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BBMI

Second Half 2023

Research Progress

The Prevention and Relief of Abnormal Affective States

Message from Chief Scientist

Shumin Duan

Chief Scientist of the BBMI Center

Understanding the brain, safeguarding its well-being, and crafting artificial brains stand as enduring objectives in scientific development. Research in brain science addresses the forefront of scientific challenges, not only holding profound implications for self-awareness but also forming a crucial theoretical foundation for the effective diagnosis and treatment of neurological and brain diseases. Moreover, it opens exciting avenues for the development of brain-like computing systems and the next generation of artificial intelligence.

The MOE Frontier Science Center for Brain Science and Brain-Machine Integration at Zhejiang University (referred to as the "BBMI center") maximizes the traditional strengths of related disciplines at Zhejiang University. It unites top-tier forces in neuroscience and related fields, fosters the convergence of neuroscience and artificial intelligence, and diligently pursues significant breakthroughs in basic theory, cutting-edge technology, and transformative progress.

In the latter half of this year, the BBMI center has made remarkable strides in various neuroscience and brain-computer interface domains, yielding compelling and high-quality results. Our investigations have unveiled stress relief as a natural resilience mechanism against depression-like behaviors and elucidated the underlying mechanisms behind the sustained alleviation of depression by ketamine. Notable achievements also include the revelation of gating regulation of negative emotions by specific neurons, the mediating mechanisms of different fear memories by distinct circuits, the fine three-dimensional structure of cannabinoid receptor signaling complexes, and the identification of specialized “appetite suppressor” neurons and genes with significant implications for obesity.

Facing complex neurological diseases, we’ve unraveled the mechanism of meningeal lymphatic dysfunction post-subarachnoid hemorrhage and identified key molecules in Parkinson’s disease, such as α-Synuclein. Pioneering the development of porous microneedle patches for acute spinal cord injury repair, these advances bring hope to patients grappling with such conditions. Additionally, we’ve designed electrochemical artificial synaptic devices and novel human-machine joint learning frameworks, contributing fresh ideas for enhancing neuromorphic brain systems and iterating brain-computer interfaces. Acknowledging these achievements, individuals such as Ge Bai, Yu Qi, Yan Yang, Jianmin Zhang, and others have received national and provincial honors, inspiring us to continually reach new heights.

The BBMI center's vibrant progress is the result of extensive communication and talent exchange. Throughout the year, we've hosted more than 10 experts from around the globe for BBMI Distinguished Lectures and organized high-profile conferences like the Liangzhu Master Forum and Xinglin Scholar Forum. Regular events such as the weekly "Luncheon Party for the Fascinated" and "First Author Forums" provide platforms for academic exchange, showcasing research experiences from postdoctoral and doctoral students.

At BBMI center, our commitment to science, the pursuit of truth, and the passion for discovery remains unwavering. We strive for ever more intriguing and impactful findings in the field of neuroscience. The BBMI center will persist in prioritizing national development, aligning with global technological trends and national strategic needs. By building a multidisciplinary research platform for neuroscience through organized research and development, we aim to make substantial contributions to accelerating the self-reliance and self-improvement of high-level technologies. This aligns with our broader goal of serving as a technological powerhouse and promoting a healthier China and world.

An enlightening trap

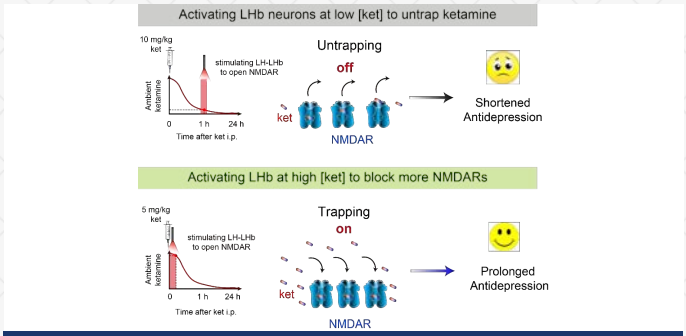
The use-dependent trapping property of ketamine for NMDAR is the essence of its sustained antidepressant effects.

Whilst we know that ketamine initially elicits its rapid and powerful antidepressant effect by blocking the activity of the N-methyl-D-aspartate receptor (NMDAR), the basis of how this antidepressant effect is sustained remains unclear. In answer to this question, the research team led by Prof. **Hailan Hu** recently published an article entitled "*Sustained Antidepressant Effect of Ketamine through NMDAR Trapping in the LHb*" in ***Nature*** online on Oct 18th, 2023. This research revealed that ketamine remains trapped in the NMDAR to mediate the mechanism of the sustained antidepressant effects of ketamine.

The lateral habenula (LHb) plays a crucial role in the antidepressant action of ketamine. Hu's team found that in depression model mice that were subjected to chronic stress, there was a significant reduction in burst firing of LHb neurons lasting for 24 hours after just a single i.p. injection of ketamine. The results from related LHb brain slice recordings showed significant decreases in NMDAR currents that continued for 24 hours post-ketamine administration and even persisted when ketamine was washed out of the preparation. This led the researchers to suggest that ketamine is trapped within the NMDAR channel upon its closing.

As ketamine is a use-dependent blocker for the NMDAR, its binding and unbinding from the receptor channel depends on both the ambient concentration of the drug and whether the channel is open or closed. To test the idea of NMDAR trapping, the researchers released ketamine from the NMDAR using a method that included the activation of the presynaptic axons and injecting current into the postsynaptic neurons. This promoted the opening of the NMDARs and resulted in the restoration of the NMDAR currents in LHb neurons.

Harnessing the dynamic equilibrium of ketamine–NMDAR interactions by activating the LHb and opening local NMDARs at different plasma ketamine concentrations, the investigators then used optogenetics to stimulate the inputs to the LHb neurons one hour after administering ketamine (at a time when the ketamine's concentration is lower, promoting its unbinding from its receptor). This intervention not only removed the blockage on NMDARs but also abolished the lasting antidepressant effects of ketamine in behavioral assessments conducted 24 hours after ketamine i.p. injection. On the other hand, activating the LHb pathways directly after ketamine administration (when its concentration is high) prolonged the ketamine's antidepressant effects.



Bidirectionally activating the LHb modulates the duration of the ketamine antidepressant effect

These results provide new insights into the causal mechanisms of the sustained antidepressant effects of ketamine. The ability to modulate the duration of ketamine action based on the biophysical properties of ketamine–NMDAR interactions should open up new opportunities for the therapeutic use of ketamine.

Ma S[#], Chen M[#], Jiang Y, Xiang X, Wang S, Wu Z, Li S, Cui Y, Wang J, Zhu Y, Zhang Y, Ma H, Duan S, Li H, Yang Y, Lingle C, Hu H[*]. Sustained antidepressant effect of ketamine through NMDAR trapping in the LHb. ***Nature***. 2023 Oct;622(7984):802-809.

HAILAN HU'S RESEARCH GROUP

For social animals, emotions and health are regulated by various social behaviors. Hailan Hu's group is 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.

The increasing prevalence of depression among adolescents is a growing societal issue, which not only affects the developmental processes for young people but also brings concern about the side effects resulting from various medical treatments. Can your research findings be applied to the treatment of adolescent depression?

Shuangshuang Ma (Co-First Author): Our current study has not specifically focused on the impact of ketamine on adolescent depression. However, the side effects of medication are indeed of significant concern in the clinical treatment of depression. Lower doses help reduce side effects. Based on the specific dynamic equilibrium of ketamine-NMDAR interaction, we found that immediately after administering ketamine injection to animals (at a brain concentration higher than the Kd value), simultaneous activation of the LHb prolongs the antidepressant duration of lower doses of ketamine. This strategy achieves lower doses of ketamine for long-term antidepressants. Furthermore, our study has found that locally infused ketamine into the lateral habenula with higher concentrations directly results in sustained antidepressant effects of ketamine. If this strategy could be applied to patients already undergoing brain surgery, by directly introducing high concentrations of ketamine into the lateral habenula, it would not only promote the binding of ketamine to NMDARs but also reduce side effects in peripheral organs or other brain regions. It may also achieve more lasting antidepressant outcomes.

In patients with severe depression, the suicide rate among females is significantly higher than that of males. Is there any study on the exploration of antidepressant drug mechanisms and clinical testing of new drug development that takes into account gender differences?

Shuangshuang Ma: Taking ketamine as an example, current preclinical research has found significant differences in the metabolism of ketamine between male and female mice (Gould, ***Nature***, 2016). The researchers have discovered that the dose of ketamine required for an antidepressant effect is lower in female mice compared to male mice. Further research into the mechanism of ketamine on gender differences is needed.

Regarding the target of the NMDAR for ketamine's sustained antidepressant effects, is there any other antagonist drug that has been applied in clinical treatment? What are its effects?

Shuangshuang Ma: In 2021, the FDA approved a medication called AXS-05 for clinical use in the treatment of major depressive disorders. AXS-05 is composed of another pore-trapping-type NMDAR inhibitor dextromethorphan and bupropion, which slow down the metabolism of dextromethorphan. In phase 3 clinical trials, AXS-05 has been shown to improve symptoms in patients with depression effectively.

Installing CB1 'traffic control' measures for disease targeting

Uncovering the molecular mechanism of the biased signaling transduction toward the cannabinoid receptor.

Figure 1. The cover is an artistic rendering of the scientific concept of synthetic cannabinoid (with cannabis leaves and fields) acting on CB1 (an off-road vehicle) in the brain (the mountain). Upon activation of CB1, the CB1 vehicle initiates locomotion on a highway and can be directed towards either specific route (Gi or β-arrestin signaling pathways)

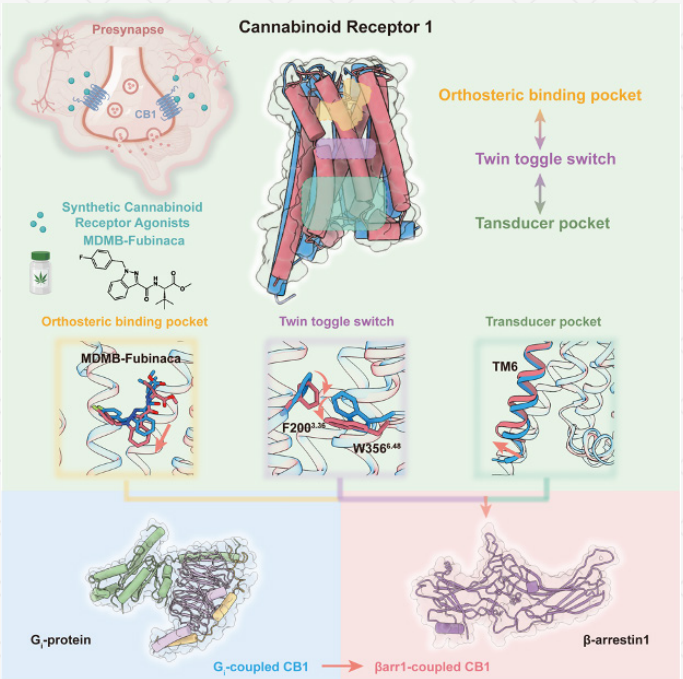


Figure 2. The high-resolution cryo-EM structure of CB1-β-arrestin1 complex offers insights into the distinction of agonists in various transducer-coupled states and reveals the molecular mechanism of the biased signaling, facilitating rational drug design targeting CB1

The cannabinoid receptor 1 (CB1) serves as the main target of Cannabis. Recent preclinical work renders CB1 a promising therapeutic target for pain relief, anti-anxiety, and anti-epileptic treatment. CB1 mediates physiological responses by predominantly signaling either through the adenylate cyclase inhibitory G-protein family ($G_{i/o}$) or by coupling to β-arrestin. The selective activation or inhibition of G-protein or β-arrestin signaling cascades therefore hold potential for the generation of drugs with a more precise targeting profiles and fewer adverse effects, ultimately expanding the therapeutic range from traditional treatments. However, owing to the paucity of knowledge relating to the biased signaling transduction mechanism towards CB1, the development of drug candidates targeting CB1 has been long hindered by their adverse effects.

Addressing the long-standing Cannabis problem relating to the biased signaling oddity that has vexed scientists for decades, the joint research team led by Prof. **Xiao-Ming Li** and Prof. **Yan Zhang** has recently published an article in ***Cell*** on Dec 14th, 2023, entitled *"Snapshot of the cannabinoid receptor 1–arrestin complex unravels the biased signaling mechanism"*. This research achieved a breakthrough by unraveling signaling bias mechanism toward cannabinoid receptor 1 (CB1), facilitating safer synthetic cannabinoid targeting of CB1.

In this study, researchers have determined the 3.1 Å cryo-electron microscopy (cryo-EM) structure of the agonist MDMB-Fubinaca (FUB)-bound CB1–β-arrestin1(βarr1) complex. So far, the CB1–βarr1 complex is the most well-resolved cryo-EM map among the available GPCR–βarr1 complexes, thus offering an unambiguous structural scaffold for subsequent conformational analysis. The availability of this high-resolution map facilitates the accurate determination of the binding features of ligand in the CB1–βarr1 structure and reveals notable differences in the transducer pocket and ligand-binding site compared with the G_i-protein complex, a task that had remained unsuccessful for most GPCR–βarr1

XIAOMING LI'S RESEARCH GROUP

The research team led by Professor Xiao-Ming Li has been dedicated to seeking key molecular targets for the treatment of nervous system diseases such as anxiety, depression, posttraumatic stress disorder, and related pain. Their current researches pursuit encompass elucidating the neural circuit mechanisms underlying emotions, unveiling the molecular mechanisms of neuro-psychiatric disorders, as well as developing corresponding treatment strategies.

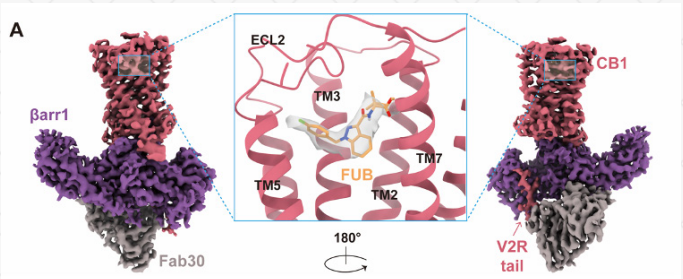


Figure 3. Cryo-EM structure of the FUB-bound CB1pp-βarr1 complex

complexes that have been characterized at lower resolutions.

The comparison between the CB1–βarr1 complex bound to the agonist FUB and the previously reported CB1–G_i complex (also bound to FUB), revealed notable differences in the receptor and FUB, which shed light on the discrepancies in coupling between β-arrestin and G-protein. On the intracellular side, βarr1 occupies a wider transducer pocket promoting substantial outward movement of the TM6 and distinctive twin toggle switch rearrangements. Combined with functional assays and structural analysis, researchers revealed that the twin toggle switch participates in constriction or expansion of the transducer pocket and serves as a fine-tune switch determining the preference of the downstream signaling pathway of CB1. In addition to revealing disparities on the transducer pocket, the FUB also displays substantial changes in different states where the FUB adopts a different pose and inserts more deeply in the βarr1-coupled state than in the G_i-coupled state. Therefore, our CB1pp–βarr1 structure presents an avenue to comprehend the manner in which slight changes in the transducer-binding interface are propagated and amplified toward the ligand-binding pocket and vice versa.

Taken together, the joint labs led by Professors Li and Zhang have pioneered studies on cannabinoid receptors. This research not only proposes a comprehensive model for the molecular mechanism of signaling bias, but also builds a solid foundation for the development of safer synthetic cannabinoids and the clinical application for the CB1 compounds in treating neurological and psychiatric disorders.

Liao YY#, Zhang H#, Shen Q#, Cai C#, Ding Y, Shen DD, Guo J, Qin J, Dong Y, Zhang Y*, Li XM*. Snapshot of the cannabinoid receptor 1-arrestin complex unravels the biased signaling mechanism. ***Cell***. 2023 Dec 12:S0092-8674(23)01267-9. doi: 10.1016/j.cell.2023.11.017.

People usually consider *Cannabis* as a drug. What prompted you to investigate the functions of cannabinoid receptors and develop their medicinal value?

Yuying Liao (First Author) : Although marijuana is an illegal drug and is restricted in many countries, it has been documented in classical ancient texts of traditional medicine dating back thousands of years as a therapeutic agent. The active components of Cannabis act on cannabinoid receptors in humans, effectively alleviating syndromes such as anxiety, depression, pain, and epilepsy. However, the severe side effects associated with cannabis-based drugs, including drug tolerance and abuse potential, significantly limit their clinical application. Therefore, it is of significance for us to pursue the development of a first-in-class pharmaceutical agent targeting CB1 that minimizes adverse effects.

What is your strategy for developing safe medicine targeting CB1? Are there any relevant studies now?

Yuying Liao: The selective activation or inhibition of G-protein or β-arrestin signaling cascades could potentially be a pharmacological strategy for the generation of drugs with a more precise targeting profile and fewer adverse effects, ultimately expanding their therapeutic ranges. An example of this is the potential for enhancing β-arrestin signaling through the 5-HT_{2A} serotonin receptor to produce an antidepressant effect without hallucinogenic side effects. Similarly, oliceridine, targeting the μ-opioid receptor (μOR), limits β-arrestin recruitment and increases analgesic effect while reducing on-target adverse effects compared to morphine.

What difficult technical challenges did the team encounter during the resolving the structure of the CB1-β-arrestin1 complex?

Yuying Liao: The stabilization of GPCR–arrestin complexes has presented a longstanding challenge due to the requisite receptor phosphorylation and the weak affinity of the arrestin–seven transmembrane domain interaction. To solve these problems, we utilized the CB1 agonist with the highest potency and efficacy and substituted the original C-tail of CB1 with the C-terminus of the vasopressin 2 receptor to optimize the CB1–β-arrestin1 complex preparation.

After this project, what progress have you made, what issues are you focusing on, and what kind of results are you expecting to achieve?

Yuying Liao: The development of biased ligands targeting CB1 represents a formidable challenge, typically necessitating substantial experimental and material resources. We have efficiently and successfully developed biased small molecules based on our CB1 structure and the structure-activity relationship. We will continue to investigate their functions in animal experiments, particularly in nervous system diseases associated with cannabinoid receptor 1 and relating to pain, anxiety, and depression. We hope our research will provide novel drugs for the treatment of these diseases that may have less adverse effects than some traditional treatments, thus bringing new hope for those patients.

Facilitating 'special delivery' to spinal chord injury sites

Porous microneedle patch with sustained extracellular vesicles delivery mitigates severe spinal cord injury.

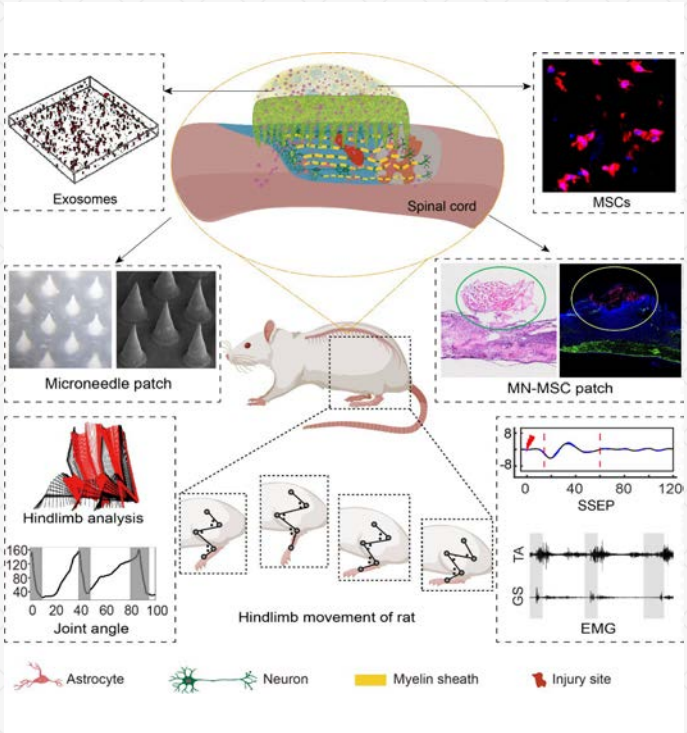
Spinal cord injury represents a central nervous system injury caused by trauma. It has an incidence rate of up to 15 to 40 cases per million people, with such incidences leading to an annual global economic loss of up to 40 billion dollars. On July 7, 2023, a research team led by **Xuhua Wang** published a study titled *"Porous microneedle patch with sustained extracellular vesicles delivery mitigates severe spinal cord injury"* in ***Nature Communications***.

The team proposed a patch for treating spinal cord injuries by continuously delivering extracellular vesicles. They evaluated the efficacy of a porous microneedle patch based on mesenchymal stem cells in a rat model of spinal cord injury. They found that the microneedle patch could improve the microenvironment of the damaged tissue area, promote blood vessel formation, and protect the remaining nerve tissue. Importantly, the microneedle patch delivered extracellular vesicles sustainably for at least 7 days, which led to significant functional recovery. This mesenchymal stem cell-based porous microneedle patch therefore may bring hope for the rehabilitation of many spinal cord injury patients.

The mesenchymal stem cell-based porous microneedle patch that the team developed exhibits excellent nanoscale dimensions (approximately 100nm), with good biocompatibility and mechanical properties. Furthermore, it can efficiently and continuously deliver extracellular vesicles *in vivo*. Mesenchymal stem cells can thereby survive at the injury site long enough to reach the optimal therapeutic window for spinal cord injury. The research team introduced this method to enhance the treatment effectiveness without the need for direct introduction of mesenchymal stem cells into the spinal cord. This microneedle patch was able to sustain the delivery of extracellular vesicles, and by the 7th day of implantation, such cells remained viable, successfully delivering extracellular vesicles to the injured area of the spinal cord for continuous treatment.

After validating the regenerative function of the mesenchymal stem cell-based porous microneedle patch, the research team conducted more systematic evaluation of the practical efficacy of the designed patch. Through comparative analysis of gene expression and tissue morphology, it was observed that while both the MN-EV and Gel-MSC showed some positive therapeutic effects, in the rats of the MN-MSC group, these were more pronounced and resulted in more significant functional recovery, up to levels approaching that of normal rats. These results indicate that the mesenchymal stem cell-based porous microneedle patch can exert neuroprotective effects, aiding in the eventual restoration of motor function in spinal cord injury.

This study has not only developed an efficient microneedle patch for the sustainable delivery of extracellular vesicles, promoting functional recovery after spinal cord injury, but also provided new insights and methods for the use of extracellular vesicles in spinal cord injury treatment. In the future, the team plans to continue optimizing the design and manufacturing of personalized MSC porous microneedle patches to successfully translate a safe and effective microneedle patch for spinal cord injury treatment into clinical practice within the next few years. The expectation is that this will benefit a greater number of spinal cord injury patients.



Physiological utility of relief and underlying dopaminergic circuit mechanisms

Fang A#, Wang Y#, Guan N#, Zuo Y#, Lin L, Guo B, Mo A, Wu Y, Lin X, Cai W, Chen X, Ye J, Abdelrahman Z, Li X, Zheng H, Wu Z, Jin S, Xu K, Huang Y, Gu X, Yu B, Wang X*. Porous microneedle patch with sustained delivery of extracellular vesicles mitigates severe spinal cord injury. ***Nature Communications***. 2023 Jul 7;14(1):4011.

XUHUA WANG'S RESEARCH GROUP

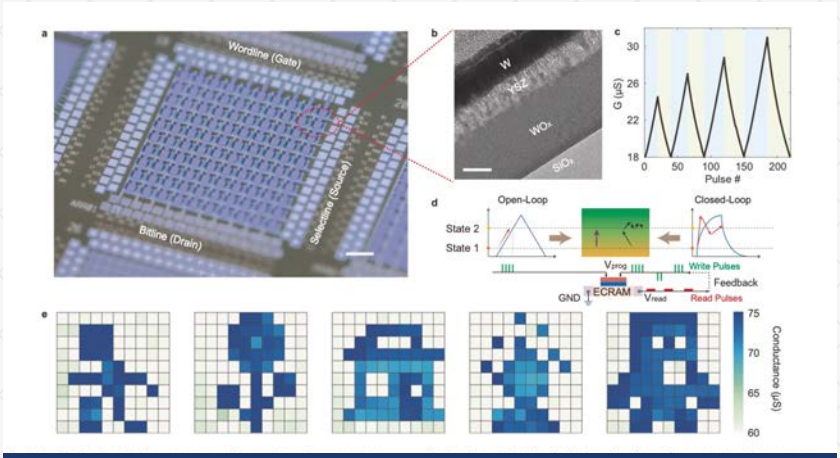
focuses primarily on drug development and drug delivery systems for the treatment of central nervous system diseases. Their main research interests include large language models, drug design based on artificial intelligence technology, and the design and development of AAV gene delivery vectors. For more information about the laboratory, you can visit their lab website at www.zjuwanglab.com.

ECRAM

A new type of artificial synapse for on-chip learning.

Developing specialized computing chips and hardware systems that mimic the information processing mechanisms of the human brain is a new trend in artificial intelligence. The co-location of processing and storage units within the hard-wired neural circuits in the brain provides great inspiration that can be utilized to mitigate the data shuttling problem between the physically-separated processor and memory in von Neumann architecture computers.

Over recent years, researchers have utilized new devices such as memristors to construct just such a kind of neuromorphic system, achieving ultra-high computational efficiency exceeding 100 TOPS/W. However, due to the limited program accuracy of these emerging memory devices, their main applications have been limited to inference tasks. Learning tasks remain a significant challenge.



Micrograph image of an ECRAM array and demonstration of its pattern programming capability. Image patterns can be programmed into the array in an open-loop fashion, without any feedback adjustment, which is significantly faster and more energy efficient than conventional devices that would require tenth of iterative programming cycles

On October 4, 2023, Professor **Gang Pan** and Professor **Peng Lin**'s research group published a research article entitled "*Open-loop analog programmable electrochemical memory array*" in the journal ***Nature Communications***. This work addressed the challenge of directly achieving high-precision weight updates in neuromorphic devices. They designed and implemented a new electrochemical artificial synapse device that is better suited for neural network learning tasks, providing a new device solution for online learning-oriented neuromorphic systems.

There has long been a dilemma in using high precision devices for online learning. On one hand, most neuromorphic devices can store more than 5-10 bits of weight values in comparison to far lower binary storage levels for traditional SRAM and DRAM units. These new devices can also perform multi-bit multiplications and matrix operations in the analog domain, and can therefore process a high volume of data with relatively low energy consumption. However, the rapid programming of high-precision values into a neuromorphic device remains a significant challenge. As a result, existing devices often require many iterative write-and-verify programing cycles to achieve desired programming accuracy. This greatly limits the speed and efficiency of such systems in training tasks.

Professor Pan and Professor Lin's group have found inspiration on how to tackle this issue from the battery charging and discharging process. In this, the team have introduced a highly controllable electrochemical artificial synapse device (ECRAM). This new device utilizes the reversible spatial movement of oxygen ions to achieve linear weight updates. A single open-loop write process can then achieve high weight precision, addressing the dilemma between high-precision weight storage and fast writing in a single device. This innovation meets the frequent weight update requirements in neural network training.

To validate the potential in various online learning tasks, the team conducted demonstrations on a prototype array chip. They achieved classification accuracy comparable to existing software in small-scale classification tasks and further evaluated its learning capabilities in large-scale tasks through simulation. In future research, the team aims to significantly expand the array integration scale through heterogeneous integration technology. In this, they are striving to realize the practical application of this technology over the next few years, potentially impacting fields such as brain-computer interfaces and contributing to the rapid development of artificial intelligence linked to life sciences.

Chen P, Liu F, Lin P*, Li P, Xiao Y, Zhang B and Pan G*. Open-loop analog programmable electrochemical memory array. ***Nature Communications***. 2023 Oct; 14(1): 6184-6193.

GANG PAN'S RESEARCH GROUP

primarily focuses on critical aspects of brain-machine interaction, fusion, simulation, and enhancement. This includes the study of spiking neural networks; brain-inspired intelligence; neuromorphic devices and neuromorphic computing chips and architectures; neural decoding methods and behavioral control; new brain-machine interfaces and fusion enhancement; human-machine symbiotic intelligence; foundational theories; and other key technologies covering similar areas. Their aim is to develop new computing models, intelligent forms, and novel hardware/software architectures.

Relief from stress naturally combats depression

Relief from stress as a homeostatic defense mechanism for mood regulation – with the underlying neural circuit also clarified.

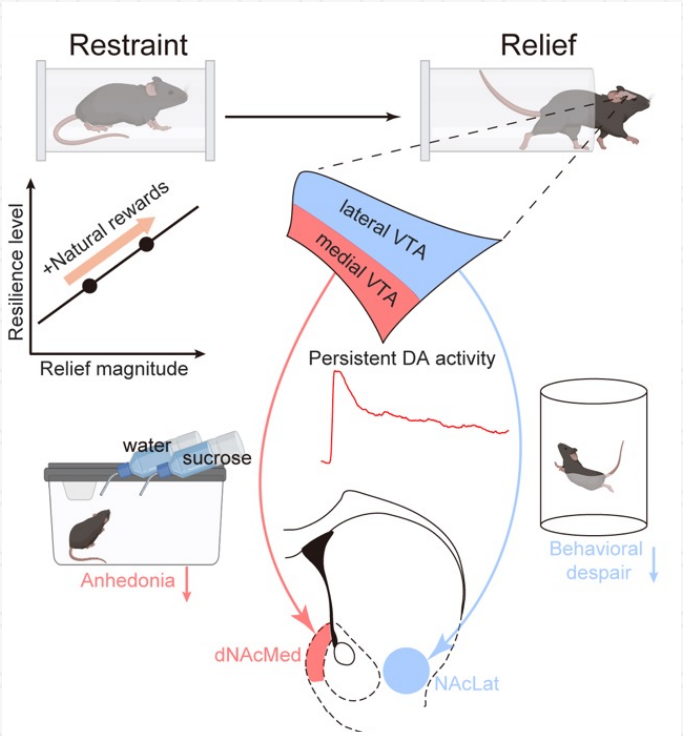
One fascinating feature of emotions is that the ending of one particular strong emotional state is often followed by a state of opposite valence. While the aversive withdrawal state from substance-induced euphoric mood has been extensively investigated, the opposite phenomenon, that is the 'appetitive state' after the termination of negative stimuli – the so-called "relief state", is much less explored.

The positive valence of relief has been demonstrated from flies to humans. Utilizing the appetitive state of relief, researchers have built up their understanding of relief learning paradigms, associating various cues occurring upon the ending/omission of stress, threat, or pain, respectively, to reinforce behaviors. However, despite progress in relief learning, several fundamental questions have remained unanswered about stress relief *per se*: What is the evolutionary purpose to have a state of relief? Can this positive emotional state be harnessed to combat psychiatric disorders such as depression?

The inherently opposite nature of the valence between stress and relief raises the intriguing possibility that relief may counteract the detrimental effects of stress, playing a role in stress resilience. However, such a possibility has not been tested experimentally.

The research team led by **Hailan Hu** has recently published an article titled "*Stress Relief as a Natural Resilience Mechanism against Depression-like Behaviors*" in ***Neuron*** online on Sep 29th, 2023. This research discovered such relief as a natural resilience mechanism against depression, having deconstructed the neural circuit mechanisms underlying relief.

Based on the discovery that relief magnitude strongly correlates with resilience level to depression, researchers further revealed that blocking stress relief causes vulnerability to depression-like behaviors on mice, whereas natural rewards supplied shortly after stress promotes resilience. Stress relief is mediated by reward-related mesolimbic dopamine neurons, which show minute-long persistent activation after stress termination. Circuitry-wise, activation or inhibition of circuits downstream of the ventral tegmental area (VTA), during the transient relief period, bi-directionally regulate depression resilience. These results reveal an evolutionary function of stress relief in depression resilience, and identify the neural substrate mediating this effect. Notably, this study also develops a behavioral strategy of augmenting the positive valence of stress relief with natural rewards to prevent depression.



Physiological utility of relief and underlying dopaminergic circuit mechanisms

Dong Y, Li Y, Xiang X, Xiao ZC, Hu J, Li Y, Li H, Hu H*. Stress relief as a natural resilience mechanism against depression-like behaviors. ***Neuron***. 2023 Sep 29; S0896-6273(23)00668-2. Advance online publication.

HAILAN HU'S RESEARCH GROUP

For social animals, emotions and health are regulated by various social behaviors. Hailan Hu's group is 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.

The YIN - YANG balance of dopamine

Dopamine release and negative valence gated by inhibitory neurons in the laterodorsal tegmental nucleus.

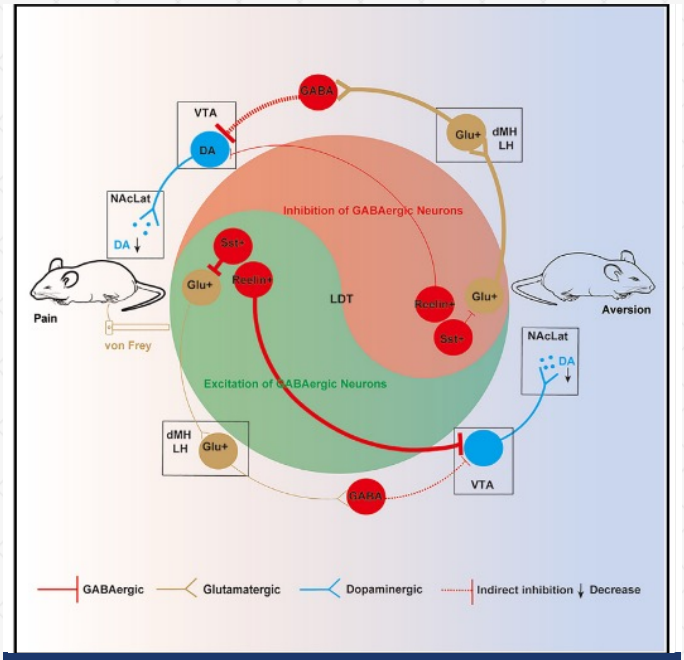
Pleasurable things often trigger the release of dopamine in the brain, inducing a sense of satisfaction and pleasure, and helping us maintain motivation. Conversely, we subconsciously avoid nauseating, painful, and other aversive stimuli. Aversive behaviors help us promptly evade risks and reduce the likelihood of harm. This "approach-avoidance" motivational behavior is crucial for the survival of animals. The mesolimbic dopamine system plays a crucial role in regulating motivated behavior. Motivated behavior is not only driven by internal states but also influenced by external environmental stimuli (external drivers). However, how the brain senses and conveys the reward or aversive information to the midbrain dopamine (DA) system and influences motivated behavior has long been an important scientific question in the field of neuroscience.

Dr. **Hongbin Yang**, has addressed those important scientific questions. They have explained how "reward information" is precisely transmitted between the ventral tegmental area (VTA) and the nucleus accumbens (***Neuron***, 2018); and how pain inhibits VTA dopaminergic subpopulations encoding negative emotional behavior through the parabrachial nucleus-substantia nigra circuit (***Nature Neuroscience***, 2021). On July 26, 2023, the team published a new research paper in the Journal of ***Neuron*** titled "*Dopamine Release and Negative Valence Gated by Inhibitory Neurons in the Laterodorsal Tegmental Nucleus*". They revealed two types of GABAergic neurons in the laterodorsal tegmental nucleus (LDT) that process sensory stimuli and regulate dopamine release in the nucleus accumbens through distinct neural circuits.

The researchers first utilized various behavioral paradigms combined with fiber photometry recording, mini-Ca^{2+} imaging, optogenetics, and chemogenetics to demonstrate that both excitation and inhibition of LDT GABAergic neurons promote aversive behavioral responses and decrease dopamine neurotransmission in the nucleus accumbens. These contradictory experimental results led researchers to speculate that LDT GABAergic neurons contain multiple neural subtypes that may participate in regulating the mesolimbic dopamine system through different parallel circuits. When using optogenetics or pharmacogenetics to non-selectively excite or inhibit LDT GABAergic cell bodies, similar phenomena of excitation and inhibition could be observed.

Through retrograde tracing and immunohistochemical staining techniques, researchers identified two molecularly defined GABAergic subtypes in LDT. The first type is somatostatin (SST)-positive GABAergic neurons, which through a disinhibitory mechanism, influence hypothalamic excitatory neurons, indirectly regulating the midbrain dopamine system and corresponding motivational behavior. The second type is Reelin-positive GABAergic neurons, which directly project to the VTA, inhibiting dopamine neurons and promoting aversive behavior.

In summary, this study found that LDT GABAergic neurons respond to various aversive stimuli and directly or indirectly transmit external information to the midbrain dopamine system through two different neural circuits, influencing the release of dopamine in the nucleus accumbens. This study further enhances our understanding of the neural circuit mechanisms regulating different motivated behaviors in the mammalian brain in response to negative valence stimuli.



Two populations of LDT GABAergic neurons modulate different motivational behaviors through different circuitry connections

Du Y, Zhou S, Ma C, Chen H, Du A, Deng G, Liu Y, Tose A, Sun L, Liu Y, Wu H, Lou H, Yu Y, Zhao T, Lammel S, Duan S, Yang H*. Dopamine release and negative valence gated by inhibitory neurons in the laterodorsal tegmental nucleus. *Neuron*. 2023 Jul 18:S0896-6273(23)00480-4.

HONGBIN YANG'S RESEARCH GROUP

predominantly employs a variety of state-of-the-art technologies to decode the processing of sensory information within dopaminergic circuits. His team's focus is on understanding how dopamine circuits integrate sensory information input, arousal state, and motor systems, to orchestrate diverse motivated behaviours. Their numerous original research papers have been disseminated in reputable journals, including ***Neuron*** and ***Nature Neuroscience***.

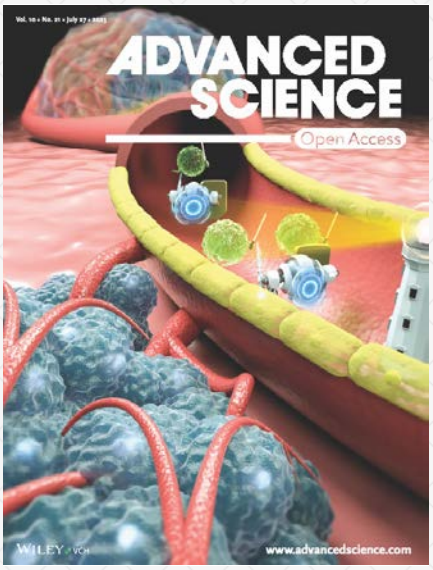
mLVs and SAH

Single-cell RNA sequencing and spatial transcriptomics reveal the pathogenesis of meningeal lymphatic dysfunction after experimental subarachnoid hemorrhage.

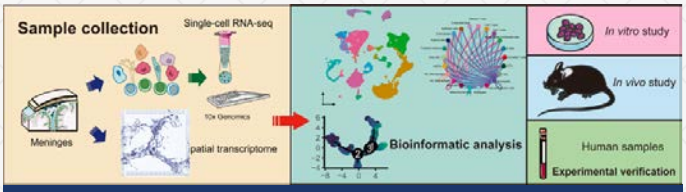
In Subarachnoid Hemorrhage (SAH) is a devastating subtype of stroke. It is mainly caused by rupture of intracranial aneurysms and is characterized by high rate of disability and mortality. Early brain injury (EBI) and delayed cerebral ischemia (DCI) are the two major pathological processes often noted as occurring beyond SAH diagnosis. Current therapies targeting EBI and/or DCI show limited clinical benefits. Therefore, there remains an urgent need to develop novel therapeutic strategies to promote neurological function recovery of SAH patients. Extravasation of erythrocytes in cerebrospinal fluid (CSF) has been shown to be crucial to SAH progress, involving severe disturbance of CSF circulation in both acute and late phases. CSF circulation dysfunction can then lead directly to the formation of brain edemas and hydrocephalus through increasing intracerebral pressure (ICP) and decreasing cerebral blood perfusion. Considering these pathological feature of SAH, accelerating extravasated blood clearance in subarachnoid space (SAS) may be an effective therapeutic approach.

The meningeal lymphatic system within dura mater transports macromolecules away from brain parenchyma and delivers CSF to the surrounding cervical lymph nodes. Weakening of this central nervous system (CNS) drainage leads to impairment of pathological substance clearance and is associated with neurodegenerative and age-associated neurological diseases. Recently, mLVs have also been reported to drain extravasated erythrocytes from CSF into deep cervical lymph nodes (dCLNs) after SAH. These findings further demonstrate that mLVs play key roles in the clearance of intracranial waste. However, little is known about cellular architecture and gene regulatory features of mLVs, especially after SAH.

On May 21, 2023, **Jianmin Zhang**'s research group published their significant findings as a cover article in ***Advanced Science***. They creatively applied single-cell transcriptomics and spatial transcriptomics to reveal the cellular, molecular, and spatial changes in mLVs following SAH, also revealling potential mechanisms of mLVs functional impairments.



Initially, the team discovered that mLVs function is markedly compromised after SAH, with the drainage capability most evidently affected 24 hours post-injury. To glean deeper insights into the cellular types, gene expression patterns, and spatial shifts of mLVs after SAH, the researchers employed single-cell and spatial transcriptomics of the meninges of mice subjected to sham operations, as well as those 24 and 72 hours post-SAH modeling. Their findings underscored that the binding between the secreted protein THBS1 and the meningeal lymphatic endothelial cells (mLECs) surface receptor CD47 is a crucial mechanism underlying the damage to mLVs after SAH. Co-cultivation systems *ex vivo* further substantiated the pivotal role of THBS1 secreted by monocytes in post-SAH mLECs damage. Finally, the researchers used bioinformatics to identify S100A6 as a potential key injury biomarker for mLVs post-SAH. Moreover, both THBS1 and S100A6 expressions in the cerebrospinal fluid of SAH patients were significantly elevated, displaying a strong correlation and association with adverse outcomes (mRS > 2).



Murine dura matters were dissociated for scRNA-seq and spatial transcriptomics. Integrated analysis of transcriptome data and the following *in vivo/vitro* experiments were performed

In summary, through an amalgamation of single-cell transcriptomics and spatial transcriptomics, the study identified the cellular types of mouse meninges, crafted a comprehensive single-cell transcriptomic landscape of post-SAH meninges, and unearthed the potential mechanisms underlying mLVs injuries post-SAH. This may lead to prospective therapeutic strategies targeting mLV protection post-SAH.

Wang X, Zhang A, Yu Q, Wang Z, Wang J, Xu P, Liu Y, Lu J, Zheng J, Li H, Qi Y, Zhang J, Fang Y, Xu S, Zhou J, Wang K*, Chen S*, Zhang J*. Single-Cell RNA Sequencing and Spatial Transcriptomics Reveal Pathogenesis of Meningeal Lymphatic Dysfunction after Experimental Subarachnoid Hemorrhage. ***Advanced Science***. 2023 May 21;e2301428.

JIANMIN ZHANG'S RESEARCH GROUP

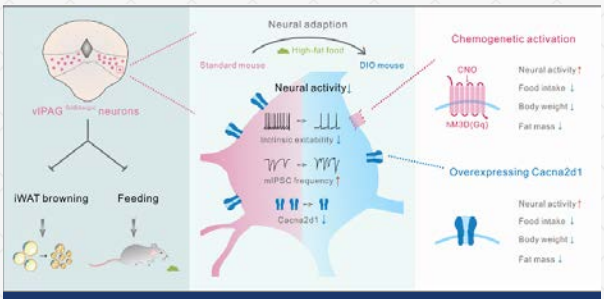
is committed to both clinical and basic research on cerebrovascular diseases, neuro-oncology, and the translational application of brain-machine interfaces. Over the past three years, their groundbreaking work has published on influential journals including ***Immunity, Nano Today, ACS Nano, Advanced Science, JCI,*** and ***PNAS***.

Obesity and the brain

Neural adaption in midbrain GABAergic cells contributes to high-fat-diet-induced obesity.

Maintaining energy homeostasis is essential for the survival of species, whereas excessive energy intake predisposes individuals to obesity. In modern society, easy access to high-calorie food and sedentary lifestyles have led to a steady increase in the incidence of obesity. Obesity is usually accompanied by a series of metabolic disorders and is a strong factor contributing to an increased risk of other related diseases such as hypertension, hyperlipidemia, and diabetes. All such outcomes place a severe burden upon both society and families with obesity now recognized as one of the most pressing worldwide public health concerns.

Although previous studies have demonstrated that improving dietary structure and lifestyle habits are effective avenues for achieving weight loss, such results are often temporary, with many people regaining weight within 5 years. This suggests that high-calorie foods may not only influence body weight and metabolism but also induce changes in the central nervous system (CNS). Exploring such alterations and revealing the mechanisms behind them may be the key to finding effective and long-lasting obesity treatment strategies.



GABAergic neurons in the periaqueductal grey regulate weight metabolic homeostasis

Prof. **Hao Wang**'s research group has dedicated themselves to investigating the neural circuit mechanisms involved in regulating energy metabolic homeostasis in the CNS. In their previous work, they made the significant discovery that GABAergic neurons in the ventrolateral periaqueductal grey (vlPAG) possess a feeding-regulated effect (***Cell Reports***, 2019). On November 1, 2023, they published an article in ***Science Advances***, entitled "*Neural adaption in midbrain GABAergic cells contributes to high-fat-diet-induced obesity*". This research discovered that vlPGA^{GABA} neurons are involved in regulating the body's energy balance and helping to maintain weight homeostasis. This provides a new idea for the treatment of obesity.

Firstly, the researchers found that long-term chemogenetic activation of vlPAG GABAergic neurons effectively reversed obesity in high-fat-diet-induced obesity (DIO) mice. This rescue effect was achieved by decreasing food intake, increasing energy expenditure, and promoting inguinal white adipose tissue (iWAT) browning.

Next, through *in vivo* fiber-photometry calcium imaging, the researchers discovered that vlPAG GABAergic neurons have a relatively high basal level of Ca^{2+} activity but are quickly and persistently suppressed during feeding bouts. However, DIO mice showed more robust Ca^{2+} signaling decreases during refeeding of high-fat food as compared to NFD mice. Further electrophysiological recordings provided insights into the mechanisms underlying these observations, and revealed that the reduced activity of these feeding-regulated neurons in DIO mice was due to an increase in presynaptic inhibitory inputs and a decrease in the intrinsic excitability of these neurons. Such findings suggest that chronic high-fat food intake leads to long-term inhibition of these feeding-regulated neurons, ultimately contributing to increased food intake and obesity.

The team further employed single-cell nucleus transcriptome sequencing technology to conduct a comprehensive analysis of gene expression changes in the vlPAG GABAergic neurons of DIO and control mice. They identified a crucial gene called CACNA2D1 which exhibited significantly reduced expression levels in DIO mice. To investigate the potential role of CACNA2D1, the researchers designed and injected AAV-cacna2d1 into vlPAG GABAergic neurons to overexpress CACNA2D1 in DIO mice. Remarkably, this intervention led to a reversing of the obesity phenotype by reducing food intake, promoting adipose tissue browning, and rescuing the excitability of these feeding-regulated neurons in the vlPAG. These findings suggest the potential of utilizing CACNA2D1 overexpression in the treatment of obesity.

Collectively, Wang's research group demonstrated that the feeding-regulated neurons in the vlPAG are involved in the regulation of energy balance and body weight homeostasis. The neuronal activity of these neurons is aberrantly reduced in the obese state. This work reveals a novel neural mechanism of diet-induced obesity where the neurons responsible for suppressing appetites stop working, and identifies the CACNA2D1 gene as a promising target for obesity treatment. It is hoped that this study will provide a mechanistic foundation for finding lasting and effective obesity interventions and therapeutic strategies.

Wang X, Wu X, Wu H, Xiao H, Hao S, Wang B, Li C, Bleymehl K, Kauschke SG, Mack V, Ferger B, Klein H, Zheng R, Duan S, Wang H*. Neural adaption in midbrain GABAergic cells contributes to high-fat diet-induced obesity. ***Science Advances***. 2023 Nov 3;9(44):eadh2884.

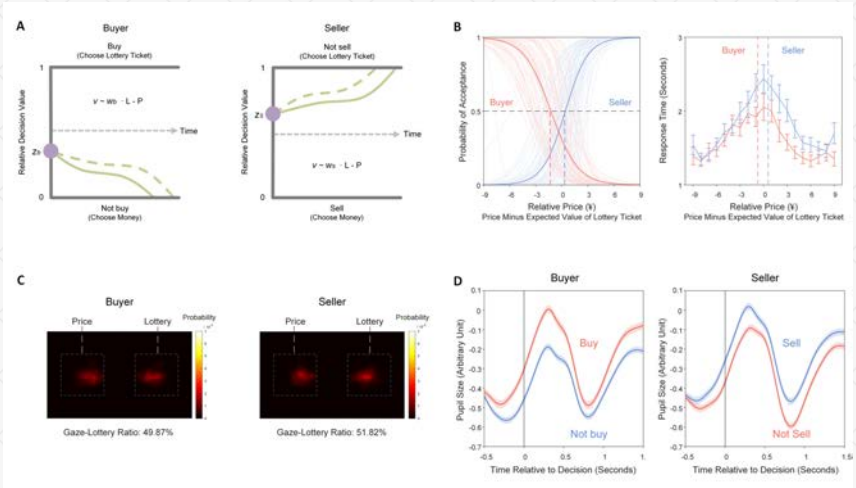
HAO WANG'S RESEARCH GROUP

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

Focusing on the eyeball economy

Cognitive computational mechanisms of trading behaviors.

The increasing scarcity of attention in the age of information explosion has given rise to what is known as the 'eyeball economy'. To date, little has been formulated about the dynamics of buyers' and sellers' attentional allocation during trading. On August 23, 2023, ***Science Advances*** reported an eye-tracking study conducted by a team led by **Feng Sheng**, detailing the development of an attention-based trading theory and addressing a classic anomaly in trading—the endowment effect.



The cognitive computational model of trading
(A) The computational model of decision-making during trading
(B) Decisions and decision times of buyers and sellers during trading
(C) Gaze allocations of buyers and sellers during trading
(D) Pupil-size changes of buyers and sellers during trading

The endowment effect refers to the phenomenon that the price a person would be willing to accept (WTA) to give up an object when acting as a seller is often higher than the price the same person would be willing to pay (WTP) to acquire the same object when acting as a buyer. In other words, sellers often value goods more than buyers do. The discovery of the endowment effect, which was made by the 2017 Nobel laureate Richard Thaler four decades ago, has largely contributed to the origin and early development of behavioral economics. However, to date, the cause of the endowment effect remains controversial.

Dr. Sheng and his colleagues provided a theoretical framework that deconstructed the endowment effect into two causes. One is greed. That is, both buyers and sellers expect financial wins from transactions. This leads sellers to overvalue goods and buyers to undervalue them. The other cause is inertia. That is, both buyers and sellers have an inertia to maintain the status quo, which could be disrupted by trading. Consequently, to overcome the inertia to achieve a deal, sellers require a premium while buyers require a discount, resulting in the endowment effect. By coupling computational modeling and eye-tracking, Dr. Sheng's team uncovered a double dissociation for eye activity and the two causes of the endowment effect.

Firstly, greed was reflected in asymmetric attention allocation of sellers vs. buyers. During trading, both sellers and buyers sampled information on the price and the goods repeatedly via gaze fixations. Dr. Sheng's team found that both sellers and buyers tended to value goods more when fixating vs. not fixating on the goods and overall sellers tended to allocate more visual fixations on the goods than buyers did, which led to higher valuation of the goods by sellers than by buyers.

Second, inertia was reflected in the change of pupil size during trading. Pupil dilation occurs as an index of mental effort. Dr. Sheng found that both sellers dilated their pupils more when choosing to sell vs. not to sell and buyers dilated their pupils more when choosing to buy than not to buy, which indicated that both sellers and buyers were reluctant to trade and additional mental effort, indicated by pupil dilation, was required for them to overcome their inertia.

This work led by Dr. Sheng contributes to both the theory and practice of trading. Firstly, they provide a general theoretical framework to dissociate distinct causes of the endowment effect. Secondly, they formulate the role of attention during trading. Thirdly, they uncover the novel relationship between pupillary reactivity and deal-making. Finally, they offer a theory-grounded guidance for promoting trading. Together, their findings suggest that a deal is to be made when both sellers and buyers attend to their potential gains and dilate their pupils. This indicates the art of the deal.

Sheng F*, Wang R, Liang Z, Wang X, Michael P. The art of the deal: Deciphering the endowment effect from traders' eyes. ***Science Advances***. 2023 Aug 9; 34: eadf211.

FENG SHENG'S RESEARCH GROUP

is dedicated to integrating theories and methods of brain science into the research and practice of economics and management, with a goal to empower human decision-making on the basis of understanding the underlying neurocomputational mechanisms. Their works have been published in peer-reviewed journals including ***PNAS, Science Advances, Cerebral Cortex, NeuroImage*** and reported by global media such as ***Forbes***.

Not all fear memories are equal

Distinct circuits from the central lateral amygdala to the ventral part of the bed nucleus of stria terminalis regulate different fear memories.

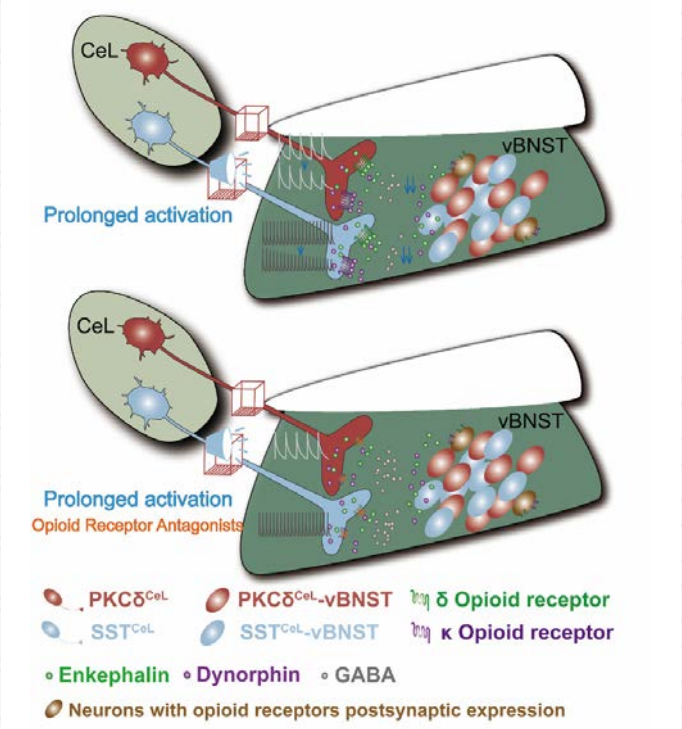
The ability of the neuronal system to trigger appropriate defensive responses to threat is critical for the ability to adapt to various stimuli and to adjust to differing threat levels. For example, fear of nuclear-contaminated water leads to salt-grabbing behavior; fear of socializing leads to avoidance behavior; and fear of spiders or snakes triggers flight behavior. Aberrant fear processing can lead to psychiatric disorders such as panic disorders and specific phobias, wherein fear levels inappropriately surpass the actual danger posed. Therefore, elucidating the neural mechanisms underlying fear learning and fear memory may yield significant insights into the pathogenesis of diverse neuropsychiatric disorders. However, how the brain organizes dedicated neuronal circuits to coordinate appropriate expressions of fear in order to flexibly adapt to changing environments remains undefined. Another key question remains what happens to our brains in the face of the differing nature of such external environmental signals?

Prof. **Xiaoming Li**'s group found that the projection from protein kinase Cδ (PKCδ) positive neurons in the central lateral amygdala (CeL) to ventral part of bed nucleus of stria terminalis (vBNST) specifically regulated contextual fear memory, whereas projection from somatostatin (SST) positive neurons in the CeL to vBNST mainly regulated tone fear memory. In addition, fear expression under exacerbated fear conditions is highly sensitive to disturbance in the activity of these circuits, as modulated by δOR and κOR. The culmination of this work was published in ***Biological Psychiatry***.

Combining transgenic mice and *in vivo* transsynaptic circuit-dissecting anatomical approaches, they identified the projections from CeL PKCδ positive neurons and SST positive neurons to the vBNST GABAergic and to glutamatergic neurons. Applying optogenetic approaches, they found that prolonged optogenetic activation or inhibition of the $PKC\delta^{CeL\text{-}vBNST}$ pathway specifically reduced contextual fear memory, whereas $SST^{CeL\text{-}vBNST}$ pathway mainly reduced tone fear memory. Intriguingly, optogenetic manipulation of vBNST neurons receiving the projection from $PKC\delta^{CeL}$ exerted bidirectional regulation of contextual fear, whereas manipulation of vBNST neurons receiving the projection from SST^{CeL} neurons could bidirectionally regulate both context and tone fear memory.

The team subsequently demonstrated the presence of δ and κ opioid receptor protein expression within the CeL-vBNST circuits, potentially accounting for the discrepancy between prolonged activation of GABAergic circuits and inhibition of downstream vBNST neurons. Finally, administration of an opioid receptor antagonist cocktail on the $PKC\delta^{CeL\text{-}vBNST}$ or $SST^{CeL\text{-}vBNST}$ pathway successfully restored context or tone fear memory reduction as induced by prolonged activation of these circuits.

This study provides the first evidence that distinct extended amygdala circuits participate in differently regulating fear memory. Furthermore, fear expression was noted as highly sensitive to disturbance in the activity of these circuits, wherein δOR and κOR can modulate resilience to fear. This work may contribute to the understanding of adaptive coping strategies in the face of adversity and provide insights for the development of treatments targeting a spectrum of fear-related disorders.



Working model for distinct extended amygdala circuits in differently regulating fear memory

Zhu Y#, Xie S#, Peng A#, Yu X, Li C, Fu J, Shen C, Cao S, Zhang Y, Chen J, Li X*. Distinct circuits from central lateral amygdala to ventral part of bed nucleus of stria terminalis regulate different fear memory. ***Biological Psychiatry***. 2023 Sep 5:S0006-3223(23)01553-6.

XIAOMING LI'S RESEARCH GROUP

is dedicated to the study of different synapses and neural circuits, aiming to find molecular targets for treating neuropsychiatric disorders such as anxiety, depression and schizophrenia, and to provide potential treatment strategies. His main research includes: (1) neural circuits of emotion and affective disorders; (2) the pathogenesis and mechanisms of anxiety, depression, schizophrenia, and other neuropsychiatric diseases.

Tansdiagnostic functional abnormality

Neural variability in three major psychiatric disorders.

Based on their distinct symptom-based criteria, Schizophrenia (SCZ), Major Depressive Disorder (MDD), and Bipolar Disorder (BD) are classified as separate diseases within the framework of the International Classification of Diseases, 11th edition (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). However, these disorders present with similar symptoms such as psychosis, anhedonia, and cognitive impairment. Genetic studies have also revealed a substantial overlap in 'risk genes' between SCZ, MDD, and BD. Furthermore, cognitive deficits, abnormal brain structures, and disrupted functional connectivity also show significant overlapping patterns across these three major psychiatric disorders (MPDs). Therefore, some levels of shared disruption in brain physiology between these three MPDs is suspected.

In July 2023, **Tao Li** and her research team published "*Neural variability in three major psychiatric disorders*" online in the journal ***Molecular Psychiatry***. In their study, they investigated the neural variability at rest, a well-established behavior-relevant marker of brain function, and probed its basis in gene expression and neurotransmitter receptor profiles across the MPDs. The study recruited 219 healthy controls and 279 patients with SCZ, MDD, or BD (manic or depressive state). The standard deviation of blood oxygenation level-dependent signal (SD_{BOLD}) obtained from resting-state fMRI was used to characterize neural variability. Transdiagnostic disruptions in SD_{BOLD} patterns and their relationships with clinical symptoms and cognitive functions were tested using partial least-squares correlation. Moving beyond the clinical sample, spatial correlations between the observed patterns of SD_{BOLD} disruption and postmortem gene expressions, neurosynth meta-analytic cognitive functions, and neurotransmitter receptor profiles were also estimated.

Two transdiagnostic patterns of disrupted SD_{BOLD} were discovered. Pattern 1 is exhibited in all diagnostic groups and is most pronounced in SCZ. This is characterized by higher SD_{BOLD} in the language/auditory networks but lower SD_{BOLD} in the default mode/sensorimotor networks. In contrast, pattern 2 is only exhibited in unipolar and bipolar depression, characterized by higher SD_{BOLD} in the default mode/salience networks but lower SD_{BOLD} in the sensorimotor network. The expression of pattern 1 is related to the severity of clinical symptoms and cognitive deficits across the MPDs. These two disrupted patterns had distinct spatial correlations with gene expressions (e.g., neuronal projections / cellular processes), meta-analytic cognitive functions (e.g., language/memory), and neurotransmitter receptor expression profiles (e.g., D2/serotonin/opioid receptors). They concluded that neural variability is a potential transdiagnostic biomarker of MPDs with a substantial amount of its spatial distribution explained by gene expressions and neurotransmitter receptor profiles. The pathophysiology of MPDs can be traced through such measures of neural variability at rest, with varying clinical-cognitive profiles arising from differential spatial patterns of aberrant variability.

Overall, this study identifies two patterns of transdiagnostic changes in neural variability in severe mental illnesses that are likely driven by specific genetic and neurotransmitter profiles. Importantly, these disruptions anchor to specific symptom dimensions or cognitive functions that are raised above diagnostic boundaries. They concluded that the transdiagnostic involvement of key cognitive systems (namely the peri-Sylvian and cognitive control networks) and its dopaminergic and serotonergic bases explain the severity of symptoms and cognitive deficits as they move along the diagnostic continuum of major psychiatric disorders.

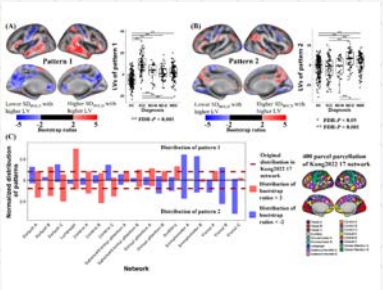


Fig. 1. (A and B) The spatial patterns of SD_{BOLD} disrupted pattern 1 and 2 and post hoc inter-group comparisons. Participants with higher SD_{BOLD}-related LVs had higher SD_{BOLD} in the brain regions with positive bootstraps ratios and vice versa. (C) The network-wise distributions of pattern 1 and 2 with respect to a 17-network system. PLSC: partial least-squares correlation; LV: latent variable; SD_{BOLD}: standard deviation of the blood oxygenation level-dependent signal

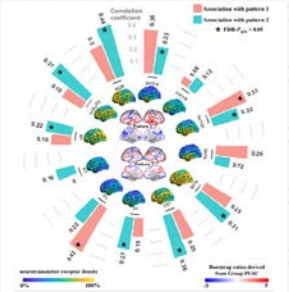


Fig. 2. Associations between spatial patterns of bootstrap ratios of SD_{BOLD} aberrant patterns and densities of neurotransmitter receptors. Correlation coefficients were estimated by Pearson's correlation tests. Statistically significances of correlations were examined by spin permutations tests. PLSC: partial least-squares correlation

Wei W, Deng L, Qiao C, Yin Y, Zhang Y, Li X, Yu H, Jian L, Li M, Guo W, Wang Q, Deng W, Ma X, Zhao L, Sham PC, Palaniyappan L, Li T*. Neural variability in three major psychiatric disorders. ***Mol Psychiatry***. 2023 Jul 13. doi: 10.1038/s41380-023-02164-2. Online ahead of print.

TAO LI'S RESEARCH GROUP

predominantly focuses on genetic, neurobiological, and translational studies of psychiatric disorders including schizophrenia, bipolar disorder, and major depressive disorder. Their emphasis is in the comprehensive exploration of the neurobiological basis of higher cognitive functions and the relationship of this with psychiatric disorders from perspectives such as brain structure, function, and biochemical metabolism. They are also interested in systematic analysis of the relationship between genes and biological genetic markers. The team has published over 370 papers in journals such as ***Nature Genetics, JAMA Psychiatry,*** and ***Molecular Psychiatry*** (with over 110 papers published over the past five years).

Human–machine joint learning framework

A Human–machine joint learning framework to boost endogenous BCI training.

Brain-Computer Interfaces (BCIs) provide a pathway of information exchange between the biological brain and the computational brain. Efficient information transmission relies upon the close collaboration between the biological brain (the subject) and the computational brain (the decoder). The subject generates effective brain signal patterns as control inputs, while the decoder identifies distinct brain signal patterns and reliably interprets them into control commands. However, due to disparities in information representation and computational models between the biological and artificial brains, the concept of "effective signal patterns" remains abstract on the side of the subject. This results in significant challenges related to learning and adaptation during the BCI training process and represents the current state of the limited applicability of current BCI systems.

Here, we propose a human-machine Joint learning framework to boost the learning process in BCIs. In this, we formally formulated the human-machine co-adaptive learning model and proposed a human-machine joint loss function, where the subject is encouraged to generate more discriminative brain signals, and the decoder optimizes the classifier to separate the different brain signal modes. Then the joint optimization of human and machines can be achieved by minimizing the joint loss function $L_{H\text{-}M}$

$$\arg\min_{\theta_H,\theta_M} L_{H-M} = \arg\min_{\theta_H,\theta_M} \left\| h(\theta_M, g(\theta_H, y)) - y \right\|,$$

where $h(\theta_M,g(\theta_H,y))$stands for the signal generated according to the given label y. The parameter of generation and the function are denoted as θ_H and $g(\cdot)$ respectively for the human side. For the machine side, the decoding function and parameter are represented by $h(\cdot)$ and parameter θ_M.

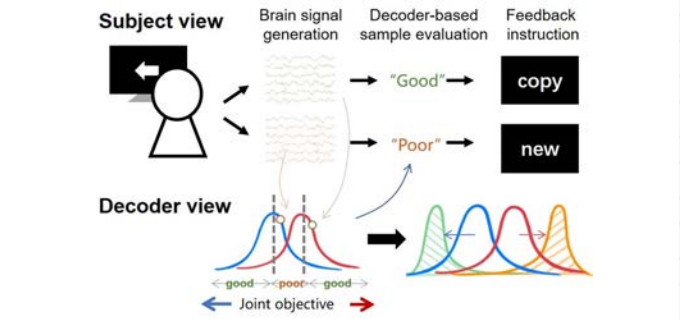
From the human side, we have formulated human behavior using a sequential trial-and-error learning process. We can regard the process as a Markov process. We divide the brain signals into two groups of "good" and "bad/poor" according to their discriminative ability with the decoder. We then denote the "good" and "bad/poor" samples as x_G and x_B, respectively. Thus, the objective of the subject is to increase the probability of generating x_G, and to decrease the probability of generating x_B. So, the function could be derived as:

$$\arg\max_{\theta_H} \frac{P(x_G)}{P(x_B)} = \arg\max_{\theta_H} \frac{1-P_{BB}}{1-P_{GG}}.$$

where P_{ab} stands for the probability of transition from condition a to condition b.

Such a novel paradigm is proposed to guide the subject to optimize brain signals by achieving a high P_{GG} and a low P_{BB}. Specifically, if a "good" signal is generated, the system encourages the subject to "copy" the state; otherwise, if a "poor" signal is generated, the subject is encouraged to change the brain signal.

From the machine side, we propose a novel adaptive learning algorithm to learn an optimal signal distribution along with the subject's learning process. Specifically, the decoder reweighs the brain signals generated by the subject to focus more on "good" samples to cope with the learning process of the subject.



The diagram of the human-machine joint learning process

Specifically, we design a novel loss function for the decoder to connect the loss and weight by the self-paced learning algorithm. The loss function of the decoder learning process can be described as:

$$\min_{w,v} E(w, v; \lambda) = \sum_{i=1}^{n} v_i L(x_i, y_i, w) + (1-\lambda)v_i - \frac{(1-\lambda)^{v_i}}{log(1-\lambda)},$$

where $\sum_{i=1}^{n} v_i L(x_i, y_i, w)$ stands for the traditional loss function with weights v and the remaining part represents the penalty function $f(v;\lambda)$, which controls the pace of the self-paced learning.

Online BCI experiments with 18 healthy subjects demonstrated that the co-adaptive learning framework can efficiently guide the subjects to generate discriminative brain signals for effective BCI control. Compared with traditional approaches, our method significantly improved the average control accuracy from 69.1% to 74.5%.

This paper introduces an innovative computational model for brain-computer fusion, which involves the joint learning of the biological brain and the computational brain. The proposed framework exhibits strong generalization capabilities across various brain-computer fusion tasks, thus holding the potential to expand the application scope of brain-computer interface systems.

Wang H, Qi Y*, Yao L, et al. A Human–Machine Joint Learning Framework to Boost Endogenous BCI Training[J]. ***IEEE Transactions on Neural Networks and Learning Systems***. 2023 Aug 30:PP. doi: 10.1109/TNNLS.2023.3305621. Online ahead of print.

The State Key Laboratory of Brain-Machine Intelligence

The Brain-Machine Interface and Brain-like Computing Group

The Brain-Machine Fusion and Computational Learning Group focuses on cutting-edge interdisciplinary research in the field of brain-computer interfaces. Addressing the challenges posed by the heterogeneity in information representation, computation, and storage between the biological brain and artificial brain, our research primarily emphasizes brain-machine mutual adaptation, collaborative computation, and co-learning. These efforts aim to provide effective computational methods for high-performance, highly available brain-computer interfaces.

Boring red blood cells

The driver of the gut-brain axis in parkinson's disease.

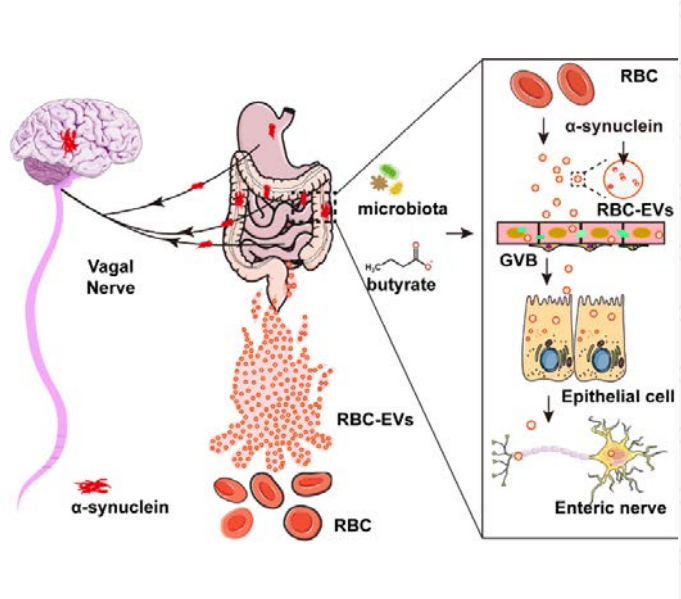
The transmission of pathological α-synuclein plays a key role in the progression of Parkinson's disease (PD). It has also been demonstrated that extracellular vesicles (EVs), small membrane-bound vesicles that transport cargos, are one mechanism by which α-synuclein pathology can be propagated. While the classical pathologies that define PD - the presence of Lewy bodies (LBs) and the death of dopaminergic neurons - are primarily localized to the central nervous system (CNS), it is increasingly recognized that PD affects multiple peripheral systems, with related pathology detectable in the skin, salivary glands, and gastrointestinal tract [1,2]. Recent research has focused on the aggregation of α-synuclein in the gastrointestinal tract and its role in the gut-brain axis. However, the specific origin of pathological α-synuclein within the gastrointestinal tract has not yet been elucidated.

On October 5, 2023, an article titled "*Erythrocytic α-Synuclein and the Gut Microbiome: Kindling of the Gut-Brain Axis in Parkinson's Disease*" was published by Prof. **Jing Zhang** in the journal ***Movement Disorders***. By demonstrating the transportation of α-synuclein through red blood cell-derived EVs (RBC-EVs) to the gastrointestinal tract, and its potential association with gut-vascular barrier (GVB) markers and the gut microbiome, this article highlights a potential mechanism by which RBC α-synuclein may impact PD initiation and/or progression.

The study initially explored the potential transfer of free plasma α-synuclein to the intestine, given its presence in both plasma and RBCs. Results revealed limited transportation of free α-synuclein from the bloodstream to the gastrointestinal tract. Subsequently, RBC-EVs were labeled with ^{125}I and lipid-binding dyes (DiR or DiI) and introduced into the circulatory system of wild-type mice via the tail vein. This led to the rapid conveyance of RBC-EVs to the gastrointestinal tract within 2 hours, followed by a gradual decrease over 24 hours. Importantly, the administration of RBC-EVs from PD patients into SNCA knockout mice led to human α-synuclein accumulating within the colonic epithelium, further confirming its transportation to the intestine through RBC-EVs.

The presence of DiI-RBC-EVs in the vagal ganglia of wild-type mice was observed 48 hours after administering DiI-RBC-EVs through the tail vein . Additionally, 2 hours after injecting radio-labeled ^{125}I-RBC-EVs into the intestinal wall of the ileum and colon, radioactivity was then detected in the vagal ganglia. The vagal ganglia of SNCA knockout mice, following the intravenous injection of RBC-EVs from A53T mice, also exhibited the presence of human α-synuclein. Taken together, the study suggests the direct or indirect transportation of RBC-EV-carried α-synuclein to the brain via the vagus nerve.

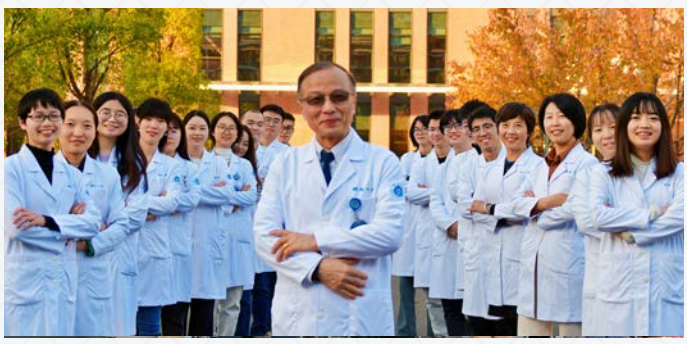
The study found varying quantities of RBC-EVs across different gastrointestinal regions, likely related to GVB permeability. Intraperitoneal LPS injection in mice increased permeability and significantly raised the presence of DiI-labeled RBC-EVs in various gut regions. The gut microbiome is known to affect GVB permeability via the production of short-chain fatty acids (SCFA) such as butyrate. Therefore, the gut microbiome of A53T mice was examined using 16S rRNA sequencing, revealing altered microbial composition which was particularly marked by a decline in butyrate-producing bacteria. After treating the mice with butyrate for 30 days, the levels of ZO-1 and Occludin trended upward in WT, SNCA-KO, and A53T mice. Additionally, butyrate-treated A53T mice exhibited decreased uptake of RBC-EVs along with decreased GVB permeability, suggesting that gut microbiome changes observed in PD patients may influence the influx of blood α-synuclin into the gut.



Erythrocyte-derived extracellular vesicles deliver α-synuclein to the gut, influenced by the microbiota's butyrate levels, and likely contribute to the initiation and development of Parkinson's disease

JING ZHANG'S RESEARCH GROUP

has been long dedicated to the pathogenetic mechanisms and early diagnostic biomarkers for neurodegenerative diseases. They have pioneered a technique to capture brain-derived exosomes from blood and were the first to explore the potential application of biomarkers like α-synuclein and tau in plasma exosomes, leading to the gaining of international patents. Additionally, based on the theory of exosome transport in peripheral fluids, the team has proposed the hypothesis that "α-synuclein in red blood cells plays a critical role in the onset and progression of Parkinson's disease", providing a novel perspective for research into the mechanisms of Parkinson's disease. To date, Professor Jing Zhang has published over 250 relevant articles in SCI journals, with a total citation count exceeding 22,515, an h-index of 82, and an i10-index of 203.



Through this newly developed technique, detecting PD markers in blood is now a simple process. If this method is generalized to clinical diagnostics in the future, it will benefit millions of patients. What is the story behind this study?

Ying Yang (First author): Liquid biopsy technology has seen gradual advancements over recent years and now plays a crucial role in the development of diagnostic biomarkers for Parkinson's disease. This innovative technology boasts notable benefits including robust organ/tissue specificity, heightened disease recognition, elevated clinical detection sensitivity, and the advantage of minimally invasive sampling. Particularly noteworthy is the swift progress in the detection of diagnostic biomarkers originating from extracellular vesicles (EVs) in the blood. EVs have the capacity to transport specific molecular information, encompassing nucleic acids, lipids, and proteins. These molecular components are influenced by diverse factors such as the cell type of the originating parent cell or cellular status, thereby reflecting the specific and current pathophysiological state of the body. Our research team, focusing on EVs derived from neural cells, astrocytes, and microglia, successfully pioneered the development of early diagnostic and discriminatory markers for Parkinson's disease. These markers not only demonstrate remarkable diagnostic efficiency but also offer valuable insights into the underlying pathogenic mechanisms of Parkinson's disease.

Neurodegenerative diseases such as Parkinson's disease have been found to be caused by several different mechanisms. Does it suggest that neurodegenerative diseases such as Parkinson's disease may be a symptom of the natural aging of the brain?

Ying Yang: Parkinson's disease and other neurodegenerative diseases share connections with the natural aging of the brain, yet their origins extend beyond the exclusive influence of the aging process. Complex biological processes characterize neurodegenerative diseases. Most notably for Parkinson's disease is the aggregation of abnormal protein, neuronal loss, and various inflammatory responses. The onset of these diseases is likely a consequence of the interplay between diverse genetic and environmental factors. In contrast, the natural aging of the brain exhibits a typical physiological progression influenced by time and genetic elements. Aging manifests as gradual alterations in brain structure and function, lacking the specific and intricate pathological changes observed in neurodegenerative diseases. While changes in the nervous system are inherent in the aging process, neurodegenerative diseases like Parkinson's are more prevalent in the elderly, yet they are not an unavoidable outcome of natural aging. Nevertheless, a comprehensive understanding of the distinct mechanisms governing these diseases is pivotal for the development of more effective preventive and therapeutic approaches.

Inflammatory bowel disease (IBD) patients have been clinically found to be more likely to develop neurodegenerative diseases. If patients suffer from certain diseases do these become triggers for developing degenerative diseases or require incorporations as early preventive markers? Do medication options require more attention in the case of multiple co-morbidities?

Ying Yang: IBD is a chronic, idiopathic disorder characterized by inflammation in the gastrointestinal tract. While the exact cause of IBD remains unclear, there is widespread acknowledgment that the microbiota, intestinal epithelial cells, and immune cells play a role. Numerous studies have indicated a higher prevalence of Parkinson's disease among individuals with IBD compared to those without the condition. The potential link between intestinal inflammation and Parkinson's disease can be explained in various ways. One possible mechanism is that persistent inflammation in the intestines may locally increase the levels of α-synuclein. Additionally, IBD may trigger systemic inflammation, potentially leading to heightened intestinal permeability and dysfunction of the blood-brain barrier. Furthermore, IBD may elevate circulating cytokines, thereby fostering inflammation. Alterations in the composition of the microbiota may also exert an influence on both IBD and the development of Parkinson's disease. Current research underscores the association between IBD and Parkinson's disease; however, a more in-depth investigation is needed to confirm the specific mechanisms involved. Presently, there is no conclusive evidence supporting the notion that all IBD patients should undergo early prevention or screening for Parkinson's disease. Nonetheless, individuals with IBD who are worried about the risk of Parkinson's disease can consult healthcare professionals for personalized advice and monitoring.

With the increasing aging of China's population, how effectively can we implement early diagnosis and early prevention, and how effective is this to delay the onset of Parkinson's disease?

Ying Yang: As fundamental scientific research advances, our comprehension of the underlying mechanisms triggering Parkinson's disease deepens. This intricate mechanism encompasses various factors such as genetics, environmental influences, and neuroprotective processes. These investigations yield additional focal points for devising novel treatment and preventive approaches. Simultaneously, extensive exploration of early biomarkers enables us to identify patients at an earlier stage by amalgamating clinical symptoms and neurological evaluations with these early indicators. Nevertheless, realizing authentic early diagnosis, prevention, and proficiently delaying the onset of Parkinson's disease necessitate collaborative efforts from society as a whole. It is imperative to bolster public education, raise awareness, augment doctors' diagnostic capabilities and expertise, conduct early screening and preventive initiatives, and to intensify research endeavors.

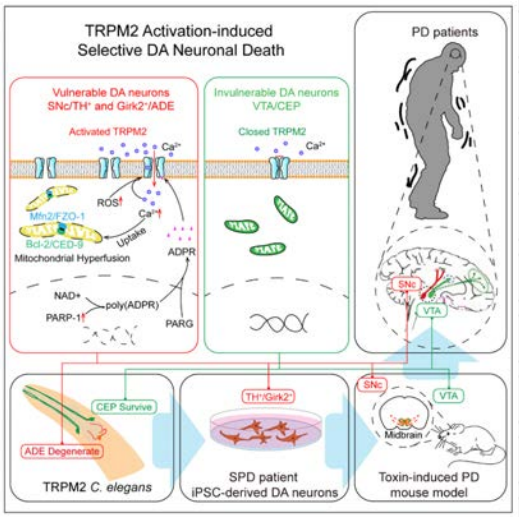
In summary, this research identified a novel source of gut α-synuclein, namely the EVs derived from RBCs. By demonstrating the transportation of α-synuclein through RBC-EVs to the GIT and its subsequent influence on gut tissues in association with GVB and the gut microbiome, this research highlights a potential mechanism by which RBC α-synuclein may impact PD initiation and/or progression.

Yang Y, Stewart T, Zhang C, Wang P, Xu Z, Jin J, Huang Y, Liu Z, Lan G, Liang X, Sheng L, Shi M, Cai Z, Zhang J*. Erythrocytic α-Synuclein and the Gut Microbiome: Kindling of the Gut-Brain Axis in Parkinson's Disease. ***Movement Disorders***. 2023 Oct 5.

Marking of vulnerable neuronal subgroups for PD

The gatekeeper of dopaminergic neurons' vulnerability—The TRPM2 ion channel.

Dopamine (DA) neurons in the central nervous system of mammals play various crucial roles including the regulation of emotions, reward perception, and motor control. DA neurons exist in several separated cell subgroups including those of substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Different subgroups of DA neurons exhibit varying vulnerability to genetic, environmental, and aging stimulation. In Parkinson's disease (PD), SNc DA neurons are sensitive to cell death, while VTA dopaminergic neurons display significant resistance. The mechanisms underlying vulnerability differences among these subgroups are not yet fully understood. The phenomenon of such DA neuron susceptibility differences is observed not only in PD patients but also in rodent animals and model organisms such as fruit flies and zebrafish, thus suggesting the conservation of this mechanism across species. Therefore, investigating the differential vulnerability of stress responses in DA neuron subgroups across species may provide a valuable opportunity towards a deeper understanding of DA neuron-related neuronal functions and disease mechanisms.



TRPM2 as a conserved gatekeeper determines the vulnerability of DA neurons by mediating ROS sensing and calcium dyshomeostasis

Recently, the research team led by **Wei Yang**, **Lijun Kang**, and **Huanxing Su** published a vital research finding in ***Progress in Neurobiology***. Through the integration and analysis of single-cell transcriptome sequencing data and PD patient databases, the study identified the preferential enrichment of transient receptor potential melastatin 2 (*TRPM2*) ion channels in susceptible DA neuron subgroups. The expression levels of TRPM2 were significantly positively correlated with the age of PD patients, a result further validated in mouse models, suggesting the close association between TRPM2 ion channels and the susceptibility of dopaminergic neurons.

To investigate this issue further, the researchers innovatively expressed human TRPM2 channels in the DA neurons of the roundworm *C. elegans*. The ADE dopamine neurons, which do not naturally express TRPM2 in this model organism, exhibited noticeable susceptibility to cell death. As the worms aged, the cell bodies and synapses of ADE degraded, while CEP dopamine neurons showed resistance. Further studies indicated that TRPM2 in ADE neurons, but not CEP neurons, could be selectively activated by the ADP-ribose (ADPR) ligand mediated by PARP-1/PARG-1, leading to calcium dyshomeostasis and oxidative stress damage. Additionally, this intracellular stress further caused hyperfusion of mitochondria which was dependent on the FZO-1/CED-9 complex interaction, leading to mitochondrial permeability transition and cell death, and where inhibiting the interaction of the FZO-1/CED-9 complex significantly suppressed such cell death for ADE neurons.

To explore the conservation of the molecular mechanism of TRPM2-mediated dopaminergic neuron death, the researchers also examined this pathway in PD mouse models via induced pluripotent stem cell-derived dopaminergic neurons from PD patients. Results showed the significant enhancement of the interaction between Mfn2/Bcl-2 (homologs of FZO-1/CED-9) in SNc neurons of PD mouse, and where TRPM2 knockout significantly inhibited SNc dopaminergic neuronal death. Furthermore, the differentiation of dopaminergic neurons from PD patient-derived induced pluripotent stem cells suggested that inhibiting the activity of TRPM2, PARP1/PARG, or the interaction of Mfn2/Bcl-2, could significantly inhibit hyperfused mitochondrial morphology, calcium dyshomeostasis, and enhance neuronal viability.

This study reveals for the first time, that TRPM2 ion channels conservatively mediate the formation of susceptibility in dopaminergic neurons across species. The findings suggest that the goal of inhibiting TRPM2 ion channels, PARP1/PARG activity, and Mfn2/Bcl-2 interactions could represent promising drug targets for PD, providing a new perspective for fundamentally inhibiting DA neuronal death in PD.

Ye P, Fang Q, Hu X, Zou W, Huang M, Ke M, Li Y, Liu M, Cai X, Zhang C, Hua N, Al-Sheikh U, Liu X, Yu P, Jiang P, Pan PY, Luo J, Jiang LH, Xu S, Fang EF, Su H*, Kang L*, Yang W*. TRPM2 as a conserved gatekeeper determines the vulnerability of DA neurons by mediating ROS sensing and calcium dyshomeostasis.***Progress in Neurobiolog.*** 2023 Dec;231:102530.

WEI YANG'S RESEARCH GROUP

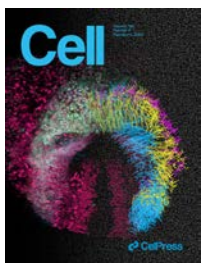
has long been engaged in the investigation of the gating mechanisms of TRP channels, as well as their physiological and pathological functions in the central nervous system. By using electrophysiology and animal disease models, they aim to discover new therapeutic drugs against neurological disorders by developing specific inhibitors targeting the TRPM2 channel and other related areas.

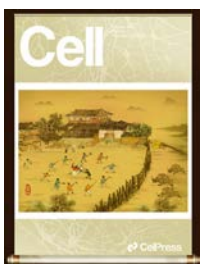
BBMI 2023

FRONTIERS IN NEUROSCIENCE

To advance the progress of neuroscience and foster effective communication and collaboration among medical practitioners in this field, the Frontiers in Neuroscience was held from August 25th to August 26th at the Conference Center of the First Affiliated Hospital of Zhejiang University School of Medicine. Esteemed neuroscience experts and scholars hailing from the United States, Canada, Japan, and China convened for this significant intellectual congregation. Distinguished participants giving academic presentations included: Haruhiko Bito, Professor of the University of Tokyo; Guoqiang Bi, Professor of the University of Science and Technology of China; Jianyuan Sun, Professor of the Shenzhen Institute of Advanced Technology, CAS; Shiqing Cai, Senior Researcher of the Center for Excellence in Brain Science and Intelligence Technology; Yelin Chen, Professor of the Interdisciplinary Research Center on Biology and Chemistry, and the Shanghai Institute of Organic Chemistry, CAS; Keqiang Ye, Professor of the Shenzhen Institute of Advanced Technology, CAS; Fang Liu, Fellow of the Canadian Academy of Health Sciences and Professor of Oujiang Laboratory; Xin Duan, Assoc Professor at the University of California San Francisco; Yutian Wang, Fellow of the Royal Society of Canada (Academician of the Academy of Science) and Professor of the Shenzhen Institute of Advanced Technology, CAS; Xiang Yu, Professor of Peking University; Xiaoming Li, Vice President of Zhejiang University; Zhihua Gao, Professor of the School of Brain Science and Brain Medicine, Zhejiang University; and Haohong Li, Professor of the BBMI center.

The series of presentations at this forum represented the cutting edge of both foundational research and technological applications in neuroscience, affording a robust platform for emerging scholars to assimilate knowledge and exchange ideas, engendering heightened enthusiasm for neuroscience and inspiring a collective pursuit of ongoing exploration and advancement within this domain. Looking forward, the BBMI center is committed to maintaining a steadfast commitment to national excellence, fearlessly undertaking strategic imperatives, and amplifying its contributions to expedite the establishment of a technologically advanced country, in alignment with the overarching objectives of the Healthy China strategy.





BBMI 2023

RESEARCH PROGRESS

A total of 41 scientific research projects were approved

- 1 New Cornerstone Investigator Program project
- 1 National Science Fund for Distinguished Young Scholars project
- 1 "Major Program"

More than 100 academic papers were published

More than 50 papers were published in high-level journals

3 in *Cell* 1 in *Nature* 1 in *Science*

BBMI 2023

TALENT DEVELOPMENT

Academician Shumin Duan

Incorporated into the Elsevier's list of "2022 Highly Cited Chinese Researchers"

1 National Science Fund for Distinguished Young Scholars

2 National Youth Talent Support Program

1 project was supported by Chinese Medical Science and Technology Awards

BBMI 2023

DONATIONS

The BBMI is very grateful for the generous donations listed below, which help build a more academic focused environment and encourage students to devote themselves to basic and clinical brain science studies.

20, 000 RMB

Shenzhen Reward Life Technology Co., Ltd.

500, 000 RMB

Guoqiang Xiao

Alumnus

3, 831 RMB

Anonymous personal donation

These donations will motivate and commend students who have excellent performances in academic research, scientific and technological innovation, social work and other aspects.

BBMI Donation Contact E-mail: brains@zju.edu.cn

The BBMI Academic Reports

2023 Second Half

Professor Liqun Luo

Department of Biology, Stanford University

September 7th, 2023

Wiring specificity of neural circuits

Professor Rurong Ji

Duke University Medical Center

October 11th, 2023

Regulation of pain, anesthesia, and cognitionby immune checkpoint pathway

Professor Liping Wang

The Brain Cognition and Brain Disease Institute of Shenzhen Instituteof Advanced Technology, CAS

October 17th, 2023

Digitizing the study of neural circuits and naturalistic mouse behavior

Professor Zhiheng Xu

Institute of Genetics and Developmental Biology, CAS

November 9th, 2023

Analyzing the pathogenesis of autism

Professor Zhian Hu

Chongqing Institute for Brain and Intelligence

November 15th, 2023

Sleep-wake regulation in brain: mechanism and function circuits

Professor Yangang Sun

Center for Excellence in Brain Science and intelligence Technology, CAS

December 15th, 2023

Functional and structural wiring diagram for pain and itch

Diagnosis and treatment of addiction: strengthening the field via multidisciplinary integration

An Interview with Professor Wanjun Guo

You have been engaged in clinical treatment and research relating to addiction for a long time. Could you elaborate on the nature of addiction as a mental illness and delineate its defining characteristics?

Wanjun Guo: Addiction is a chronic and relapsing brain disease. It mainly manifests as repeated use of some substances or repeated behaviors to achieve psychological or spiritual effects. It is worth noting that there are significant differences in substance use between addicted patients and ordinary people. Firstly, the tolerance of patients addictive substance or behaviors increases unexpectedly. In the process of alcohol addiction, for example, over time patients need to drink more and more to achieve similar effects. Secondly, patients engage in the repeated consumption of substances, surpassing normal quantities, thereby posing a threat to their health. In the process of increasing tolerance, the patient will gradually develop both psychological and physical dependence on the substance. Psychological dependence is mainly manifested as "craving" for repeated use of substances and/or performed addictive behaviors. The individual becomes notably responsive to pertinent cues and encounters challenges in exerting control over the compulsion to gratify the craving. Physical dependence primarily manifests through withdrawal syndromes, i.e., predominant pathological reactions and physical symptoms associated with the withdrawal of repeated use of specific substances. For instance, withdrawal from sleeping pills may manifest as seizures, while phased reactions to heroin can induce pain, among other symptoms.

Wanjun Guo, a chief psychiatrist, PhD and MD supervisor, high-level innovative health talent of Zhejiang province, hold PhD degree in Psychiatry and Mental Health. He is the dean for education and research of the Affiliated Mental Health Center (Hangzhou Seventh People's Hospital), Zhejiang University School of Medicine. His research is significantly focused on the Multi-omics risk factors and multi-modal interventions of addiction, emotional disorders and their comorbidities.

Consequently, how can one clinically identify when substance use has progressed to the point of addiction?

Wanjun Guo: In addition to the previously mentioned indicators (such as increased tolerance, psychological craving, and physical withdrawal reactions), the diagnosis of addiction necessitates particular consideration of the harm inflicted by addictive substances or behaviors on patients. This entails an evaluation of whether the use of substances or engagement in addictive behaviors (such as gambling or excessive gaming) has reached a level that is evidently harmful to health. This harm includes damage to the brain and other organs, as well as adverse effects on the mental health of patients. The impairment of social functions serves as a crucial criterion for diagnosis. Addiction significantly disrupts the patient's daily life, rendering them incapable of carrying out routine study and work activities. For individuals grappling with addiction, their notable underperformance in a specific measured aspect become a key consideration in the diagnostic process.

Do individuals with addiction often present comorbid psychiatric disorders, and what is the relationship between addiction and emotion?

Wanjun Guo: Our studies have revealed the association between addiction and other mental illnesses. For example, we found that there is a very high correlation between Internet addiction and other mental illnesses, the most prominent of which is depression. Through subsequent follow-up investigations, we discovered that individuals initially experiencing depression had an elevated likelihood of developing Internet addiction, and conversely, those initially addicted to the Internet had an increased probability of developing depression. The two conditions exhibit reciprocal predictability, making it challenging to definitively attribute causation. It is plausible that a shared pathological mechanism underlies the association between the two conditions.

The connection between addiction and other negative emotions also occurs during the withdrawal treatment process. Some patients experience anxiety and depression during the withdrawal process, which is related both to psychological and physical factors. For patients with pre-existing mental or emotional disorders, the starting use of addictive substances may be a way of self-medication because one of the

characteristics of addictive substances is that they bring rapid and intense pleasure, thereby providing swift and substantial relief from emotional distress or pain.

What are the main intervention methods currently used to treat addiction, and what strategies are implemented to prevent relapse post-detoxification?

Wanjun Guo: To treat addiction, we need to take a comprehensive approach. The most effective treatment for acute withdrawal reactions is substitution therapy, which uses drugs that are less addictive and less harmful to the body. In addition, for decrease withdrawal reactions, some long-acting drugs are used to substitute the short-acting addictive drug. On the other hand, some strategies are developed to prevent the relapse. For example, we treat patients who addictive to opioids with antagonists of opioid receptor. Then the patients may not feel pleasure when they use opioids. To lower the harm of addiction, substitution therapy is also applicable to addictive patients whose relapse is hard to prevent.

However, drug treatment alone is not enough. We also advocate intervention at the level of psychotherapy, social rehabilitation and management. The effect of this intervention is significant. In psychotherapy, some increasingly feasible strategies have been emerging, the main purpose of these being to mobilize the motivation of addicted patients for treatment, (also known as 'motivational intervention'). Certain therapeutic effects can be achieved through methods such as mindfulness. Of course, there are also some physical therapy methods, such as neuromodulation, which also represent a promising direction for the treatment of addiction.

Zhejiang University translational research center for brain-computer neuromodulation (division for mental disorders) has launched in Hangzhou Seventh People's Hospital. How can brain-computer interface research help the diagnosis and treatment of addiction?

Wanjun Guo: We are currently in the process of developing digital therapeutics (DTx) grounded in gaming or virtual reality (VR). For example, The underlying principle revolves around evaluative conditioning theory. Within the gaming context, addiction is paired with negative information, while self-image is associated with positive information. The adjustment of matching difficulty is utilized to concurrently enhance cognitive functions such as memory and attention in patients. During the intervention process, the patient's desire for addictive substances and behaviors is repeatedly aroused, but cannot be satisfied, and is even inhibited by the matching negative information. This deliberate approach results in a gradual reduction of desire, potentially culminating in the establishment of an aversive conditioned reflex. Thereby stimulating the patient's motivation for staring and/or maintaining abstinence.

We are also presently in the process of developing a real-time closed-loop non-invasive DTx task-based neuromodulation technology system designed for addiction and other mental disorders. This task-state based modulation system can gather brain function signals, such as EEG, while patients engage in specific digital therapy tasks. Automatic adjustments of the stimulation parameters of neuromodulation based on the variance in correlation between the signal and the disease state as well as the task state is then facilitated, to optimize intervention outcomes.

In your opinion, what are the problems and challenges facing the treatment of addiction?

Wanjun Guo: I believe the most significant challenge lies in the lack of effective means to prevent addiction, given that numerous addictive substances are integral to our daily lives. Our original intention in using these substances is to obtain happiness or mitigate some sense of pain, but it is difficult for us to prevent a small number of people from becoming addicted to these substances. In addition, the challenge of addiction relapse is noteworthy. While achieving short-term abstinence is comparatively attainable, the recurrence rate of addiction remains high. The preservation of discipline to sustain abstinence poses a substantial problem.

Addiction is a prominent focus in neuroscience research. In which domains do you anticipate breakthroughs in basic research on addiction? How can the newly identified circuits and mechanisms from basic research contribute more effectively to addiction treatment?

Wanjun Guo: I think basic research can provide good targets for physical clinical neuromodulation interventions. Previous studies have suggested that the nucleus accumbens is an important regulatory nucleus for addiction. There are now some deep transcranial magnetic stimulation devices that can regulate these brain areas. On the diagnostic side, the development of biomarkers may be useful in predicting addiction and relapse. We have undertaken a series of studies utilizing early brain imaging to forecast the relapse of alcohol dependence, and our predictive accuracy achieved notably high. Nevertheless, this technology is still a considerable distance from clinical application and further research is required.

Within the framework of the BBMI, in what form do you hope to conduct collaborative research with collaborators from different fields such as brain-computer interfaces, basic research, brain-inspired computing, and psychology?

Wanjun Guo: I think the key is to strengthen exchanges, such as academic lectures in different fields. Many exchange activities currently play a role in cross-field cooperation. Concerning the collaboration model, a more efficient approach may involve mobilizing researchers from diverse fields to collaboratively address specific scientific or technical challenges. Of course, the premise is that all participants possess a mutual understanding of each other's research fields and areas of expertise.

On the other hand, I also hope to integrate basic and clinical research teams. At present, our hospital has rich clinical resources, with an annual outpatient volume of more than 500,000 and nearly 25,000 discharged patients. More clinical trials of some new drugs and new treatments can be carried out in our hospital. We hope to effectively cooperate with colleagues in basic research to jointly promote the clinical translation of basic research findings.

Deciphering the learning and memory mechanisms of conditioned fear

An Interview with Professor Shuang Qiu

You and your team are committed to the mechanisms of learning and memory in the brain. These are often considered "advanced" functions. Can animal models effectively replicate these functions and behaviors? What caveats should be considered when extrapolating these advanced functions from laboratory animal behavior?

Shuang Qiu: Learning and memory are categorized under cognition, which is frequently considered as an advanced function. However, within 'advanced functions', learning and memory are notably conservative. For animals, the comprehension of the dynamic environment is contingent upon learning and memory, and their survival is intricately linked to this cognitive ability. Numerous model animals therefore may serve as valuable subjects for the research of learning and memory. It is notable that plasticity was initially identified in laboratory animals such as the Aplysia mollusk, while Drosophila has also been long employed for the study of learning, memory, and forgetting. In this way, these laboratory animals are well-recognized in the areas of learning and memory.

Nevertheless, it is essential to emphasize that researchers can't use rodents or other less complicated animals to address all scientific questions related to learning and memory. For instance, the theoretical framework in the field of learning and memory is relatively mature. It is recognized that various memory types exist, including explicit and implicit memory. Describability is pivotal to explicit memory, a crucial aspect in animals, albeit one that poses considerable number of challenges for study. Presently, our focus in animal studies primarily revolves around implicit memory, particularly associative memory, working memory, and related constructs. The behavioral paradigms employed for investigating these memories are relatively well-established and classical.

Shuang Qiu, PhD, Professor at Zhejiang University, Outstanding Youth of Zhejiang Province, Qiushi Young Scholar. Prof. Qiu mainly studies the cellular and molecular mechanisms and circuits of memory and negative emotions. In the past five years, Prof. Qiu has published research papers as a corresponding author in academic journals such as ***Nature Communications***, ***Biological Psychology***, and ***JMCB***.

Your recent research focuses on the retrieval of extinction memory in the prefrontal cortex. What distinctions and connections exist between extinction memory and the process of forgetting?

Shuang Qiu: The fundamental concept underlying forgetting is loss, denoting the gradual erosion of a memory which is often following prolonged absence of similar stimuli and accompanied with the acquisition of new information through learning. The extinction of a memory is not the same. This delineates the process of forming a memory associating a noxious stimulus with a signal through learning, followed by the recurrent presentation of the signal without the accompanying noxious stimulus. This active repetition serves to disassociate the noxious stimulus from the signal, leading to the cessation of responses to the signal. Forgetting and extinction are therefore two different processes, involving different mechanisms.

Professor Yi Zhong from the School of Life Sciences of Tsinghua University has put forward an interesting view of active forgetting which, I think, emphasizes the functional importance of forgetting. The prevailing perspective regarding memory extinction posits it as an active learning process, encompassing the stages of memory formation, storage, and retrieval. Our recently published work aims to delineate a cohort of engram cells in the medial prefrontal cortex (mPFC) responsible for storing fear extinction memory, providing direct evidence that the fear extinction process entails the formation of new memories.

Considering engram cells are distributed in different regions throughout the brain, do they have a common mechanism for encoding and retrieval?

Shuang Qiu: You are correct that engram cells have now been identified in many brain regions. By labeling the engram cells activated during learning activities, we can subsequently employ optogenetic and pharmacogenetic techniques to manipulate them. Alternatively, we can trace their upstream and downstream projections at the circuit level to observe their impact on learning and memory.

As for the recruitment mechanism, one

current explanation is that when learning activities occur, cells that maintain higher activity are more likely to be recruited to become engram cells. Some researchers also believe that, from a circuit perspective, these neurons receive information input from certain circuits that leads to the tendency for them to become engram cells. Other studies have found that neurons in target brain areas innervated by noradrenergic neurons are activated and recruited as engram cells during stress or attention-demanding situations. However, how do these engram cells encode and store information? What are the molecular population characteristics of these engram cells? These are issues of concern for the field. We prefer to comprehend the principles of engram cells from a collective standpoint. For example, do they encode information through specific neural oscillations?

What is the relationship between engram cells and synaptic plasticity?

Shuang Qiu: This is a very important question. In 1921, the German scientist Richard Semon proposed the concept of engram to describe the material basis of memory storage and retrieval. This represented what scientists interested in learning and memory mechanisms had been looking for for more than a hundred years. I believe that synaptic plasticity and engram cells are both memory traces, exhibiting complementary or synergistic functions.

Prior to the discovery of engram cells, researchers predominantly relied on synaptic plasticity to explain learning and memory. Yet this theory faced challenges towards explaining long-term memory, which can endure for months or years. Durative long-term potentiation (LTP) or depression (LTD) can itself lead to cellular damage. With the proposition that memory resides in mature engram cells, the issue of memory duration finds resolution.

In addition, Bong-Kiun Kaang, a neuroscientist at Seoul National University in South Korea, proposed the concept of an "engram synapse". In this, memories are not stored in trace cells, but at the synapses between these cells. This created an attractive link between engram cells and synaptic plasticity. Susumu Tonegawa's work also shows that although engram cells are responsible for memory storage, without normal synaptic plasticity, memories will not be retrieved.

Thus, engram cells may focus on the storage of memories, while synaptic plasticity focuses on the retrieval of memories, both of which are indispensable for the proper execution of memory functions.

Are there factors that impede the spontaneous resolution of memory-related symptoms, such as those observed in post-traumatic stress disorder (PTSD)?

Shuang Qiu: I strongly agree with the idea that these symptoms are closely intertwined with memory. In fact, our current studies of emotional disorders including anxiety are also strongly related to memory. The paradigm employed in our research revolves around discrimination and generalization. To test discrimination ability, it is necessary to observe whether the tested animal can accurately correlate the unconditioned stimulus related to the harmful stimulus. To test the generalization ability, it is necessary to present a series of generalized stimuli similar to the original conditional stimulus and then observe whether the animal will have a negative response to the generalized stimulus. If the discrimination ability is impaired, the animal is likely to develop anxiety about irrelevant stimuli, just as many of us now react negatively to unrelated events. Those with a strong generalization ability may show PTSD, and veterans with PTSD in the United States exhibit this, such as a strong fear response from the sound of a door closing, as it is similar to a gunshot.

There is currently no designated pharmaceutical intervention for the treatment of PTSD, with cognitive therapy emerging as a preferred approach. This therapeutic modality employs the principle of fear extinction, involving the systematic exposure of patients to stimuli that resemble the original trauma but is absent of any corresponding harm. After the patient realizes that these irrelevant stimuli are not accompanied by harm, he gradually loses his fear, which helps him learn to establish this new association.

In the treatment of mental diseases related to learning and memory, such as PTSD, anxiety disorder, etc. How do you envision fostering collaboration between basic research scientists, translational scientists, and medical practitioners to effectively aid patients?

Shuang Qiu: We now feel that it is very difficult to find molecular markers and molecular targets of engram cells that could be used to develop drugs to block or intervene with such processes. Our work found that engram cells contain both excitatory and inhibitory neurons, which makes finding specific molecular markers difficult. It is also difficult to intervene in some abnormal functions of the cortex through drugs without affecting normal functions.

We therefore prefer to treat the activity of engram cells as a network. We hope to find some characteristics of the network by studying the common characteristics of the abnormal network state, and learn how to enhance or inhibit network activity at a specific time. Thus, we can explain the mechanisms of some physical non-invasive methods that have been found to be effective (such as transcranial magnetic stimulation, transcranial electrical stimulation), and guide the clinical application of these methods through research, such as what frequencies to choose and what states of stimulation to use.

SHUANG QIU

Interdisciplinary Forum

Lusha Tong: Welcome to participating in this issue of our "Interdisciplinary Forum". Here, we aim to provide a platform for researchers from different backgrounds to engage in mutual discussions and interdisciplinary cooperation. The theme of this conversation is "**Relief and Prevention of Abnormal Affective States**". Let us start by inviting the participants to give brief introductions of themselves and their current research directions.

Shuangshuang Ma: I am a postdoc from Prof. Hailan Hu's Lab, where I conducted my Ph.D. research under Prof. Hu's supervision. Through my doctoral training, I participated in a project focusing on the sustained antidepressant mechanism of ketamine. Ketamine has revolutionized depression treatment for its robust, rapid and sustained antidepressant effects. Our previous study demonstrated that the rapid antidepressant actions of ketamine are mediated by blockade of NMDAR-dependent bursting activity in the lateral habenula (LHb). Building upon this framework, we aimed to further investigate the sustained antidepressant effects of ketamine. Our findings revealed that the sustained antidepressant effects of ketamine depend on its use-dependent trapping on opening NMDARs. This study, based on the biophysical properties of ketamine–NMDAR interactions, presents new opportunities for the therapeutic use of ketamine.

Lusha Tong: Ketamine exhibits enhanced binding affinity to NMDA receptors in their open state. Does this mean that the drug will be more effective for depression patients who are experiencing symptomatic episodes?

Shuangshuang Ma: Yes. According to the dynamic equilibrium of ketamine-NMDAR interaction, the binding of ketamine to NMDARs is strongly regulated by the ambient concentration and local neural activity in the LHb. In the state of depression, the NMDA receptors in the LHb remain open. In this open state, if the ambient concentration of ketamine in the brain exceeds the dissociation constant (Kd), ketamine tends to bind with NMDARs; otherwise, they dissociate. To enhance the therapeutic efficacy of ketamine, it can be administered during a depressive episode or combined with moderate aversive stimuli such as noise or other acute stressor to activate the LHb and open more LHb NMDARs for ketamine trapping.

Lusha Tong: To address depression, Dr. Ma employs a neuropharmacological approach, encompassing the decoding of neural signals in specific brain regions. A key question is whether this decoding process could be enhanced through artificial intelligence techniques? Dr. Yang's research focuses on this area, utilizing brain-computer interfaces to decode human emotions, particularly in the context of depression.

Yuxiao Yang: My research focuses on the brain-computer interface treatment of severe brain diseases, with a particular emphasis on addressing abnormal emotions and various mental disorders. We attempt to use brain-computer interfaces to modulate these disorders through intracranial electrical stimulation. Our primary research directions include decoding emotions from multi-brain region electrical signals, investigating the effects of electrical stimulation on emotion-related brain signals, and optimizing stimulation protocols in real-time based on decoded emotions to achieve optimal therapeutic outcomes. As Dr. Ma mentioned earlier, the real-time state of the patient may modulate the effect of drugs. A similar state-dependent phenomenon may also exist in intracranial electrical stimulation. Several randomized double-blind clinical trials that have been conducted since 2015 have shown that applying fixed parameters for stimulation only produces effects in some patients, with varied and inconsistent results at the population level. Our ongoing research has revealed that, for certain patients, stimulation is only effective in improving mood when they are specifically in a negative emotional state. This state-dependent phenomenon calls for a more sophisticated, state-based closed-loop electrical stimulation system that administers different stimuli based on distinct emotional states.

Lusha Tong: Dr. Ma just mentioned that the burst firing of the lateral habenula is also a characteristic electrical signal in the state of depression, but we have to be cautious that this phenomenon was observed in animal models. I wonder if Dr. Yang's brain-computer interface technology, which accesses deep brain electrical signals in patients, such as through clinically applied Deep Brain Stimulation (DBS), can capture similar signals.

Yuxiao Yang: Yes, basic research in neuroscience has provided many insights for the design of brain-computer interfaces. The critical role of lateral habenula offers such an inspiration. To establish its relevance to the treatment of depression, it is imperative to seek evidence of the role of the lateral habenula in real human cases. Our brain-computer interface team collaborates with the Neurosurgery Department at the Second Affiliated Hospital of Zhejiang University School of Medicine and the Department of Mental Health at the First Affiliated Hospital of Zhejiang University, where we implanted electrodes into a severely depressed patient in 2021. Following one year of lateral habenula DBS, this patient has transitioned from a severe depressed state to clinical remission, providing evidence for the efficacy of lateral habenula stimulation. However, due to physical limitations of the implanted DBS electrodes, we have only collected local field potential signals from the lateral habenula. Single-neuron spike activity at a long-term scale has not yet been obtained. In the future, we aim to employ more refined electrodes to investigate the variations in spike activity of lateral habenula neurons during DBS. This will allow us to compare and analyze these findings in contrast to phenomena observed in animal models.

Lusha Tong: In the case Dr. Yang discussed, did the implanted electrodes in the patient's lateral habenula capture the distinctive electrical activity during depressive episodes?

Yuxiao Yang: Over a year of continuous DBS, the patient's symptoms gradually relieved. We aimed to infer symptom changes from the recorded neural signals. We found significant correlations between various temporal and spatial features of the lateral habenula's local field potential signals and changes in the patient's depressive state. Using machine learning, we identified neural biomarkers capable of tracking the depressive state. Additionally, our ongoing work involves collecting and analyzing stereotactic electroencephalogram (SEEG) signals from multiple brain regions in epilepsy patients with depression. Preliminary results suggest individualized characteristics in emotion-related signal decoding, while certain emotion-related brain regions, such as the amygdala, insula, and hippocampus, consistently appear across individuals. Thus, we hypothesize that the emotional state network involves both common and specific interactions, with precise connectivity mechanisms awaiting foundational research.

Shuangshuang Ma: Dr. Yang, how did you choose the DBS treatment parameters, such as the frequency of stimulation?

Yuxiao Yang: The most straightforward method is manual parameter adjustment through trial and error, thereby attempting various combinations to then identify the most effective ones. However, this approach is time-consuming. Thus, we're developing a computational model, aiming at the prediction of stimulation effects with fewer parameters. Our primary focus is on short-term changes post-stimulation, such as emotional reactions measured within minutes or hours. To address the gap in long-term effectiveness, we plan to later validate this through extended time periods during DBS.

Lusha Tong: In clinical practice, non-invasive imaging methods, particularly high-field MRI, are crucial for patient assessment. Now, let's hear from Professor Jia Ke about their research.

Ke Jia: Our lab mainly utilizes ultra-high-field fMRI technology to investigate human cognitive functions, including the processes related to reward and punishment. Instead of traditional 3T magnetic resonance imaging (MRI) scans, which offer a spatial resolution of approximately 27 cubic millimeters, we use a state-of-the-art 7T scanner that allows us to discern sub-structures as small as a 0.5-millimeter cube. For comparison, the structure of habenula has a volume of about 18 cubic millimeters. Although the spatial resolution of MRI technology may not match that of single-electrode recordings, it offers non-invasive monitoring of neural activity throughout the entire brain, with higher participant acceptance.

Shuangshuang Ma: Dr. Jia, what is the approximate duration of the fMRI scan you mentioned? Is it feasible to administer ketamine to patients with depression and observe the most rapidly responding brain areas?

Ke Jia: The current time resolution is about two seconds, allowing us to obtain a whole-brain activation level every two seconds. However, due to the extensive acquisition area and the low signal-to-noise ratio at each point, it is often necessary to extend the scanning time to improve this ratio. It should be feasible if we categorize the conditions into pre-dose and post-dose. The experimental design will also depend on the duration of the drug's effectiveness in individuals.

Shuangshuang Ma: Although the concentration of ketamine in the bloodstream may rapidly decrease to undetectable levels, its effects may persist for up to a week. We aim to understand its impact on different neural clusters. I wonder if functional magnetic resonance imaging (fMRI) can record both excitatory and inhibitory brain activities?

Ke Jia: fMRI signals can reveal increased or decreased activation levels in different brain regions, but they may not necessarily correspond to excitatory or inhibitory neural activities. Our research team is currently exploring the use of magnetic resonance spectroscopic imaging to measure the levels of GABA and Glutamate in different brain regions. This approach aims to reflect the excitatory and inhibitory neural activities of specific brain areas.

Lusha Tong: We've recently delved into the profound investigations of abnormal emotional states from the angles of pharmacology, electrophysiology, and radiology. In our session today, we're honored to have Dr. Lai Jianbo from the Psychiatry Department of the First Affiliated Hospital of Zhejiang University, a distinguished physician in clinical practice. We eagerly anticipate Dr. Lai's insights and seasoned experiences regarding the management and intervention strategies for abnormal emotional conditions.

Jianbo Lai: The situations faced by clinical verses laboratory settings are quite different. The ketamine just mentioned should soon be launched in China, but we are still far away from practical clinical application. This is because of the strict requirements relating to ketamine in its use as an addictive drug and the lack of experience of domestic doctors on this unfamiliar drug.

Moreover, the clinical presentations and motivations for medication in patients are often complex. From a safety perspective, ketamine may be currently suitable only for emergency cases where there is explicit suicidal behavior or in confirmed treatment-resistant depressive patients with suicidal inclination. Furthermore, taking depression as an example, the etiology and pathogenesis in clinical patients remains far more complex than in animal models. There are various clinical subtypes, ranging from simple melancholic to those with anxiety features, and many cases of bipolar disorder are misdiagnosed as depression. The sophisticated techniques mentioned by the professors earlier for subtype identification require significant human and time resources, which are not feasible given the overwhelming number of patients in clinical settings.

Yuxiao Yang: Dr. Lai just mentioned that there are multiple subtypes of clinical depression. Is there any consensus on how to change the existing diagnostic standards to respond to discoveries in scientific research?

Jianbo Lai: There may be a number of new technologies and ideas, but the current diagnostic criteria are limited. The prevailing DSM-V and ICD-11 diagnostic standards, along with the treatment guidelines based on these criteria, constitute a stable framework. The introduction of new standards could imply a fundamental restructuring of existing frameworks, necessitating careful consideration of the distribution of diagnostic and treatment costs. Ideally, patients could be classified into specific subtypes based on neuroimaging patterns of brain network connectivity. However, in the current clinical environment, where physicians manage a high patient load, the feasibility of implementing novel and intricate approaches is limited. As a result, clinicians often resort to leveraging their personal expertise, focusing on symptom-targeted treatments to facilitate patients' reintegration into their normal professional and personal routines.

Ke Jia: Although subtyping based on imaging studies is currently feasible, reversing this process to achieve precise individualized treatment based on imaging still has a long way to go. The primary reason for this is the significant inter-individual variability which might require data from thousands of subjects to extract stable group differences.

Jianbo Lai: Professor Qiyong Gong from West China Hospital mainly focuses on imaging analysis of mental disorders. His article mentions the differences in imaging structures and functions between bipolar disorder, pure depression, or schizophrenia brains. When asked if these findings could guide clinical practice, his response was that intervening in areas with local structural differences may not necessarily be effective as these differences may not represent the particular fundamental cause of the disease. However, a new idea may be to conditionally induce different clinical subtypes to a similar state, in which all of them are sensitive to a specific intervention, similar to the conjecture just mentioned that administering negative stimuli to open NMDA receptors before administering ketamine.

Lusha Tong: Back to the prevention and relief of abnormal affective states, when ordinary people encounter major psychological setback, is it advisable for them to seek clinical psychiatric treatment or undergo psychological interventions?

Jianbo Lai: Some patients have obvious triggers for abnormal emotions, and they recover from symptoms when these triggers are removed. When the trigger cannot be addressed, therapeutic interventions mainly focus on ensuring and restoring an individual's social function. In many cases, we don't necessarily focus on psychiatric therapy, but rather start with methods such as medication to improve sleep quality, or encouraging patients to change their lifestyle habits and increase exercise. On the one hand, in today's society, mental illnesses such as depression are still stigmatized and labeled, so doctors consider a lot before making decisive diagnoses. On the other hand, negative abnormal emotions are not uncommon in the lives of ordinary people, and many patients can adjust themselves without medication or only taking medication for a short period of time.

Lusha Tong: Thank all the researchers for sharing your valuable opinions and ideas! Through this conversation, we have learned about new drugs for treating abnormal emotions, brain-computer interfaces, and high-precision brain imaging technology, and the potential implications of these cutting-edge discoveries in clinical diagnosis and treatment. We have also acknowledged the distance that still needs to be traversed across from bench to bed. We are looking forward to future improvement that will further facilitate collaboration between basic and clinical research.

Ke Jia, researcher at the BBMI center and Affiliated Mental Health Center, Zhejiang University, School of Medicine. His research focuses on the cognitive neural mechanisms of visual perceptual learning and working memory.

Yuxiao Yang, researcher at the BBMI center, the State Key Laboratory of Brain-machine Intelligence, and the Department of Neurosurgery, the Second Affiliated Hospital, Zhejiang University, School of Medicine. He received the National Distinguished Young Scholars in 2021. His research centers on designing closed-loop brain-machine interface systems for neural decoding and control, aiming to provide new therapies for neurological and neuropsychiatric disorders.

Lusha Tong, chief physician in Neurology Department, the Second Affiliated Hospital of Zhejiang University, School of Medicine. She is now the administrator of Neurology Department in CVD-specialized branch hospital and interested in the acute injury and chronic recovery in cerebral vascular diseases.

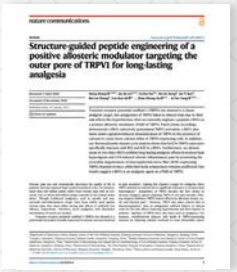
Jianbo Lai, attending physician and distinguished research fellow at the Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School of Medicine. He was honored as the Elsevier 2022 China Highly Cited Scholar (Clinical Medicine). His research interests include (1) neuro-immune and brain-gut axis mechanisms of affective disorders; and (2) psychiatric rehabilitation.

Shuangshuang Ma, postdoctoral fellow at the Fourth Affiliated Hospital of Zhejiang University School of Medicine. Under the supervision of Professor Hu Hailan, she participated in the research on the brain mechanism of ketamine' antidepressant effects, with a view to analyzing the causes of depression.

Prof. Yan Zhang's Research group

Mao C[#], Xiao P[#], Tao XN[#], Qin J[#], He QT[#], Zhang C[#], Guo SC, Du YQ, Chen LN, Shen DD, Yang ZS, Zhang HQ, Huang SM, He YH, Cheng J, Zhong YN, Shang P, Chen J, Zhang DL, Wang QL, Liu MX, Li GY, Guo Y, Xu HE, Wang C, Zhang C, Feng S[*], Yu X[*], Zhang Y[*], Sun JP[*]. Unsaturated bond recognition leads to biased signal in a fatty acid receptor. ***Science***. 2023 Apr 7;380(6640):eadd6220.

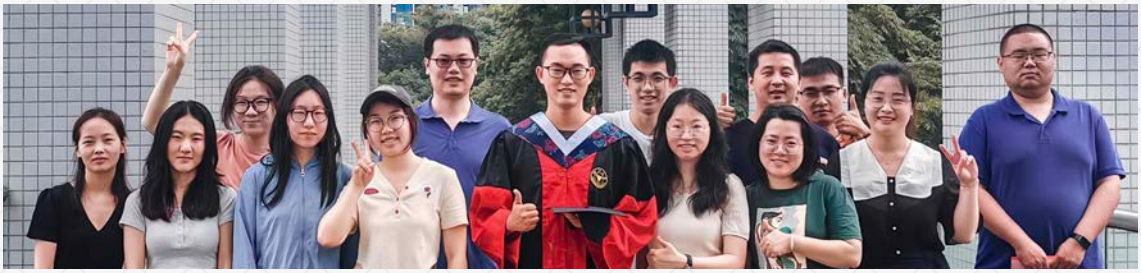
Individual free fatty acids (FAs) play important roles in metabolic homeostasis, many via engagement with more than 40 GPCRs. Searching for receptors to sense beneficial ω-3 FAs of fish oil enabled the identification of GPR120, involving with a spectrum of metabolic diseases. This study reported six cryo-EM structures of GPR120 in complex with FA hormones or TUG891 and Gi or Giq trimers. Aromatic residues inside the GPR120 ligand pocket were responsible for recognizing different double-bond positions of these FAs and connect ligand recognition to distinct effector coupling. The study also investigated synthetic ligand selectivity and the structural basis of missense single nucleotide polymorphisms. The study revealed how GPR120 differentiates rigid double bonds and flexible single bonds and may facilitate rational drug design targeting to GPR120.

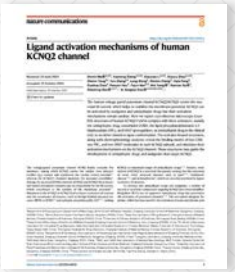


Prof. Zhenzhong Xu's Research group

Zhang H[#], Lin J[#], Xie Y, Song X, Sun J, Zhang B, Qi Y[*], Xu Z[*], Yang F[*]. Structure-guided peptide engineering of a positive allosteric modulator targeting the outer pore of TRPV1 for long-lasting analgesia. ***Nature Communications***. 2023 Jan 3;14(1):4.

In this study, the researchers rationally engineered a positive allosteric modulator (PAM) s-RhTx targeting the outer pore of TRPV1, discovered the molecular mechanism for the binding of sRhTx and TRPV1, and observed the long-lasting analgesic effect of s-RhTx in pain model mice. Furthermore, it exerts analgesic effects by inducing reversible degeneration of intra-epidermal nerve fiber (IENF) expressing TRPV1 channels, without impacting the body temperature. This study confirms the potential of developing positive allosteric modulators for the TRPV1 channel as a promising analgesic strategy, laying the foundation for the development of novel analgesic drugs targeting TRPV1 in the future.

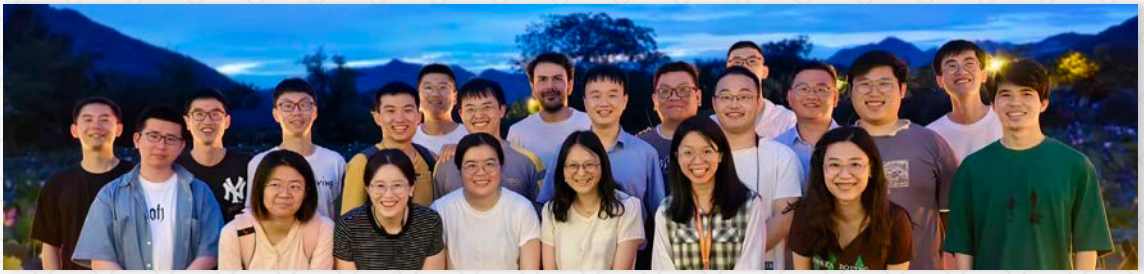




Prof. Jiangtao Guo's Research group

Ma D[#], Zheng Y[#], Li X[#], Zhou X[#], Yang Z, Zhang Y, Wang L, Zhang W, Fang J, Zhao G, Hou P, Nan F, Yang W, Su N, Gao Z[*], Guo J[*]. Ligand activation mechanisms of human KCNQ2 channel. ***Nature Communications***. 2023 Oct 19;14(1):6632.

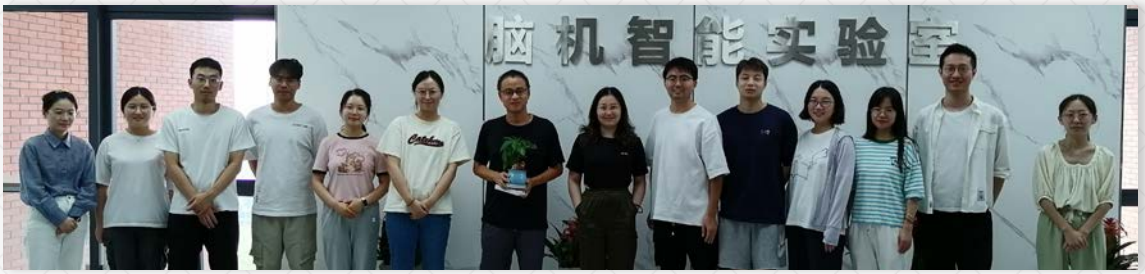
In this study, researchers systematically studied ligand activation mechanisms of the potassium channel KCNQ2 using simple particle cryo-EM and electrophysiology assays. The researchers determined structures of KCNQ2 in complex with the anti-epileptic drug cannabidiol (CBD), pynegabine (HN37), and phosphatidylinositol (4,5) bisphosphate (PIP2), revealed the binding modes of two CBD, two HN37, and one PIP2 molecules in each KCNQ2 subunit, and elucidated ligand activation mechanisms of KCNQ2 by comparing closed- and open-state structures of KCNQ2. This study provides accurate structure models and solid theory basis for the development of anti-epileptic drugs targeting KCNQ2.



Researcher Hongtao Lin's Research group

Zhong C[#], Liao K[#], Dai T, Wei M, Ma H, Wu J, Zhang Z, Ye Y, Luo Y, Chen Z, Jian J, Sun C, Tang B, Zhang P, Liu R, Li J, Yang J, Li L, Liu K, Hu X[*], Lin H[*]. Graphene/silicon heterojunction for reconfigurable phase-relevant activation function in coherent optical neural networks. ***Nature Communications***, 2023, 14(1): 6939.

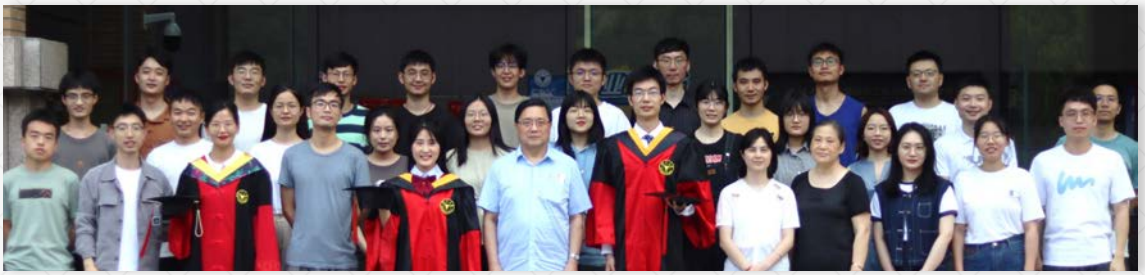
The pursuit of efficient and flexible activation functions in optical neural networks (ONNs) has intensified with the rapid advancements in optical computing. This study introduces a reconfigurable complex photonic nonlinear activation function device based on a micro-ring resonator integrated with a graphene/silicon heterojunction, which possesses dual modulation and detection capabilities. It also demonstrated its capabilities in information classification tasks such as handwritten digit recognition and color image recognition. This approach offers several advantages, including high speed, low power consumption, and reconfigurability, paving the way for the development of large-scale, high-performance coherent ONNs, holding promise for future applications in areas such as intelligent optical networks and optical information processing.

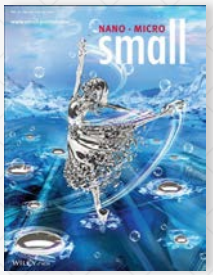


Prof. Huan Ma's Research group

Ma H*, Khaled H, Wang X, Mandelberg N, Cohen S, He X, Tsien R*. Excitation–transcription coupling, neuronal gene expression and synaptic plasticity. ***Nature Reviews Neuroscience***. 2023 Nov;24(11):672-692.

Excitation–transcription coupling (E–TC) links synaptic and cellular activity to nuclear gene transcription. E–TC begins with the activation of glutamate-gated NMDA receptors and voltage-gated L-type Ca^{2+} channels at the membrane and culminates in the activation of transcription factors in the nucleus. These receptors and ion channels mediate E–TC through mechanisms that include long-range signaling from the synapse to the nucleus and local interactions within dendritic spines, among other possibilities. Growing experimental evidence links these E–TC mechanisms to late-phase long-term potentiation and learning and memory. These advances in our understanding of the molecular mechanisms of E–TC mean that future efforts can focus on understanding its mesoscale functions and how it regulates neuronal network activity and behaviour in physiological and pathological conditions.





Prof. Ping Wang's Research group

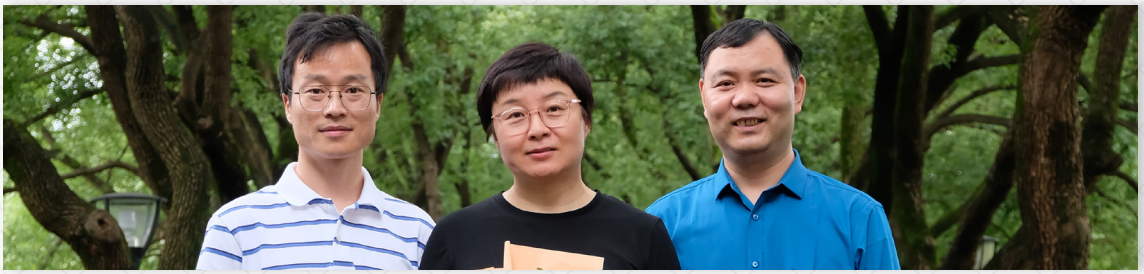
Duan Y, Wang S, Yuan Q, Shi Y, Jiang N, Jiang D, Song J*, Wang P*, Zhuang L*. Long-term Flexible Neural Interface for Synchronous Recording of Cross-Regional Sensory Processing along the Olfactory Pathway. ***Small***. 2023 Jul;19(29):e2205768.

In this study, a biohybrid olfactory system is proposed by integrating living mammals with implantable flexible neural electrodes, to employ the outstanding properties of mammalian olfactory system. The olfactory information encoded in the neural activity is recorded from both OE and OB simultaneously using flexible neural electrodes. Results reveal that spontaneous slow oscillations (<12 Hz) in both OE and OB closely follow respiration. This respiration-locked rhythm modulates the amplitude of fast oscillations (>20 Hz), which are associated with odor perception. Further, by extracting the characteristics of odor-evoked oscillatory signals, responses of different odors are identified and classified with 80% accuracy. This study demonstrates for the first time that the flexible electrode enables chronic stable electrophysiological recordings of the peripheral and central olfactory system *in vivo*. Overall, the method provides a novel neural interface for olfactory biosensing and cognitive processing.

Prof. Tao Li's Research group

Xie M#, Cai J#, Liu Y, Wei W, Zhao Z, Dai M, Wu Y, Huang Y, Tang Y, Xiao L, Zhang G, Li C, Guo W, Ma X, Deng W, Du X, Wang Q*, Li T*. Association between childhood trauma and white matter deficits in first-episode schizophrenia. ***Psychiatry Research***. 2023 May;323:115111.

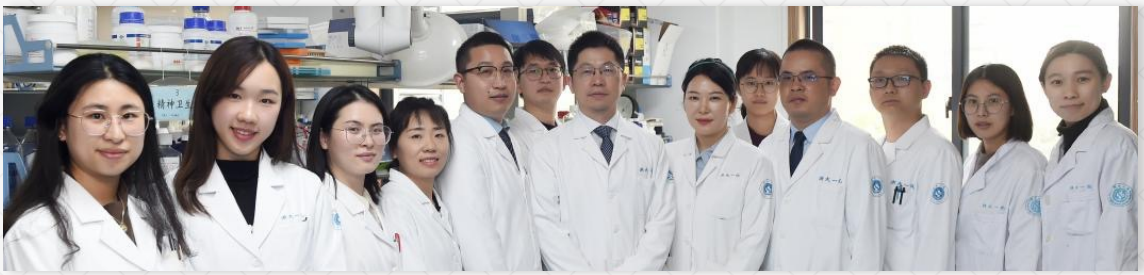
This study showed that compared with the healthy controls, the first episode schizophrenia (SZ) showed significantly lower fractional anisotropy (FA) in left anterior thalamic radiation, left inferior frontal-occipital fasciculus, left cingulum, forceps major, and forceps minor. In addition, the mean FA value in these white matter bundles was inversely related to the total childhood trauma score. These results provide clues about the neural basis and potential biomarkers of SZ.



Researcher Xinjian Li & Lixia Gao's Research group

Jia G, Bai S, Lin Y, Wang X, Zhu L, Lyu C, Sun G, An K, Anna Wang Roe, Li X*, Gao L*, Representation of conspecific vocalizations in amygdala of awake marmosets, ***National Science Review***, Volume 10, Issue 11, November 2023, nwad194, https://doi.org/10.1093/nsr/nwad194

For social communication, responses to distinct patterns of vocalization are usually highly specific to an individual conspecific call, in some species. This includes the specificity of sound patterns and embedded biological information. Authors conducted single-unit recordings in the amygdala of awake marmosets and presented calls used in marmoset communication, calls of other species and calls from specific marmoset individuals. They found that some neurons in the amygdala distinguished 'Phee' calls from vocalizations of other animals and other types of marmoset vocalizations. Interestingly, a subset of Phee-responsive neurons also exhibited selectivity to one out of the three Phees from two different 'caller' marmosets. Their findings suggest that, while it has traditionally been considered the key structure in the limbic system, the amygdala also represents a critical stage of socially relevant auditory perceptual processing.



Prof. Shaohua Hu's Research group

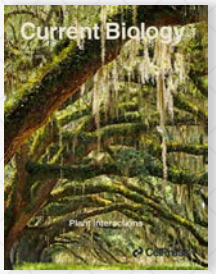
Li S#, Huang S#, Hu S*, Lai J*. Psychological consequences among veterans during the COVID-19 pandemic: A scoping review. ***Psychiatry Res***. 2023 Jun;324:115229.

This study reviewed the existing literature regarding the psychological consequences of COVID-19 on veterans. Veterans experienced more mental health problems than civilians. The prevalence rates of alcohol use, anxiety, depression, post-traumatic stress disorder, stress, loneliness, and suicide ideation significantly increased during the pandemic, ranging from 9.6% to 47.4%, 9.4% to 53.5%, 8.6% to 55.1%, 4.1% to 58.0%, 4.3% to 39.4%, 15.9% to 28.4%, and 7.8% to 22.0%, respectively. The main risk factors of negative consequences included pandemic-related stress, poor family relationships, lack of social support, financial problems, and preexisting mental disorders. In contrast, higher household income and greater community interaction and support appeared to be resilience factors. In conclusion, the COVID-19 pandemic has increased adverse mental health consequences among veterans. Tackling mental health issues due to the COVID-19 pandemic among veterans should be a priority.

Prof. Yi Zhang's Research group

Wang K#, Wen Q#, Wu D, Hsu Y, Heo H, Wang W, Sun Y, Ma Y, Wu D, Zhang Y*. Lateralization of Temporal Lobe Epileptic Foci with Automated Chemical Exchange Saturation Transfer Measurements at 3 Tesla. ***eBiolMedicine***. 2023 Mar;89:104460.

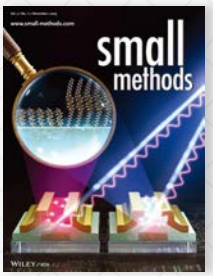
Magnetic Resonance Imaging (MRI) is an indispensable tool for the diagnosis of temporal lobe epilepsy (TLE). However, about 30% of TLE patients show no lesion on structural MRI (sMRI-negative), posing a significant challenge for presurgical evaluation. This study aimed to investigate whether chemical exchange saturation transfer (CEST) MRI at 3 Tesla can lateralize the epileptic focus of TLE and study the metabolic contributors to the CEST signal measured.



Prof. Zhihua Gao's Research group

Cao K[#], Qiu L[#], Lu X, Wu W, Hu Y, Cui Z, Jiang C, Luo Y, Shao Y, Xi W, Zeng L, Xu H, Ma H, Zhang Z, Peng J, Duan S[*], Gao Z[*]. Microglia modulate general anesthesia through P2Y12 receptor. ***Current Biology***. 2023 Jun 5;33(11):2187-2200.e6.

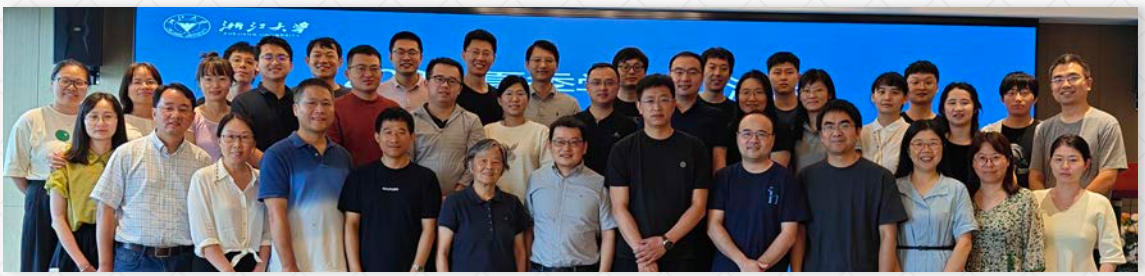
This study shows that microglial ablation reduced the sensitivity of mice to anesthetics and substantially shortened duration of loss of righting reflex (LORR) or unconsciousness induced by multiple anesthetics, thereby promoting earlier emergence from GA. Microglial repopulation restored the regular anesthetic recovery, and chemogenetic activation of microglia prolonged the duration of LORR. In addition, anesthesia-accompanying analgesia and hypothermia were also attenuated after microglial depletion. Single-cell RNA sequencing analyses showed that anesthesia prominently affected the transcriptional levels of chemotaxis and migration-related genes in microglia. By pharmacologically targeting different microglial motility pathways, blocking P2Y12 receptor (P2Y12R) reduced the duration of LORR in mice. Moreover, genetic ablation of P2Y12R in microglia also promoted quicker recovery in mice from anesthesia. These results present the first evidence that microglia actively participate in multiple processes of GA through P2Y12R-mediated signaling and expand the non-immune roles of microglia in the brain.



Prof. Wei Yang's Research group

Zhuang S[#], He M[#], Feng J[#], Peng S[#], Jiang H, Li Y, Hua N, Zheng Y, Ye Q, Hu M, Nie Y, Yu P, Yue X[*], Qian J[*], Yang W[*]. Near-infrared Photothermal Manipulates Cellular Excitability and Animal Behavior in Caenorhabditis elegans. ***Small Methods***. 2023: e2300848.

The study showed that exogenous expression of TRPV1 in AFD sensory neurons and D-class motor neurons causes to Ca^{2+} influx, leading to increased neural excitability and related behaviors, in the presence of ICG and NIR stimulation. Moreover, it successfully applied in different types of muscle cells, enhancing muscular excitability, leading to muscle contractions and physiological behavior changes in C. elegans. Meanwhile, ICG shows no biotoxicity to nematodes as an FDA-approved photothermal agent. This study demonstrates a noninvasive and effective method to precisely regulate the excitability of different types of cells and related behaviors *in vivo* by NIR photothermal manipulation, which may be applied in mammals and clinical therapy.



Prof. Gang Pan & Researcher Qian Zheng's Research group

Hu Y[#], Zheng Q[#], Jiang X,Pan G[*]. Fast-SNN: Fast Spiking Neural Network by Converting Quantized ANN. ***IEEE Transactions on Pattern Analysis and Machine Intelligence***. vol. 45, no. 12, pp. 14546-14562, Dec. 2023, doi: 10.1109/TPAMI.2023.3275769.

Aiming at the problem that it often requires lots of time steps to achieve high performance, this study demonstrates the equivalent mapping between temporal quantization in SNNs and spatial quantization in ANNs. This study introduces quantized ANN, a signed IF neuron model and a layer-wise fine-tuning mechanism to realize fast spiking neural network by converting ANN. It is the first time to achieve low time steps and near lossless conversion on classification datasets, and the first time to achieve the equivalent effect of ANN in segmentation and detection tasks.

Researcher Xuhua Wang's Research group

Guo B, Zheng H, Jiang H, Li X, Guan N, Zuo Y, Zhang Y, Yang H, Wang X*, Enhanced compound-protein binding affinity prediction by representing protein multimodal information via a coevolutionary strategy. ***Briefings in Bioinformatics***. 2023 Mar 19;24(2):bbac628.

In this paper, a co-evolutionary strategy is developed to jointly represent the structural and sequence characteristics of proteins, and finally optimize the mathematical model for predicting CPA. In addition, from the data-driven point of view, a reasonable method is proposed, which can use high-quality and low-quality databases to optimize the accuracy and generalization ability of FeatNN in CPA prediction tasks. It is worth noting that in a well-designed architecture, we intuitively explain the process of feature interaction between sequences and structures. Therefore, FeatNN is much better than the most advanced (SOTA) baseline in virtual drug evaluation tasks, indicating the feasibility of this method in practical application. FeatNN effectively represents the multimodal information of proteins through co-evolution strategy, which provides an excellent method for improving the prediction accuracy and generalization ability of CPA.

Prof. Wei Chen's Research group

Yan YJ, Zhou P, Ding LR, Hu W*, Chen W*, Su B*. T Cell Antigen Recognition and Discrimination by Electrochemiluminescence Imaging. ***Angew Chem Int Ed Engl.*** 2023 Dec 11;62(50):e202314588.

The paper introduces the development of label-free electrochemiluminescence (ECL) imaging technology for visualizing the immune synapse triggered by T cell recognition of tumor antigens. This technology is employed for the identification of tumor-specific antigen peptides and TCR clones. The potential application of this technique in the screening of tumor-specific antigens and TCR clones is crucial for the advancement of T cell epitope antigen vaccines and TCR-T cell therapies.

Prof. Hailan Hu

New Cornerstone Investigator Program

▼ **Neural mechanism of social behavior and emotion disorder**

Emotions color our lives and drive our behaviors. The emotion-behavior connection is one of the most fundamental approaches through which animals get selected in evolution. On top of that, the complex impact of interpersonal relationships, social experiences, and hierarchy structure further convolute our primitive emotion. Disorders in emotional and social behaviors lead to mental illness. Thus the brain mechanisms coding emotions and social behaviors are not only the boundary of human knowledge, but also the inevitable pathway towards remedies for mental diseases. With an ultimate goal to decipher brain mechanisms, my research program is established on three pillars: neuronal coding of emotions, brain machinery controlling social behaviors, and molecular, cellular, and circuitry mechanisms underlying depression. Growing together with this emerging field, aided by cutting-edge technologies and in-house methodology innovations, my group has made progresses in these three interconnected areas (summarized in research achievement). The current research is not only a direct extension but a bold leap from our previous program. In the next 5 years, we plan to focus on three areas: (1)Neural mechanism of emotional homeostasis in relief, (2) Neural mechanism of social dominance and status-loss-induced emotional disorder, (3) Etiology of depression and neural mechanism of novel antidepressants.

Prof. Bo Zhao

National Key Research and Development Program of China

▼ **A Bioinspired Neural-Organoid Chip and System with Integrated Sensing and Computing**

With the demographic longevity and aging, neurological diseases lead to serious economic and social burdens. All the conventional medical treatment such as neural organoids, electrical stimulation, and drug therapy induce side and limited effects to human body, which cannot apply to various complicated neurological diseases. Therefore, a new concept of bio-inspired neural-organoid chip composed by an electronic chip and a neural organoid is proposed, which is expected to become a new treatment method for various neurological diseases.

Prof. Zhefeng Gong

Major Project of National Natural Science Foundation

▼ Motor control mechanism of Drosophila larvae and bionic intelligent robot

Natural selection in the natural world has led to the remarkable locomotor intelligence of mollusc. Invertebrate mollusks have a natural advantage in movement. They are able to achieve a variety of behavioral movement patterns and switch between different movements smoothly and flexibly through a much simpler nervous and muscular system than vertebrates. In addition, because the degrees of freedom of movement of invertebrate holomollusks are theoretically almost infinite, their movement control is difficult and requires a high degree of cooperation between their nervous and muscle systems, that is, there are coupling effects and structural associations between neural control signals and muscle mechanical responses. On the mechanics and control coordination mechanism widely exists in life, make its can be realized through low cost control and structure complex behaviors, comprehensive sport ability far beyond the current artificial mechanical structure. Since the beginning of the software of the robot research field, has been attended by the illumination of life science and traction, through multidisciplinary cross research, discovery and the cognitive mechanism of life movement, form a kind of living organisms drive and control, perception, motor function integration of design and manufacture of theory, realize the integration and fusion of life and engineering system.

Prof. Shaohua Hu

Key Research and Development Plan "Common Disease Prevention and Control Research" Key Project

▼ Study on mechanism and intervention strategy of comorbidity between mental and physical diseases

Depression has the clinical characteristics of being highly prevalent, suicidal and disabling, and the global burden of disease is increasing. Depression is often co-morbid with various types of somatic diseases, and psychological and somatic symptoms are causative and mutually affect each other. Clinically, patients with depression co-morbidities often have poor outcomes and poor prognosis. Studies have shown that immune disorders play an important role in the pathogenesis of depression, with the presence of microglia activation in the brain and elevated levels of peripheral pro-inflammatory cytokines, and that the levels of immune-related indicators are significantly correlated with the degree of depression. Meanwhile, studies have also shown that immune-inflammatory factors are involved in the pathogenesis of a variety of somatic diseases, including Alzheimer's disease, pain, inflammatory bowel disease and metabolism-related diseases. This suggests that immune dysfunction may be a common pathological mechanism in depressive co-morbid somatic diseases. Therefore, the study of immune pathways and key molecules in depression co-morbidities and the establishment of scientific, effective, and novel intervention techniques are of great clinical value and scientific significance in reducing the disease burden and exploring the underlying disease mechanisms.

Researcher Yu Qi

Key Project of Zhejiang Province

▼ Research on hand fine movement with invasive brain-computer interface based on brain-inspired computing

Investigating the intricacies of how the brain captures and regulates the nuanced, high-degree-of-freedom fine movements of the human hand presents a formidable challenge. The human hand, comprising 27 degrees of freedom, stands as one of the most intricate organs within the human body. Deciphering how the brain adeptly encodes and manages such complex hand movements is a pivotal scientific pursuit within the scope of this project. Addressing the aforementioned scientific and technological challenges, our focus centers on the objectives of advancing invasive hand fine movement brain-computer interface technology and systems. This exploration unfolds across three distinct levels: delving into basic principles, unlocking key technologies, and showcasing application demonstrations. To realize these goals, our project aims to engage patients grappling with high paraplegia resulting from trauma, stroke, ALS, and related conditions. Through clinical interventions, we plan to implant electrodes in the motor area, enabling the acquisition of cortical brain electrical signals. Building upon this foundation, our research encompasses an in-depth examination of the neural coding mechanisms underlying fine hand movements, the development of modeling methods for high-degree-of-freedom hand movements, and the exploration of brain-like computing neural decoding technology for fine hand movements. In parallel, our efforts extend to the creation of wearable dexterous sports gloves. Ultimately, we aspire to seamlessly integrate these various components into a cohesive prototype system for fine hand movement control. This system is founded on invasive brain-computer interface technology, and its efficacy will be demonstrated through clinical applications.

Prof. Yan Zhang

Major Program of National Natural Science Foundation

▼ Precise Modulation Mechanisms of Dynamic Post-Translational Modifications and Chemical Interventions in G-Protein-Coupled Receptor Signaling

Dynamic chemical modifications of G protein-coupled receptors (GPCRs) play a precise regulatory role in modulating downstream signaling pathways and are essential in various physiological and pathological processes. Understanding the molecular mechanisms underlying specific chemical modifications in GPCR signal transduction and developing functionally selective modulatory drugs hold significant advantages and urgent significance. In this study, we aim to employ advanced visualization techniques, such as ultra-high-resolution cryo-electron microscopy analysis of GPCR signal transduction intermediates, to unravel the interaction mechanisms between chemical modifications (e.g., glycosylation, esterification, phosphorylation, fatty acylation) and signal transduction intermediates. Concurrently, we will integrate multidisciplinary approaches, including biophysics and chemical biology, to develop innovative technologies such as site-specific fluorescent labeling for dynamic GPCR modifications, enabling a comprehensive exploration of the molecular mechanisms underlying GPCR dynamic chemical modifications. By leveraging multidisciplinary cross-integration of DNA-encoded compound libraries, 3D small molecule chips, artificial intelligence-assisted molecular design, and other cutting-edge techniques, our research aims to discover precise targeted intervention strategies and functionally selective lead compounds related to dynamic chemical modifications of GPCRs, offering novel ideas and methodologies for innovative drug development.

Prof. Li Zhao

National Key R&D Program of China

▼ Neuronal Activity Imaging using Magnetic Resonance Imaging

Neural activity imaging is a key technique in the fields of neuroscience, diagnosis of brain diseases, and development of drugs for brain diseases. Magnetic resonance imaging plays an irreplaceable role in brain cognition and neural research, allowing for non-invasive acquisition of structural information of the whole brain. Additionally, with functional magnetic resonance technology, it is possible to image changes in blood oxygen levels caused by neural electrical activity. However, direct collection of neuronal potential still relies mainly on electrodes such as electroencephalograms, making it difficult to achieve accurate and non-invasive localization of neuronal discharge information. In response to the challenges of high temporal resolution and high spatial resolution in neuroimaging, this project will provide imaging methods for detecting neural activity and function by magnetic resonance signals and image processing. Specifically, this project will use line scanning sequence design, complete spatial and temporal separation of image acquisition through data reorganization and backtracking, achieve 25-millisecond and 1-millimeter spatial resolution.

Prof. Ge Bai

The National Science Fund for Distinguished Young Scholars

▼ Peripheral nerve development and disease

The peripheral nervous system is an important interface that carries interactions between the human body and the environment. Taking the sensory-motor nerve circuit as an example, it mediates the intake of major sensory information such as pain, touch, and proprioception to help the human body perceive itself and the surrounding environment. At the same time, it helps the human body make corresponding adjustments according to its own and surrounding environment by mediating the output of motor instructions, controlling body muscle movement, and regulating internal organs. Peripheral nervous system diseases are common in clinical practice, but most of them lack effective treatment plans, so they have always been a research hotspot and a difficulty in related fields internationally. In the past few decades, our country has achieved a large number of important scientific research results in the research of brain circuits, brain diseases, and other central nervous system research, however, the research strength for the peripheral nervous system is relatively weak and urgently needs to be strengthened. The research goal of this project is to elucidate the molecular mechanism of the development and maintenance of the peripheral nervous system, especially the sensory-motor nerve circuit, and on this basis, to analyze the pathogenesis of peripheral nervous system diseases and explore related treatment strategies.

Prof. Wei Chen

Key Project of National Natural Science Foundation

▼ Mechanical regulation of viral invasion and evolution

Numerous viruses constantly mutate and evolve to evade our biological defenses, posing a serious threat to human health. Virus invasion is initiated by the interaction of their envelope proteins with host-cell receptors. However, conventional research strategies only consider static and steady-state, while not considering dynamic mechanical regulation that is necessary to reveal the accurate mechanisms of virus invasion. How mechanical force triggers virus invasion, and whether virus evolves to enhance the invasion ability through better adapting to the mechano-microenvironment remain unclear. This project will focus to reveal the mechano-regulation mechanism of various envelope proteins in viral invasion and to understand the mechano-shaped adaptation of viral envelope proteins. Multidisciplinary techniques, including biomechanics, biophysics, bioinformatics, and virology will be applied in this project. Based on these mechano-regulation mechanisms, novel antiviral strategies could be developed. Taken together, this project will develop a new theory and explore a new paradigm for studying viral invasion dynamics, evolution, and antiviral drug discovery.

Prof. Li Zhao

National Key R&D Program of China

▼ Ventriculoperitoneal Shunt Evaluation using Human-in-the-loop Models

Hydrocephalus is a common brain disorder characterized by the excessive accumulation of cerebrospinal fluid in the cranial cavity. VP shunt surgery is one of the main methods for clinically treating hydrocephalus, but its main bottleneck lies in the high incidence of postoperative complications and difficulties in evaluating effectiveness, leading to a large number of patients requiring follow-up or secondary surgery. To address this problem, this project proposes using machine learning methods within a closed-loop system to extract multimodal features such as brain morphology, brain function, and clinical indicators to establish an evaluation model for postoperative effectiveness of hydrocephalus that has self-checking capabilities and can be generalized across multiple centers. Based on this, a prototype machine will be designed and clinical demonstration research will be conducted. This project will focus on the target population, imaging modalities, disease-specific approaches, model algorithms, and outcome translation in hydrocephalus research.

Prof. Yanqin Yu

Key Project of National Natural Science Foundation

▼ The intervention effect of electrical stimulation on sleep-wake system

Sleep is of vital importance as a brain function, while sleep disorders and accompanying diseases can cause severe problems upon human psychological and physical health. Nowadays, studies have identified multiple nuclei and circuits involved in sleep-wake regulation, but the regulation mechanism of sleep-wake, such as the initiation and maintenance of sleep, remains evasive. Therefore, effective non-drug interventions for sleep disorders are yet to be developed. In our research group, based on previous work on the analysis of sleep-wake neural circuits, the functions of sleep, and the network level exploration of the sleep-wake system, we plan to adopt a novel micro-nano electrode array with high temporal and spatial resolution to conduct multi-brain regional in situ real-time detection to investigate the dynamic characteristics of neuronal networks in multiple brain regions and multiple cells in natural sleep-wake and sleep disorders, so as to reveal the initiation and maintenance mechanism of sleep-wake, as well as the pathological network characteristics of sleep disorders. By combining electrical stimulation of sleep-wake-related neuronal clusters, our new methods and effective therapeutic targets for deep-brain adaptive closed-loop regulation of sleep disorders will be discovered and evaluated. This subject is of great significance for understanding the scientific mystery of sleep, promoting human health and seizing the highest point of life science research.

Prof. Ping Wang

Original Exploration Project of National Natural Science Foundation of China

▼ Construction of bionic nose and olfactory regeneration and intelligent regulation based on *in vivo* neural-electronic complex

Anosmia is a common clinical symptom. Infection and inflammation can cause irreversible anosmia and affect the cognitive function of the brain. At present, the commonly used treatment options in clinic include olfactory training, surgery and drug therapy, but the effect is not ideal. Therefore, this project innovatively proposed a bionic nose based on neuro-electronic complex to achieve olfactory regeneration. The implanted olfactory organ-flexible electrode complex is used to detect odors, and the signals are analyzed and recognized online through wireless transmission. The recognition results are fed back to the olfactory bulb region of the organism through the implanted stimulus module. By training the animals with olfactory function impairment, the olfactory function can be repaired and intelligently regulated. Science and key technologies are bionic nose preparation, olfactory injury model and complex implantation regeneration, organoids and olfactory neural circuit regulation, etc. This research will contribute to olfactory manufacturing and olfactory regeneration.

Prof. Huajin Tang

Key Project of National Natural Science Foundation

▼ Hybrid architecture brain-like system and application verification for simulating biological intelligence

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

Prof. Ping Wang

Key R&D program of Zhejiang

▼ **Development of a rapid screening instrument and reagents for disease biomarkers and drugs based on intelligent micro-nano sensors**

The project proposes the development of a rapid screening instrument for disease biomarkers and drugs based on intelligent micro-nano sensors. It involves the design of highly sensitive and highly specific micro-nano sensors along with complementary reagents. The instrument aims to achieve rapid screening of oral and bladder cancers through the detection of nucleic acids and protein biomarkers in saliva and urine. Additionally, it facilitates the swift screening of drugs for lung cancer through the design of lung cancer cells and organoid chips. The integration of micro-nano sensors with 3D lung cancer cells and organoids, which closely mimic the human body environment, will further enable the quantitative, rapid, real-time detection, and analysis of biological samples and cellular functional biomarkers. This approach offers advantages in terms of visualization, intelligence, miniaturization, and continuous monitoring of cells and organoids. Simultaneously, the development of intelligent analysis software and databases, coupled with collaboration with enterprises for engineering development, application demonstrations, and industrial promotion, will facilitate the widespread application of this technology in the fields of biomedicine and medicine.

Prof. Yan Zhang

Key R&D program of Zhejiang

▼ **Key Technological Research through Structural Analysis of Membrane Receptors such as GPCR and Structure-Guided Innovative Molecular Discovery**

GPCRs and other membrane receptors play a critical role in the development of major diseases. Our goal is to establish a stable preparation and purification platform for GPCRs and other membrane receptors in various states, including inactive, intermediate, and different binding states with effector proteins. By analyzing the cryo-electron microscopy structures of GPCRs and other membrane receptors at different stages of signal transduction, we aim to uncover the selective signal transduction mechanisms regulated by functional molecules and elucidate their dynamic molecular processes. This will provide a comprehensive understanding of the systematic relationship between precise signal pathways of relevant GPCR and other membrane receptor drug targets and their efficacy or side effects, enabling us to identify precise intervention drug targets and strategies for preventing and treating major diseases. Additionally, we will leverage the structure-based drug discovery technology system to design intervention molecules with dual specificity for receptors and downstream signaling pathways, followed by conducting preclinical studies of candidate drugs.

Prof. Yueming Wang

Key Project of National Natural Science Foundation

▼ **Research on Chinese-language Brain-machine Interfaces**

Language is the most direct and efficient way for people to communicate. Language brain-machine interfaces can help aphasic patients to achieve efficient communication with the outside world, by directly translating brain intentions into speech and text through implanted electrodes and chips in the brain. Thus, this technology has important clinical applications. In recent years, significant progress has been made in English-language brain-machine interfaces, while research on Chinese-language brain-machine interfaces is still in its early stages. Chinese differs significantly from English in terms of phonemes, tone, and written composition. The unique neural representation of Chinese in the brain, the encoding methods for generating Chinese, and the specific neural mechanisms for executing Chinese (speaking or writing) are all unsolved problems. This project aims to study the basic principles of Chinese language generation and execution in the brain and the key technologies for language brain-machine interaction from three scales: whole brain, local, and neuron. Techniques such as brain imaging, intracranial electroencephalography (iEEG), and spike potentials will be used. The focus will be on breaking through the mechanism of information processing in the whole brain Chinese language network based on a fine-grained Brainnetome Atlas, the language-specific encoding and decoding methods for the Chinese language in the language area for language generation, and the specific encoding and decoding methods for Chinese speech and writing in the motor area for language execution. Ultimately, we demonstrate the brain-to-text and brain-to-speech of the Chinese language by BMI systems.

Researcher Yi Zhang

National Key Research and Development Project of China

▼ **Artificial Intelligence-Empowered Molecular Magnetic Resonance Imaging for the Brain**

Aiming at the major challenges facing the field of molecular magnetic resonance imaging, this project intends to develop a series of efficient and reliable artificial intelligence algorithms by exploring a new paradigm of the complementary integration of artificial intelligence and molecular magnetic resonance imaging physical models, so as to realize the overall optimization of the whole chain of molecular magnetic resonance imaging, and build a high-contrast, fast and accurate molecular magnetic resonance imaging technology. Break through the application and development bottleneck of molecular magnetic resonance imaging technology, and promote the industrial transformation and clinical application of this technology.

Prof. Jianmin Zhang

"Pioneer" and "Leading Goose" research and development projects of Zhejiang Province

▼ **Research on new technologies for diagnosis and treatment of neuropsychiatric diseases—Research, development and application of new adaptive deep brain stimulation technology for the treatment of Parkinson's disease**

This project will be oriented towards adaptive neural regulation of clinical Parkinson's disease, optimizing electrical stimulation targets through neurological functional imaging and non-invasive neuroelectrophysiological quantitative assessment, and pre-response algorithms for Parkinson's biomarkers based on neuroelectrophysiological information in the brain. Optimization of aDBS and electrical stimulation modes improves the effect of aDBS in the treatment of clinical Parkinson's disease, and uses computational simulation models and animal experiments to explore and verify the therapeutic effect of aDBS, and build a new set of aDBS treatment technologies for Parkinson's disease. Independently develop aDBS regulation Prototype product, complete preclinical research on the product and conduct preliminary clinical research on product safety and effectiveness. Through the above research, a set of new technologies and new equipment for clinical diagnosis and treatment of Parkinson's disease with QDBS with independent intellectual property rights will eventually be formed.

Prof. Han Xu

Major Project of Zhejiang Natural Science Foundation

▼ **Molecular and circuit basis and regulatory mechanisms of anxiety disorder**

Anxiety disorders are chronic disabling and the most prevalent mental disorders, in which patients exhibit excessive and intense worry, avoidance behaviours, and over-excitement of the autonomic nervous system, which seriously endangers physical and mental health of patients. Currently, the low cure rate and inadequate treatment system for anxiety disorders are attributed to our limited knowledge of the neurological basis and regulatory mechanisms of anxiety disorders. For individuals, anxiety level is influenced by both genetic and environmental factors. In today's fast-paced society, chronic stress-induced anxiety disorders have become a very common phenomenon. The brain's neural network that regulates anxiety involves multiple brain regions and complex neural networks, and the understanding of the key brain regions, neural circuits and their molecular mechanisms of chronic stress-induced anxiety disorders is still unclear. This project intends to comprehensively screen the key brain regions involved in the occurrence and development of anxiety disorders in patients through functional magnetic resonance imaging, and develop animal models to systematically investigate the cellular, molecular and neurological mechanisms of the target brain regions in regulating anxiety behaviours, and ultimately return to the clinic to explore the practical strategies and translational applications of targeting the key brain regions and molecular targets to regulate anxiety disorders. We hope to provide theoretical support and intervention targets for the clinical treatment of anxiety disorders and related neuropsychiatric diseases.

Researcher Yihui Cui

Major Project of Zhejiang Natural Science Foundation

▼ Neural mechanism of autophagy in regulating emotional homeostasis and its application in novel antidepressant strategies

Stress is widely engaged in our daily life. The brain is the pivot in mediating stress, depending on the brain region, cellular and subcellular processes are involved in changing the brain during stress. However, how the brain dynamically copes with stress and how these accumulated alterations sculpt our stress coping behavior remains elusive. One of the most vulnerable targets of stress is the lateral habenula (LHb), which has been shown extensively activated by multiple stressors. Our previous findings suggested that LHb hyperacitivity is necessarily required for stress-induced depression onset. We therefore questioned what cellular and subcellular mechanisms are underlying the dynamic change during chronic stress. Macroautophagy, hereafter refer to autophagy, is a major catabolic step-wise process in which cytoplasmic proteins, defective organelles and pathogens are engulfed in autophagosomes and subsequently transported to lysosomes for degradation. However, little is known about the precise role of autophagy in neurons, especially its potential role in synaptic functions and its related normal and abnormal brain functions. Our preliminary data identified an unsuspectedly protective role of autophagy against stress in the development of stress related mental disorders. We hypothesized that autophagy can be potentially targeted for prevention and treatment of stress induced depression. In this project, we will combine multiple cutting edge technologies, including cannula pharmacology, viral transfection, electron microscopy, molecular biology, electrophysiology, fiber photometry etc., our goal is to uncover the cellular target of neuronal autophagy in regulating stress and depression onset. Our finding will provide new insights of novel antidepressant target, which might be potential for early prevention and treatment strategy.

Researcher Yuxiao Yang

Major Project of Zhejiang Natural Science Foundation

▼ Dynamic Encoding and Decoding of Brain Disease States across Mesoscopic-Macroscopic Scales for Depression

Depression is one of the most common neuropsychiatric disorders, with approximately 30% of patients not responding to existing treatments. Deep brain stimulation (DBS)-based brain-computer interface (BCI) neuromodulation system provides a new therapy for depression; such a system implants electrodes and chips into the brain and uses real-time recorded neural signals to guide DBS to accurately modulate the brain disease state. Encoding and decoding (coding for short) of brain disease states for depression is the core basis for realizing BCI neuromodulation, but three critical issues have yet to be resolved: how is emotion coded? how are the DBS effects coded? how do the inter- and intra-subject coding principles differ? This project aims at resolving the above questions by utilizing the neurophysiological characteristics of coding, i.e., the coding of emotion spans mesoscopic-macroscopic scales, the coding of DBS effects is dynamic causal, the inter- and intra-subject coding has both common and specific aspects. Accordingly, this project will collect multiscale neural signals during emotional tasks and DBS, including spikes, local field potential (LFP), and intracranial electroencephalogram (iEEG). Based on such data, this project will use a unified dynamic graph convolutional meta modelling framework to simultaneously build mesoscopic-macroscopic coding models for emotion, dynamic causal coding models for DBS effects, and generalizable models for inter- and intra-subject coding. The results of this project will provide theoretical and methodological basis for realizing BCI neuromodulation of depression.

2023 BBMI Selected Publications

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2. Cui Q#, Bi H#, Lv Z#, Wu Q#, Hua J#, Gu B#, Huo C, Tang M, Chen Y, Chen C, Chen S, Zhang X, Wu Z, Lao Z, Sheng N, Shen C, Zhang Y, Wu Z, Jin Z, Yang P, Liu H, Li J*, Bai G*. Diverse CMT2 neuropathies are linked to aberrant G3BP interactions in stress granules. ***Cell***. 2023 Feb 16;186(4):803-820.

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4. Ma S#, Chen M#, Jiang Y, Xiang X, Wang S, Wu Z, Li S, Cui Y, Wang J, Zhu Y, Zhang Y, Ma H, Duan S, Li H, Yang Y, Lingle C, Hu H*. Sustained antidepressant effect of ketamine through NMDAR trapping in the LHb. ***Nature***. 2023 Oct;622(7984):802-809.

5. Liao Y#, Zhang H#, Shen Q#, Cai C#, Ding Y, Shen D, Guo J, Qin J, Dong Y, Zhang Y*, Li X*. Snapshot of the cannabinoid receptor 1-arrestin complex unravels the biased signaling mechanism. ***Cell***. 2023 Dec 12:S0092-8674(23)01267-9.

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9. Zhang H#, Lin J#, Xie Y, Song X, Sun J, Zhang B, Qi Y*, Xu Z*, Yang F*. Structure-guided peptide engineering of a positive allosteric modulator targeting the outer pore of TRPV1 for long-lasting analgesia. ***Nature Communications***. 2023 Jan 3;14(1):4.

10. Duan J#, Xu P#, Zhang H#, Luan X#, Yang J, He X, Mao C, Shen D, Ji Y, Cheng X, Jiang H, Jiang Y, Zhang S*, Zhang Y*, Xu H*. Mechanism of hormone and allosteric agonist mediated activation of follicle stimulating hormone receptor. ***Nature Communications***. 2023 Jan 31;14(1):519.

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