prevention and intervention methods.

Prof. Yan Zhang

Key Project of National Natural Science Foundation

▼ Study on the mechanism of dynamic regulation of signal transduction by different oligomeric forms of Apelin receptor and discovery of ligands

The Apelin receptor (APLNR) is a member of the A-class G protein-coupled receptor family. It is considered a promising target for cardiovascular disease intervention due to its crucial roles in cardiovascular protection, positive inotropy, and inhibition of myocardial fibrosis. The receptor can exist in monomeric, homodimeric, or heterodimeric forms with AT1R, dynamically transitioning between these forms to mediate complex downstream signaling pathways involved in regulating cardiovascular physiological and pathological functions. However, the specific mechanisms by which APLNR dynamically regulates downstream signaling through different oligomeric forms require further investigation. This project aims to determine the differences in downstream signaling spectra mediated by APLNR in different oligomeric forms by detecting the receptor's selectivity for downstream signaling molecules. Subsequently, by analyzing the structures of monomeric, homodimeric, and heterodimeric complexes with G proteins and β-arrestins, combined with functional experiments, the dynamic regulatory mechanisms of downstream signaling mediated by APLNR in different oligomeric forms will be comprehensively elucidated. Ultimately, precise ligands will be designed based on the above signaling mechanisms to regulate different physiological functions, and the safety and efficacy of these designed ligands will be validated in cardiovascular physiological and pathological models. The completion of this project will provide a novel strategy for improving cardiovascular drug development targeting APLNR.

Prof. Ping Wang

Horizontal scientific research projects

▼ Bio-Inspired Olfactory and Gustatory Sensors and Digital Evaluation Technology for Cigarette Smoke Detection

Cigarettes have complex components, and the aroma produced during combustion is diverse. The sensation experienced after the smoke leaves the mouth and nose is referred to as the aftertaste of the cigarette. A more pleasant and clean aftertaste brings a better experience to the smoker. Therefore, evaluating the fragrance, aroma quality, and aftertaste of cigarettes is a crucial aspect of tobacco sensory evaluation. Relying solely on human assessments of odors lacks objectivity and repeatability. This project focuses on the sensory quality of cigarette smoke, using bio-inspired sensory technology that simulates human olfactory and gustatory senses, and intelligent digital sensory technology. It aims to establish evaluation methods for cigarette fragrance and aroma, as well as off-odors, using bio-inspired olfactory sensors, and to develop evaluation methods for cigarette aftertaste using bio-inspired gustatory sensors. Corresponding olfactory and gustatory bio-sensors for sensory detection and digital sensory evaluation characterization devices will also be developed. Based on this, combined with mass spectrometry analysis and machine learning techniques, the digital characterization and further prediction of cigarette smoke sensory indicators will be achieved. This will lay a technical foundation for large-scale, refined, digital sensory evaluation of tobacco leaf materials and cigarette products, thereby supporting the digital evaluation and research and development design of cigarette products.

Prof. Hongtao Lin

Young Scientist Key Project of Ministry of Industry and Information Technology

▼ **Wafer-Scale Integrated Electrically Controlled Non-Volatile Optical Programmable Gate Array Chip Technology**

With the explosive increase in computational power demands driven by large-scale artificial intelligence models and the emergence of new demands in the post-Moore's Law era, photonic processing chips are recognized for their vast potential across applications in artificial intelligence, data centers, 6G communications, and biomedicine. The development of Optical Field-Programmable Gate Array (OFPGA) chips, enabled by software-defined functionality, has the potential to drastically reduce research and development costs and timeframes, thereby accelerating the deployment of photonic technologies and facilitating the development of diverse future application systems. However, current OFPGA chips, which rely on thermo-optic control mechanisms, face significant limitations in terms of the performance and scalability of programmable optical networks. To overcome these challenges, this project aims to achieve key breakthroughs in the wafer-scale integration of electrically controlled non-volatile OFPGA chip technology. The integration of phase-change materials into non-volatile OFPGA chips will break through existing technological barriers and provide a foundation for the next generation of programmable photonic processors.

2024 BBMI Selected Publications

1. Brain region–specific action of ketamine as a rapid antidepressant. Chen M, Ma S, Liu H, Dong Y, Tang J, Ni Z, Tan Y, Duan C, Li H, Huang H, Li Y, Cao X, Lingle C, Yang Y, Hu H*. ***Science.*** 2024 Aug 9;385(6709):eado7010.

2. Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice. Li W#, Li J#, Li J, Wei C, Laviv T, Dong M, Lin J, Calubag M, Colgan L, Zhou B, Shen Y, Li H, Cui Y, Gao Z, Li T, Hu H, Yasuda R, Ma H*. ***Science.*** 2024 Dec 20;386(6782):1363.

3. Structural basis for sugar perception by Drosophila gustatory receptors. Ma D, Hu M, Yang X, Liu Q, Ye F, Cai W, Wang Y, Xu X, Chang S, Wang R, Yang W, Ye S, Su N*, Fan M*, Xu H*, Guo J*. ***Science.*** 2024 Feb 23; 383: eadj2609.

4. Structure-based design of non-hypertrophic apelin receptor modulator. Wang W#, Ji S#, Zhang W#, Zhang J#, Cai C#, Hu R#, Zang S, Miao L, Xu H, Chen L, Yang Z, Guo J, Qin J, Shen D, Liang P, Zhang Y*, Zhang Y*. ***Cell.*** 2024 Mar 14;187(6):1460-1475.e20.

5. Phasic/tonic glial GABA differentially transduce for olfactory adaptation and neuronal aging. Cheng H, Chen D, Li X, Al-Sheikh U, Duan D, Fan Y, Zhu L, Zeng W, Hu Z, Tong X, Zhao G, Zhang Y, Zou W, Duan S, Kang L*. ***Neuron.*** 2024 Mar 1:S0896-6273(24)00090-4.

6. Friend or foe: The role of stress granule in neurodegenerative disease. Cui Q*, Liu Z#, Bai G*. ***Neuron.*** 2024 Aug 7;112(15):2464-2485.

7. A hypothalamic-amygdala circuit underlying sexually dimorphic aggression. Zhu Z#, Miao L#, Li K, Ma Q, Pan L, Shen C, Ge Q, Dd Y, Yin L, Yang H, Xu X, Zeng L H, Liu Y, Xu H, Li X M, Sun L, Yu Y Q*, Duan S*. ***Neuron.*** 2024 Sep 25;112:0896-6273.

8. Deconstructing the neural circuit underlying social hierarchy in mice. Xin Q, Zheng D, Zhou T, Xu J, Ni Z, Hu H*. ***Neuron.*** 2024 Dec 6:S0896-6273(24)00807-9.

9. A molecularly defined amygdala-independent tetra-synaptic forebrain-to-hindbrain pathway for odor-driven innate fear and anxiety. Wang H#, Wang Q#, Cui L#, Feng X#, Dong P, Tan L, Lin L, Lian H, Cao S, Huang H, Cao P, Li X*. ***Nature Neuroscience.*** 2024 Mar;27(3):514-526.

10. Multiple Loci for Foveolar Vision in Macaque Monkey. Qian M#, Wang J#, Gao Y#, Chen M, Liu Y, Zhou D, Lu H, Zhang X*, Hu J*, Roe A*. ***Nature Neuroscience.*** 2024 Dec 05. doi: 10.1038/s41593-024-01810-4.

11. Immunological nanomaterials to combat cancer metastasis. Pan Y#, Cheng J#, Zhu Y*, Zhang J*, Fan W*, Chen X*. ***Chemical Society Reviews.*** 2024 Jun 17;53(12):6399-6444.

12. Alzheimer's disease early diagnostic and staging biomarkers revealed by large-scale cerebrospinal fluid and serum proteomic profiling. Tao Q, Cai X, Xue Y, Ge W, Yue L, Li X, Lin R, Peng G, Jiang W, Li S, Zheng K, Jiang B, Jia J*, Guo T*, Wu Z*. ***The Innovation.*** 2024 Jan 2;5(1):100544.

13. Structural basis of tethered agonism and G protein coupling of protease-activated receptors. Guo J#, Zhou Y#, Yang Y, Guo S, You E, Xie X, Jiang Y, Mao C*, Xu H *, Zhang Y*. ***Cell Research.*** 2024 July;34:725–734.

14. Structures and ion transport mechanisms of plant high-affinity potassium transporters. Wang J, Luo Y, Ye F, Ding Z J, Zheng S J, Qiao S, Wang Y, Guo J*, Yang W*, Su N*. ***Molecular Plant.*** 2024 Mar 4;17:409-422.

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