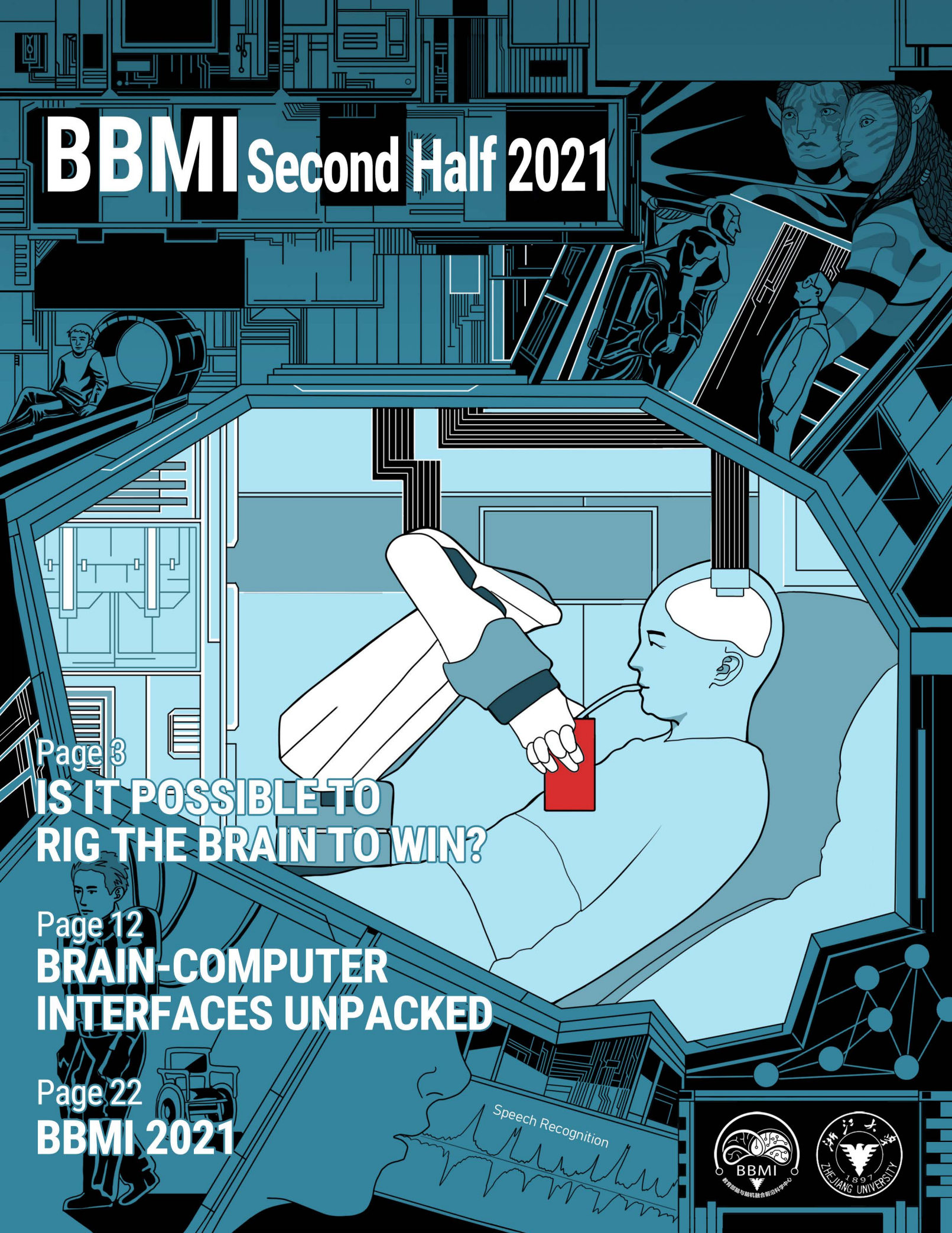
BBMI Second Half 2021



RESEARCH DISCOVERIES

RESEARCH INNOVATIONS

Scholar Column

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Director Message

Hailan Hu

Director of the BBMI Center

Brain science aims to explore the nature and laws of cognition and consciousness. Artificial intelligence is committed to using machines as carriers to realize human intelligence. To promote the convergence of brain science and artificial intelligence, the BBMI Center has built a broad platform of interdisciplinary research, allowing deeper exploration into the ultimate secrets of human wisdom.

In the second half of 2021, we have made advances in several scientific fronts. We discovered a microcircuit in the medial prefrontal cortex that regulates social competition behavior, constructed a neuronal connectivity map of the basolateral amygdala, and identified key brain areas related to neuropathic pain. In addition, we revealed a novel mechanism by which tyrosine phosphorylation of NMDA receptors selectively mediates depression, and developed a closed-loop neuromodulation chip that facilitates the treatment of depression. We have also developed dynamic and adaptive methods for decoding neural signals in high-performance brain-computer interfaces to assist in the application of a self-developed, brain-controlled robotic arm, and further optimized the brain-inspired computer "Darwin Mouse". These advances span from both our "wet" (biological experiments) to "dry" (software and hardware design) labs.

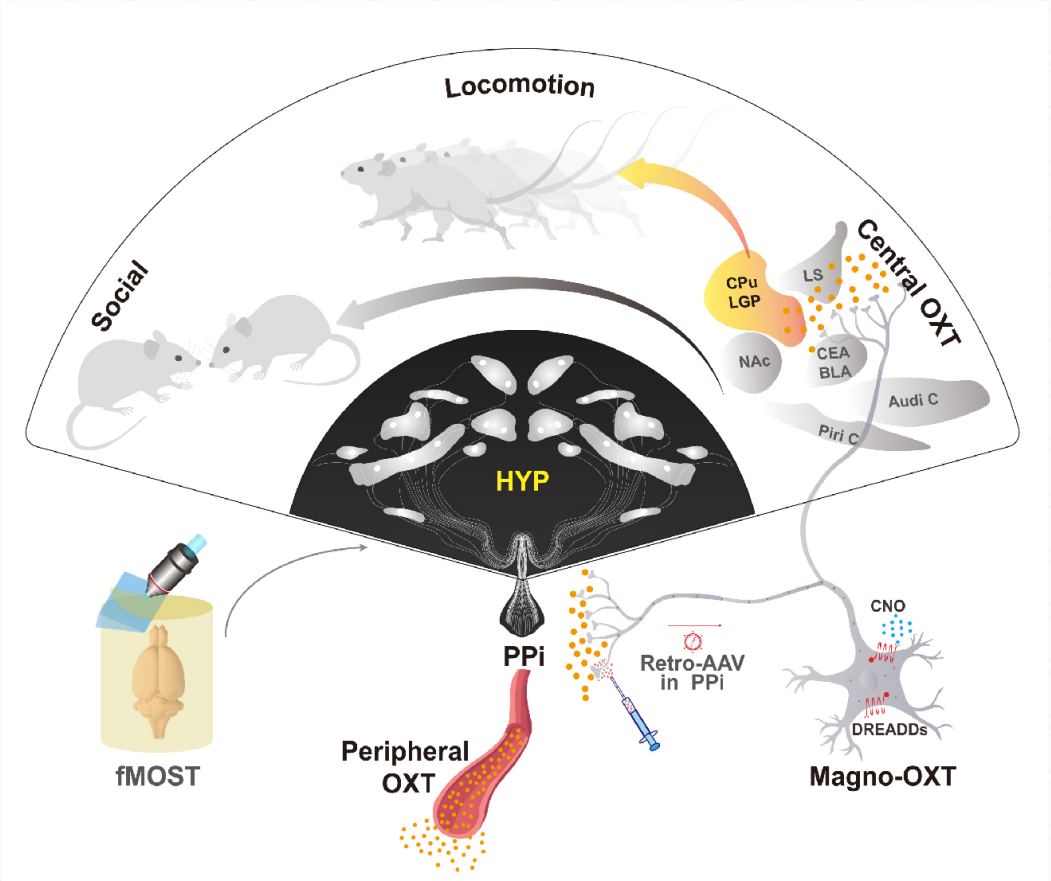
We are dedicated to promoting academic interactions, nurturing interdisciplinary cooperation, and developing an open culture of resource sharing. We have invited esteemed scientists, such as Professors Guoping Feng, Zihe Rao, Hesheng Liu, Yan Shen, Kwok-Fai So, Moo-Ming Poo, Mingjie Zhang, Tao Xu, Qingming Luo, Anming Meng, Jinsong Li, Dewen Hu, Aike Guo, Youming Lu, Xin Jin, Wen-Biao Gan, Aaron D Giltler and Huafu Chen for visits and to share their innovative ideas. With the official launch of the Chinese "Brain Project", we have already successfully led the application of two group-based grants on emotions and emotion disorders.

We warmly welcome experts from different disciplines and technical fields to work together and help us to build the BBMI center as a globally-recognized leading base of excellence for brain science and brain-machine integration.

The two headed sprayer

Projection mapping finally demonstrates how the hypothalamo-neurohypophyseal system can project both into the pituitary and into the brain

Love, loyalty, and trust are linked to oxytocin neurons in the hypothalamo-neurohypophyseal system (HNS). The HNS is composed of magnocellular neuroendocrine cells (MNCs) and the posterior pituitary gland (also known as the neurohypophysis). MNCs send long axons into the posterior lobe of the pituitary gland where oxytocin (OXT) and arginine vasopressin (AVP) are released into the bloodstream to regulate reproductive behavior and water-salt balance. Emerging studies have shown that oxytocin and vasopressin also play important roles in the brain and directly regulate social and stress-related behaviors. However, after being released into the bloodstream, these hormones are unable to cross the blood-brain barrier and re-enter the brain. Therefore, how they enter the brain remains to be clarified.



The HNS of rats was reconstructed using the fMOST technique. Chemogenetic manipulation of OXT cells can affect the level of OXT in the peripheral blood and regulate the social behavior of rats

Using retrograde viral tracers and fluorescent micro-optical sectioning tomography (fMOST), Prof. **Shumin Duan, Zhihua Gao** and An'an Li's group managed to construct the first precise 3D projection map of MNCs. They found that some oxytocinergic neurons (OXT-MNCs) not only project to the posterior pituitary but also collaterally project to multiple brain regions including the amygdala and caudate putamen.

To further determine the functions of OXT-MNCs, scientists used chemogenetic tools to selectively activate or inhibit OXT-MNCs. They found that selective activation of OXT-MNCs not only increased oxytocin levels in the peripheral circulation, but also promoted social behavior in rats, mediated by OXT released from collateral projections. Conversely, inhibition of these neurons reduced blood oxytocin levels and inhibited social behavior in the animals. This suggests that endocrine neurons coordinate both peripheral and central activities by a twin release of hormones into the blood mainly through axons, and also via neuropeptides into the brain through collateral projection. These OXT-MNCs neurons therefore act as a two-headed sprayer with one nozzle directed towards the peripheral blood to regulate reproduction behaviors and the other directed towards the central nervous system to regulate emotions. These findings were published in ***Neuron*** in 2021.

SHUMIN DUAN / ZHIHUA GAO'S RESEARCH GROUP focuses on the role of homeostatic regulatory mechanisms in brain development and brain diseases. They use in vivo two-photon microscopy, viral tracing, optogenetic/chemogenetic manipulation, along with cellular and molecular biology tools to characterize the function of neuroimmune-endocrine system in emotion and related disorders.

Don't push my button!

Revealing the brain-switch that controls rage

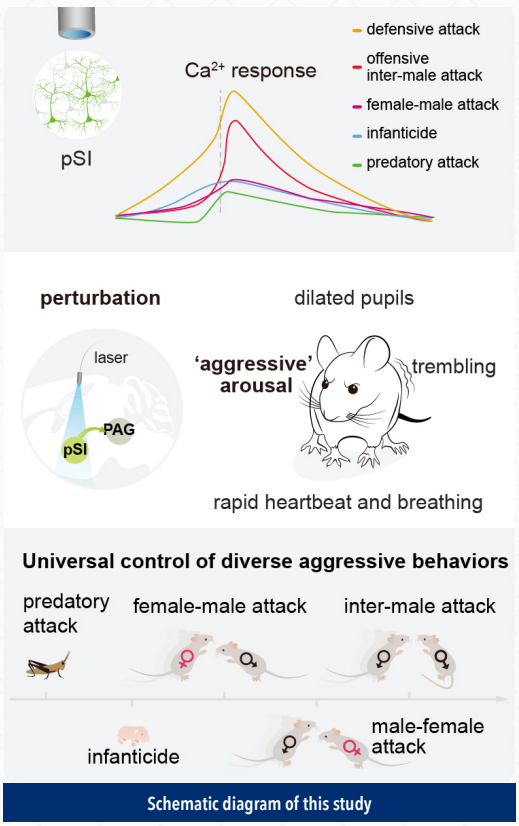
In the popular documentary "Animal World", lively commentary vividly displays various fights and conflicts occurring in animal societies. As we watch, we realize that many scenes seem familiar. Aggression and conflict, provocation with an angry response, threat and self-defense, failure and frustration, these and many other dramas are so reminiscent of the similar triggers and responses that occur in cases of human aggression.

In studying the neural circuitry underlying aggression and anger, the team of **Shumin Duan** and **Yanqin Yu** highlighted a key brain region for its regulation - the posterior substantia innominata (pSI). In mouse-based studies, this region became abnormally active when the mice started a fight or even made a threatening gesture prior to conflict initiation. Conversely, the previously combative and irritable mice immediately became perfect gentlemen when this brain region was suppressed!

This finding, published in the journal ***Neuron*** in 2021, provided new evidence on a key brain region involved in emotional regulation. Though this brain area had remained unnoticed for quite a while, it has gradually come to be understood that the pSI is a defined region located at the brain's emotional center - the extended amygdala. Duan and Yu's team's findings went further. They confirmed that the pSI is not simply mysterious like its name – "an unknown area", but is actually a critical brain region regulating various aggressive behaviors in mice.

In the face of different intensities of threat or stimuli, ranging from cricket predation to conspecific threats, pSI neurons in mice were seen to dynamically increase their activity. Temporal and magnitudinal responses in neuronal dynamics are highly efficient and accurate and often used for predicting and evaluating various internal states and intensities of behaviors. Such observations revealed that the pSI is not isolated, and showed that the pSI projects into the midbrain periaqueductal gray (PAG), an area responsible for motor control in social interactions. The activation of pSI-PAG neurons instantly switched the mice from a peaceful to a combative state. The mice then exhibited dilated pupils, notably increased respiration and heart rates, body tremors, and were primed to attack at the slightest provocation. Regardless of the initial state of the mouse, activating the pSI made the mouse instantly enter such an aggressive state. It was noted that these stimulation-induced physiological changes and motor outputs highly reflect many aspects of human anger. The pSI-PAG circuit was therefore concluded to be closely related to anger and generalized aggressive control for mice in a manner that could also relate to human aggression.

Alleviating pathological aggression in humans is a major challenge that relates to the whole of society. Understanding how inappropriate aggressive behaviors are linked to specific brain circuits or gene targets is a critical path for next-generation therapy. The next goal for the team is to study how individual neurons in the pSI encode internal states related to specific aggressive behaviors in rodents. Moreover, studies have shown that pan-amygdala lesions can effectively control severe and excessive violence in humans. The team is also interested in testing whether alterations in the human pSI could be used to curb attacks from these clinical cases. New imaging techniques with the high spatial and temporal resolution are now able to be applied to this question.



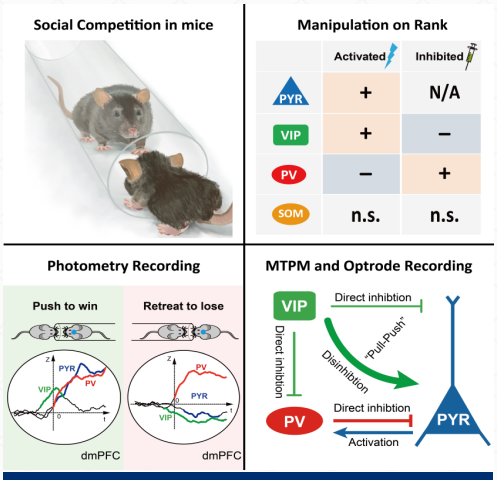
Schematic diagram of this study

SHUMIN DUAN / YANQIN YU'S RESEARCH GROUP analyzes the neural circuit mechanism that regulates important instinctive behaviors and emotional activities of our body, using transgenic mice, virus labeling and neural circuit tracing technology, patch clamp electrophysiology, light/pharmacological genetic manipulation, optical fiber recording and behavioral analysis, etc. Their studies provide important clues for specific manipulation of neural circuits, improvement of sleep and treatment of mood disorders and other diseases.

Is it possible to rig the brain to win?

How regulation of the medial prefrontal cortex microcircuit can prime the outcomes of socially competitive behavior

Dominance hierarchy is a fundamental organizing mechanism for most animal societies. The health and quality of life of social animals strongly depend on their dominant status, which is acquired through repeated bouts of social competition. The lab of Professor **Hailan Hu** has been committed to exploring the neural basis behind social hierarchy. In previous studies they used the tube test, a validated method for measuring social hierarchy in mice, to confirm the key role of the medial prefrontal cortex (mPFC) in controlling how the mice performed in social competition. Recently, Hu's team, in collaboration with Heping Cheng's team from Peking University, have taken this research a stage further. Their latest findings further decipher the regulatory role of the medial prefrontal cortex microcircuits in social competition behavior. Their results have just been published in ***Neuron*** (November 2021).



Summary of mPFC microcircuits in social competition regulation

Approximately 80% of cortical neurons are excitatory pyramidal (PYR) neurons which are generally responsible for the processing of information. However, the other 20%, comprised of inhibitory interneurons (such as parvalbumin (PV)-positive neurons, vasoactive intestinal polypeptide (VIP)-positive neurons and somatostatin (SOM)-positive neurons), must not be overlooked as they are also highly involved in the precise control of information processing within the brain. Researchers from Hu's lab found that using optogenetic methods either to activate the PYR and VIP neurons in the mPFC or to inhibit the mPFC's PV neurons, could instantaneously induce subordinate mice to win against previously dominant opponents in the tube test. Detailed video analysis revealed the extent to which these rank-elevated mice showed dramatically increased vigor and effort in their push and resistance behaviors, linked with a highly decreased tendency to retreat.

The research teams then used fiber photometry to observe the fluorescent calcium activity of these distinct neuronal populations in the process of social competition in real-time. They found that in the pushing behavior of mice, VIP neurons were first activated, followed by PYR and PV neurons. To further explore the functions of PV and VIP neurons, they collaborated with Heping Cheng's group using miniature two-photon microscopy (mTPM) combined with optogenetic manipulation to verify the inhibitory effect of PV neurons and excitatory effect of VIP neurons in regulating mPFC activity.

In addition, through *in vivo* electrophysiological recordings, the research teams also found that when PV neurons were activated, approximately 90% of other neurons in the mPFC were strongly inhibited. Conversely, when activating VIP neurons, which account for only approximately 3% of all neurons in the cortex, nearly 45% of mPFC neurons were also activated. Interestingly, VIP activation generated direct inhibition or inhibition-activation upon PV neurons, also causing PYR neurons to exhibit delayed activation. Such results enabled the research team to derive a medial prefrontal cortex microcircuit model (Figure 1) where VIP neurons were seen to achieve the effect of PYR neurons disinhibition by inhibiting PV neurons, thereby regulating the activities of the entire mPFC network and ultimately affecting social competition behavior.

Dr. Chaoyi Zhang, the first author of the article explains, "VIP neurons, as a special inhibitory neuron group, mainly act on other inhibitory neurons. They play a disinhibitory role and provide an especially fine level of regulation of information processing in the brain's microcircuits. We found these neurons to be the first to respond when push behavior occurs. Combined with the understanding that their distribution in the neocortex is mainly in layer II/III, we hypothesize that these neurons may initiate the processing of upstream information input by the cortex. If so, such neurons are shown to be the true 'VIPs' of the mPFC microcircuits."

Professor Hailan Hu adds: "This study outlines a diverse and dynamic microcircuit model and uncovers a new VIP-PV-PYR disinhibitory pathway which regulates social competition behavior. It also deepens our understanding of how the medial prefrontal cortex processes social information and provides new insights into social abnormalities linked to social competition."

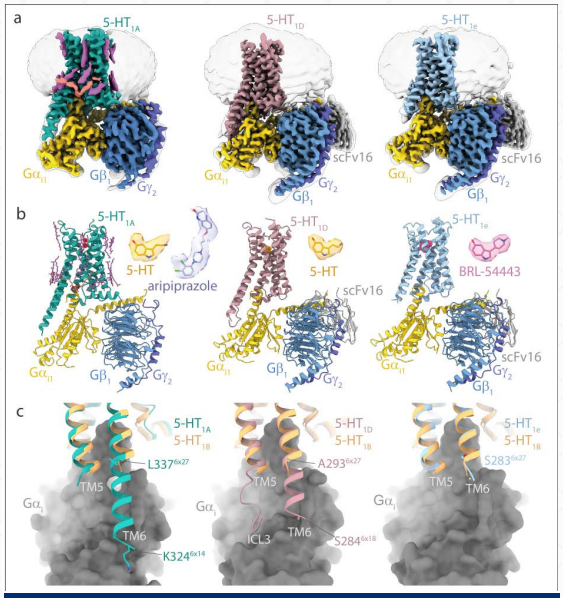
How mice recognize high-rank individuals or low-rank individuals in social competition, and how that information is processed within the mPFC, will be the next focus for the team's research.

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 electrophysiology, optogenetics, cell and molecular biology, and other multi-level research methods to conduct a deep analysis of emotion-related neural circuits at the cell and circuit level.

The Brain-switch for happiness?

Analysis of the structural code of the "pleasure neurotransmitter" receptor

In our brains, a pleasure neurotransmitter called serotonin (5-HT) helps us feel happy, relaxed, and confident, and is linked to our sense of satisfaction. Most of the physiological functions of 5-HT are mediated by G-protein-coupled receptors (GPCRs) on the cell membrane. Studies have shown that 12 GPCRs mediate serotonin function in humans. These receptors are important targets for the treatment of psychiatric disorders such as depression, schizophrenia, and migraine. Although the function of serotonin and its receptors have been a long-term focus for neuroscience and many aspects having been deeply explored, there are still many unsolved problems and questions regarding its function and molecular regulation mechanisms.



Cryo-EM structures of 5-HT1A, 5-HT1D and 5-HT1E receptors, ligands and Gi protein complexes

In March 2021, the team of **Yan Zhang** (Zhejiang University) with Huaqiang Xu and Yi Jiang (Shanghai Institute of Materia Medica, Chinese Academy of Sciences) co-published an important research in ***Nature***. In this, they successfully analyzed five structures of three types of serotonin receptors. This study was the first to show how the phospholipid PI4P (PtdIns4P) and cholesterol regulate function of these receptors. It also revealed how the antipsychotic drug aripiprazole recognizes the serotonin-receptor to function. As a first-line drug, aripiprazole is clinically used in the treatment of schizophrenia, depression, bipolar disorder, autism, and other common psychiatric disorders. The results provided an important theoretical support for more precise use and treatment for this important drug.

A key question was "What actually lies behind this 'happy neurotransmitter', the serotonin receptor?". Using single-particle cryo-electron microscopy (SEM), the team was the first to analyze five near-atomic resolution complexes of the serotonin receptor and Gi protein (inhibitory G protein). They were able to newly identify a phospholipid molecule at the interface between the 5-HT1A receptor and Gi protein. This was named PI4P. PI4P was shown to significantly promote the activation of G protein. In addition to PI4P, the team also identified at least 10 cholesterol molecules at the receptor-cell membrane interface, confirming that these molecules play key roles in the regulation of receptor function.

Further investigation delved into the question of how serotonin receptors are so accurately and selectively identified by drugs to perform their unique work. The team uncovered key evidence in the case of aripiprazole. As a highly selective ligand for the 5-HT1A receptor, aripiprazole is 10 to 1,000 times less active against 5-HT1B, 5-HT1D, and 5-HT1E receptors than against 5-HT1A receptors. Structural analysis showed that the extracellular terminal of TM7 of the 5-HT1A receptor, the receptor that binds aripiprazole, had been shifted outward by 3 angstroms relative to other less selective receptor subtypes, resulting in a relatively larger ligand-binding pocket to hold the quinolinone group of aripiprazole. At the same time, a cholesterol molecule bound to the 5-HT1A receptor was implicated in the formation of the aripiprazole ligand-binding pocket, being able to maintain the TM1 and TM7 conformations near the quinolone group of the ligand. Taken together, these findings elucidated the mechanism of the high selectivity of aripiprazole to 5-HT1A receptors.

In this study, the structures of various serotonin receptors, their small molecular ligands, their therapeutic agents, and their corresponding Gi protein complexes, were analyzed for the first time using near-atomic resolution electron microscopy. Based on structural information and functional analysis, they were able to reveal the constitutive activation mechanism of 5-HT receptors and the molecular mechanism of selective recognition of serotonin receptor subtypes by antipsychotic drugs. The continuing unraveling of the code for the receptors of this "pleasure neurotransmitter" is a cornerstone that should soon enable scientists to pinpoint more precise and selective targets for mental illness, leading to increased drug efficiency and enabling increasing relief of patients suffering from such conditions.

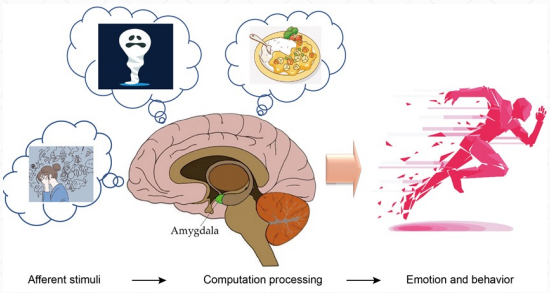
YAN ZHANG'S RESEARCH GROUP is dedicated to the research of the structural pharmacology of G protein-coupled receptors associated with major human diseases. Combined with high-resolution cryo-EM technology, computer-aided drug design and a variety of molecular and cellular biology assays, ZHANG's team conducts in-depth research on the signal transduction mechanisms and drug development related to such receptors.

In the lion verses antelope, it all boils down to the basolateral amygdala

Development of new tools for analyzing how the basolateral amygdala processes external information and mediates the appropriate responses for survival

Animals are constantly scanning the environment for opportunity or advantage, while simultaneously avoiding danger or detriment. Take the classic lion vs antelope (predator vs prey) scenario as an example. The ability not just to sense the appropriate olfactory, acoustic, or visual cues, but also to have those cues trigger an appropriate emotional feedback and behavioral response, are aspects equally valuable to the lion seeking his next meal or the antelope seeking not to become it!

The amygdala nuclei, named for its almond-shaped cluster, has been identified by scientists as the prime processor of this kind of evaluation, emotional response and subsequent behaviors in many complex vertebrates. Positioned deep in the brain's cerebrum, the amygdala is active in determining the emotional valence and importance of information. It provides appropriate emotional feedback and ultimately governs the behavioral responses to a wide range of different external and internal stimuli. However, exploration into the organization of the amygdala neural circuitry has been limited by the pre-existing versions of neural projection "tracing tools". In order to analyze the complex input and output loop connections of the amygdala, the design and development of yet more specific tools are urgently needed.



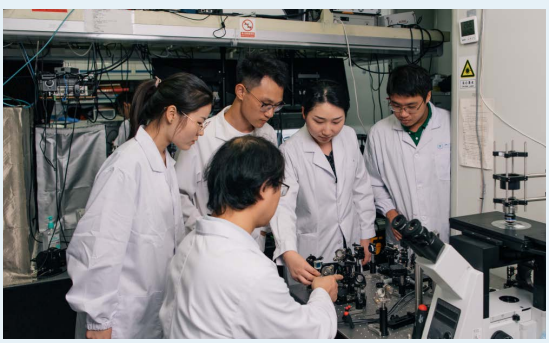
Professor **Wei Gong** and Professor **Ke Si**'s team at the BBMI has been combining novel self-developed technologies with more standard neurobiological research methods, to analyze the brain's working modes, information processing, and transmission mechanisms. The research team used the rabies virus and adeno-associated virus to achieve cell-type-specific and projection-site-specific retrograde trans-single synaptic tracking. Using these they were able to "light up" the upstream connections of specific groups of neurons in the particular brain regions of interest. This method is simple to operate and has strong tracking specificity, thus applicable for exploring many complex and important neural circuit connections.

By analyzing the connection patterns of the neural circuits of the basolateral amygdala (BLA), the research team was able to reveal its "input homology and output independence" information processing mechanism by which the amygdala integrates complex input signals and passes information independently to downstream brain regions. This breakthrough research has now been published in the August 2021 edition of ***Molecular Psychiatry***.

The research team focused on four neural circuits closely related to survival behavior: the basolateral amygdala-stria terminalis nucleus, basolateral amygdala-ventral hippocampus, basolateral amygdala-medial prefrontal cortex, and the basolateral amygdala-accumbens. Systematic quantitative analysis of the distribution of information inputs through these circuits revealed that, although the BLA accepted a wide range of information inputs from the whole brain, the input ratios of different types of information varied dramatically, with the contextual information as the most important one. The proportions of neurons that mediate the different stages of survival behavior were seen to be highly consistent. These results showed that the BLA neural circuitry combined information of different weights from sensory, integrated, contextual, and neuromodulation levels, and then delivered the processed information to the downstream brain regions without relying on output targets. This "same input and independent output" information processing model formed a multi-dimensional processing path, mediating the initiation, acquisition, evaluation, and decision-making behavior required for survival.

Professor Wei Gong also highlighted how the use of VR technology in their study contributes to a virtuous circle between clinical treatment application and basic research. "Since the first use of virtual reality (VR) to treat acrophobia in 1995," she explains, "VR exposure has become an important clinical tool for the treatment of post-traumatic stress disorder, social disorders, and other mental illnesses. Our VR related research results show that contextual information plays a dominant role in the information integration of the BLA. VR exposure therapy can effectively edit the fear-defense system of the BLA, thus explaining how and why VR can effectively treat anxiety disorders. Simultaneously, VR allows more accurate quantification of different types of BLA input information, helping guide the design of better virtual reality treatment methods."

WEI GONG'S RESEARCH GROUP is a cross-disciplined laboratory of medical, industrial, and information technology. It aims to use the most advanced technology to solve life-science problems with the focus upon simple, direct and effective applications into clinical medicine. The major research directions include: 1) analysis of the structure and function of neural networks (brain reading), particularly in the development of advanced microscopic imaging and other methods to study the information communication and regulation mechanisms between neural networks, aspects of transparent brain technology, 3D imaging, and other related areas; 2) the functional regulation of the neural circuitry of learning, primarily based on optogenetic control of the brain.



Needles and pins

New revelation of the relationship between the orphan receptor GPR151 and the P2X3 ion channel may lead to novel treatments for neuropathic pain

Neuropathic pain can be caused by a lesion or dysfunction of the somatosensory nervous system. Despite the term 'pain', it can manifest in a broad range of abnormal sensations, usually triggered from non-painful stimuli, including 'pins-and-needles', burning, coldness, mechanical allodynia or numbness. Whilst an increasingly serious clinical problem, with approximately 5%–10% of the world's population affected, it is notoriously difficult to treat due to its elusive mechanisms. The search to identify new effective therapeutic targets is one of the focus areas for Prof. Xu's group from the BBMI.

G protein-coupled receptors (GPCRs) collectively represent a seven-transmembrane protein superfamily. They play important roles in cell signal transduction and are widely involved in physiological and pathological processes including pain sensation. One-third of FDA-approved drugs target GPCRs, thus highlighting the GPCRs as a "domain of extreme interest" for finding new therapeutic targets.

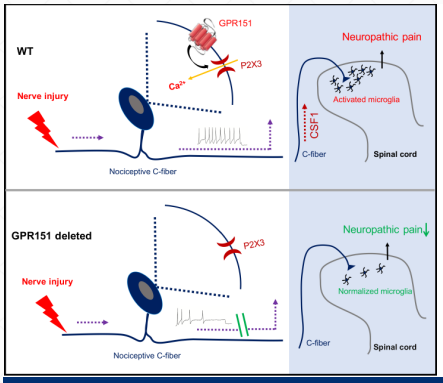


Figure 1. GPR151 modulates neuropathic pain by regulating P2X3 function and microglial activation

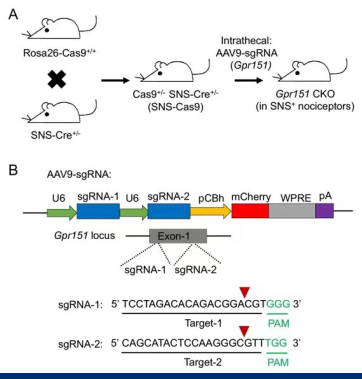


Figure 2. Conditional knockout of *Gpr151* in nociceptive sensory neurons of adult mice based on the CRISPR/Cas9 strategy

Zhen-Zhong Xu's team from the BBMI Center has just published their latest related research results in the journal ***Brain*** (2021). The team revealed that the orphan G protein-coupled receptor GPR151 in primary sensory neurons modulates neuropathic pain by regulating P2X3 function and microglial activation (Figure 1).

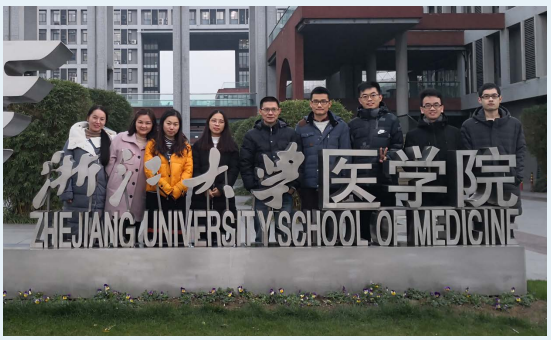
Although GPCRs contain more than 800 members, 15% of these are a specific type labelled orphan GPCRs. The functions and endogenous ligands of this type of receptor have not been clearly identified. Interestingly, the orphan receptor GPR151 is the most upregulated GPCR in the primary sensory neurons of the dorsal root ganglia (DRG) after nerve injury. This led the team to consider GPR151's potential involvement in the regulation of neuropathic pain.

Xu's group firstly studied the expression pattern of GPR151 in DRG tissues and found it to be selectively expressed in non-peptidergic nociceptive C-fiber sensory neurons, with expression particularly upregulated beyond nerve injury. Sensing they were on the right track, the research team then conducted conditional knock out of *Gpr151* in adult mouse nociceptive sensory neurons using CRISPR/Cas9 technology (Figure 2). The result was encouraging. Neuropathic pain model mice displayed effective relief of neuropathic pain induced by nerve injury, whilst their basal pain threshold remained unaffected. The conditional knockout of *Gpr151* also significantly inhibited nerve injury-induced DRG neuronal hyperexcitability, colony-stimulating factor 1 (CSF1) upregulation, and spinal microglia activation (Figure 1).

P2X3 is the ion channel exhibiting the most significant upregulation in DRG after nerve injury. Interestingly, P2X3 ion channels co-localize well with GPR151 in DRG neurons. This led the team to consider whether P2X3 was also involved in regulating neuropathic pain? In a mouse model of neuropathic pain, the research team revealed that GPR151 had coupled with the P2X3 ion channels and promoted their functional activity. This resulted in increasing P2X3-mediated calcium elevation and spontaneous pain behavior. Knockout or knockdown of *Gpr151* was then shown to significantly inhibit these increases of P2X3-mediated calcium elevation and the related spontaneous pain behavior in the model mice. The team also found that knocking down P2X3 in DRG could effectively reverse nerve injury-induced CSF1 upregulation, spinal microglia activation, and neuropathic pain in mice.

As both GPR151 and P2X3 are also co-expressed in human DRG neurons, this suggests that the above research results might be applicable to human neuropathic pain. In particular, the finding that GPR151/P2X3 in primary sensory neurons plays a key role in neuropathic pain induced by nerve injury may provide an exciting potential target for the treatment of clinically relevant neuropathic pain.

ZHEN-ZHONG XU'S RESEARCH GROUP studies the molecular, cellular, and circuitry mechanisms underlying sensory signaling and neuronal plasticity, including pain and itch. They also focus upon the molecular mechanisms and circuits related to negative emotions induced by chronic pain. They are committed to exploring novel drug targets and interventional strategies for chronic pain and chronic itch.

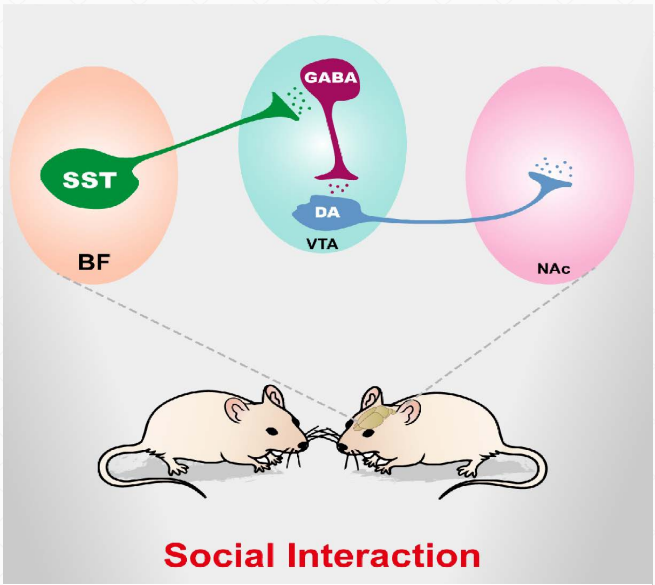


Wired for sociability

Novel neural circuitry mechanisms for regulating social behavior

When we see someone in trouble, we want to step forward and help. When we experience something pleasant, we want to share it with our friends. When our own abilities are insufficient to complete a task, we want to seek aid from others. Satisfying such social behaviors is the cornerstone of normal life. Abnormal social behavior is often highlighted when such tendencies seem somehow absent, distorted, or disordered, and often relate to psychiatric conditions such as autism or social phobias. These in turn may relate to the mechanisms of the neural circuitry of social behavior, many aspects of which are little understood.

A team led by Professor **Han Xu**, has just published their latest research in ***PNAS*** in 2021. In this, the neural circuitry that regulates social behavior in the basal forebrain (BF) was revealed for the first time. In addition, it was observed that inhibitory projections from the BF to the ventral tegmental area (VTA) could regulate social behavior by disinhibiting dopamine (DA) neurons.



The basal forebrain (BF) promotes social behavior via its neural circuitry mechanism

As the first author of the study, Associate Professor Jun Wang, reports, "The understanding that the VTA-NAc DA reward pathway can regulate social behavior has been widely recognized and has been the focus of many previous publications. 'Social reward theory' was then proposed based on such observations. Our study further explored the activation of the upstream brain region of DA neurons as an important complement to 'social reward' theory. We revealed that an entirely new function of the BF is to regulate the behavior of social interactions."

To explore the relationship between the BF and the regulation of social behavior, the research team used calcium fiber photometry to directly measure the activity of BF neurons during a three-chamber social approach test. In this, the activity of BF to VTA projection neurons is concurrently regulated by light through optogenetic methods. GABAergic neurons expressing somatostatin in the BF (BF-SST) were seen to be strongly activated during social interactions in mice. However, inhibition of the BF-SST to VTA projection pathway led to a breakdown in social behavior for these animals, suggesting that the BF-SST to VTA projection pathway is necessary for normal social behavior.

Based on these results, the team further explored how SST neurons work through the VTA. The reward-related DA neuron activity in the VTA is regulated by tight feedforward inhibition of local GABAergic neurons. By combining in vitro electrophysiology and optogenetics, the research team found that activating the BF-SST to VTA projection led to a recording of the postsynaptic inhibitory current from a larger proportion of VTA-GABA neurons. Upon such activation, the amplitude of the inhibitory current was also noted as significantly larger in GABA neurons than in DA neurons. These observations indicate that SST neurons are less likely to directly act on VTA-DA neuons but tend to project onto the local GABAergic neurons of the VTA, thereby relieving their inhibitory effects on DA neurons and thus regulating social behavior.

This study revealed the neural circuitry of the BF which regulates social interactions under normal physiological conditions. As for the next research plan, Jun Wang (the first author of this paper) suggests, "Social deficits are common symptoms in many mental illnesses. Whether our newly discovered neural circuit is involved in the occurrence of social behavior disorder in mental illness will be an important research direction for the future. In addition to exploring the specific mechanisms by which the BF neural circuit regulates social disorders in animal models of mental illness, we will also work closely with experts from multiple clinical disciplines, including psychology and psychiatry. Further validation of such research from functional brain imaging and targeted physical interventions in the disease population are expected to lead to the development of new strategies for clinical intervention for a number of social disorders related to mental illness."

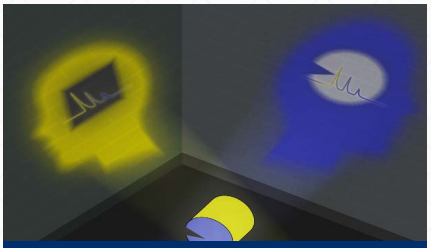
HAN XU'S RESEARCH GROUP has long been engaging in the research on the structure and function of neural circuits, especially focusing on the neural circuit mechanism of social behaviors and social dysfunction in neuropsychiatric diseases. They aim to provide theoretical insights and intervention targets for clinical treatment of social dysfunction-related mental diseases.

Neuronal "self-eating" for long-term plasticity

Mechanism of autophagy and gene transcription in the maintenance of long-term synaptic depression

Adjusting future behavior based on past experience is a necessary survival strategy for almost all higher organisms. But what is going on in our brains during such a process? Biological learning depends upon a nervous system that readily allows structural and functional changes in its connection network at a micro level, a concept called "neuronal synaptic plasticity".

Long-term depression (LTD) and potentiation (LTP) are two opposing processes of neuronal synaptic plasticity that can last from minutes to up to several weeks. They represent the essential cytological basis of advanced brain functions. Previous studies have found that excitation-transcription coupling plays a very important role in the maintenance of LTP. This results in late-phase long-term potentiation (L-LTP), which is essential for learning and the storage of memories. However, the mechanism of late-phase long-term depression (L-LTD) maintenance remains poorly understood.



The same cylinder (the transcriptional regulatory complex formed by CRTC1 and CREB) produces different light and shadow effects (yellow LTP or blue LTD) under different angles of light (different neuronal activities)

Professor Eric Kandel, recipient of the 2000 Nobel Prize in Physiology or Medicine, previously suggested that L-LTD may also require gene transcription in a manner similar to L-LTP. However, after decades, the academic community has still remained undecided on how gene transcription could possibly participate in the two distinct plasticity regulations of L-LTP and L-LTD simultaneously. The potential role of gene transcription in L-LTD has therefore remained unclear up to the present time.

The occurrence of long-term synaptic plasticity requires recomposition of the synaptic protein, in which protein degradation is crucial. PSD-95 is a scaffold protein that is highly expressed at post-synaptic sites and is essential to the overall strength of synaptic connections. Researchers found that the ubiquitination of PSD-95, resulting in its degradation and removal, could be induced by neural activity to initiate LTD. However, such a period of PSD-95 ubiquitination initiated by neuronal activation has always been noted as relatively short-term, generally lasting no more than a few minutes. It was therefore highly unlikely that this could be the mechanism underlying the maintenance of the L-LTD, which could run up to several weeks in duration. The search for an alternative protein degradation pathway mediating the expression of PSD-95 and other post-synaptic proteins in L-LTD, therefore continued.

Over recent years, autophagy, the process by which the cell removes unnecessary or dysfunctional components, has also been noted to target synaptic proteins. Since neuronal plasticity disorders make up a significant proportion of neurological diseases, the role of autophagy in neuronal long-term plasticity, especially LTD, has attracted attention. Zheng Li's group of the NIH and Vassiliki Nikoletopoulou's group of UNIL have confirmed autophagy as highly important for early-phase LTD (E-LTD), though they hold different views as to why. The former believes that autophagy could inhibit E-LTD (Shen et al., 2020), while the latter believes that autophagy is necessary for E-LTD (in-press in ***Nature Communications*** - available as a preprint in ***BioRxiv,*** 2020).

Whlist how autophagy participates in E-LTD awaits further investigation, its significant role in L-LTD has been confirmed by three different research groups over the 2020-2021 period: Daniel Choquet's group focused upon how autophagy regulates synaptic function (published in ***Nature Communications*** in May 2021); Vassiliki Nikoletopoulou's group concentrated on how autophagy in nerve cells mediates various behavioral phenotypes (available as a preprint on ***BioRxiv*** in 2020); **Huan Ma**'s group highlighted how autophagy occurs and regulates synaptic function (July 2021 Published in ***Cell Reports***).

Applying cultured primary neurons and electrophysiological recordings of brain slices, Huan Ma's group reported that CRTC1 and CREB, two transcription factors mediating L-LTP, could be regulated by different forms of neural activity. When neural activity induces LTD, CRTC1 is selectively dephosphorylated at Ser-151 and enters the nucleus to regulate the expression of new autophagy genes together with CREB. This eventually activates transcription-dependent autophagy to degrade postsynaptic proteins, such as PSD-95, thereby maintaining L-LTD.

In the competitive research field of autophagy and LTD, Huan Ma's research group has made this first discovery that neural activity-gene transcription coupling can be regulated by different forms of neural activity, thereby activating different genes to support L-LTP and L-LTD, respectively. Since L-LTD disorders are closely related to Alzheimer's disease, addiction, and autism, this study may have broad clinical significance, suggesting that transcription-dependent autophagy could become a new target for brain diseases related to synaptic plasticity disorders.

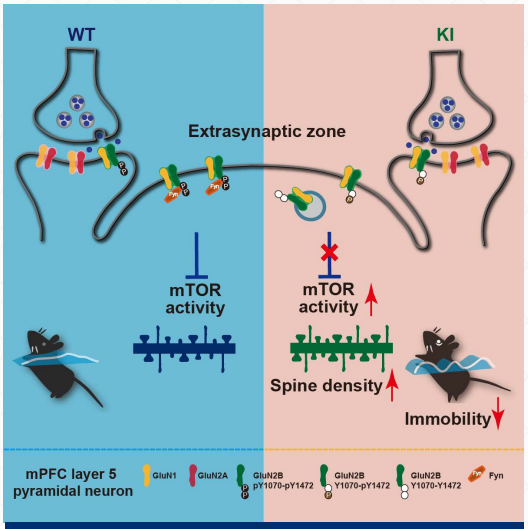
HUAN MA'S RESEARCH GROUP uses clinical data as a guide; genetically modified mice as models and electrophysiology, molecular biology, and behavioral methods; to study the signaling pathways encoded by disease-causing genes and their functions *in vivo*. The implications of their research primarily cover three areas, namely 1) learning and memory, 2) the relationship between neuroplasticity disorders and mental diseases such as autism and intellectual disability, 3) aging and neurodegenerative diseases.

Is it possible to "close down" depression?

NMDA receptor GluN2B phosphorylation-mediated depression

As the global number of collective covid cases, past and present, is currently rising towards the 300 million mark, we must not forget that there is another epidemic of even larger proportions. More than 350 million people worldwide suffer from depression. Whilst not of pathogenic origin, nonetheless the corresponding threat to human life and health is directly comparable. Stress-and stress-related mood disorders cause extremely high rates of disability and suicide, bringing huge economic burden and loss to societies and families. Correspondingly, we at the BBMI are urgently seeking to deepen our understanding of the pathogenesis of depression.

In August 2021, the culmination of the latest results of **Wei Yang's** and **Jianhong Luo's** research group were published in ***Cell Reports***. These findings highlight a newly discovered anti-depression mechanism that could pave the way for new ideas and options for the treatment of depression. More specifically, Yang and Luo's team were able to demonstrate that the medial prefrontal cortex (mPFC) NMDA receptor GluN2B subunit tyrosine 1070 phosphorylation selectively regulates antidepressant-like behaviors. It is hoped that this new mechanism will provide novel options for the treatment of depression.



GluN2B-Y1070 phosphorylation selectively regulates the number of excitatory synapses in the layer 5 pyramidal neurons of medial prefrontal cortex (mPFC)

Earlier research by the team had demonstrated that the NMDA receptor GluN2B subtype plays some important roles related to depression. GluN2B selective inhibitors, for example, have been shown to significantly reduce depressive-like behavior. However, the mechanism of how exactly this occurred has remained unclear. The team then discovered that the phosphorylation of tyrosine 1070 of the GluN2B subunit could coordinate and regulate the phosphorylation of tyrosine 1472 to prevent NMDA receptor cell membrane internalization. Based upon this the team then used CRISPR/Cas9 technology to construct genetically mutant GluN2B Y1070F (KI mice) and, through a series of behavioral tests, confirmed that the mutation strongly and selectively affects depression-related behaviors. For example, KI mice showed decreased immobility durations in the forced swimming test (FST) and tail suspension test (TST), which suggested that the Y1070F mutation had conferred antidepressant-like effects on the mice.

In examining the question of how the phosphorylation of tyrosine 1070 of the GluN2B subunit mediates antidepressant-like behavior, it was found that mutant mice showed selective decreases in their phosphorylation levels of GluN2B tyrosine 1472 in the mPFC. The electrophysiological data of brain slices showed that whilst the synaptic NMDA receptors of the mPFC in the 5th layer of pyramidal neurons had functioned normally in mutant mice, the function of extra-synaptic GluN2B subtype NMDA receptors was significantly downregulated compared to those in control mice. However, synaptic NMDA receptors and extra-synaptic NMDA receptors of hippocampal pyramidal neurons were not affected. These results suggest that the mPFC mediates the production of antidepressant-like behaviors. Subsequently, through a combination of biochemical and Golgi staining methods, the team found that mTORC1 activity in the mPFC of mutant mice was significantly increased. This resulted in an increase in the number of neuronal excitatory synapses and clear links to antidepressant-like behaviors.

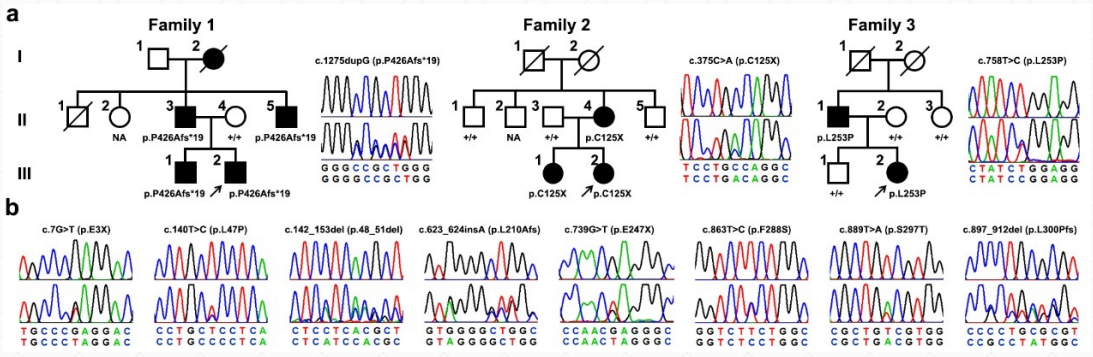
Whilst major global pharmaceutical companies and scientific research institutions are collectively rushing to develop antidepressant drugs based on NMDA receptors, it must be noted that NMDA receptors are also the key molecules active in the brain's overall synaptic functions. A bottleneck surrounding drug development is a clear side effect. The development of increasingly specifically targeted drugs, locally intervening in the pathogenesis of depression and selective as NMDAR antagonists, are therefore becoming a more specialized focus of antidepressant drug research.

By revealing a new mechanism of the mPFC brain region NMDA receptor tyrosine phosphorylation that selectively mediates depression, Wei Yang's and Jianhong Luo's group may have opened up new options for the design of selective NMDA receptors that can avoid unwanted influences upon other physiological functions. This could provide novel application potential for the development of drugs that specifically target NMDA receptors in the treatment of depression.

WEI YANG'S RESEARCH GROUP has long been engaged in the research of ion channel regulation mechanisms and their functions in the nervous system. They have a particular focus upon exploring ionotropic glutamate receptors and TRP channels and developing inhibitors for specific channels with the aim of discovering new treatment methods for neurological diseases.

The unwelcome dance!

Deciphering the newly identified pathogenic genes for paroxysmal kinesigenic dyskinesia



Identification of *TMEM151A* mutations in both familial and sporadic paroxysmal kinesigenic dyskinesia

Dance is among the most beautiful and expressive of human activities, but the "dance" induced by certain neurological diseases can be devastating. Clinically, there is a disease in which patients exhibit involuntary movements and chorea-like twists throughout the body. This disease is called paroxysmal kinesigenic dyskinesia (PKD) and it seriously affects the patient's functional abilities and quality of life.

PKD is the most common type of paroxysmal dyskinesia, manifesting mainly as chorea, athetosis, ballismus, and dystonia. PKD, presenting in clinical practice with sudden movements or changes in body position, is unfortunately often misdiagnosed as epilepsy or hysteria. In 2011, Zhi-Ying Wu cooperated with the research teams of Ning Wang and Zhi-Qi Xiong to identify the first gene known to cause PKD (*PRRT2*) (***Nature Genetics*** 2011, 43:1252-1255). This finding has now been widely confirmed in subsequent studies. However, some patients have presented with PKD symptoms without exhibiting any such mutations in the *PRRT2* gene, suggesting the existence of additional causative genes.

Recently published in ***Cell Discovery***, the latest research results of a team led by **Zhi-Ying Wu** (Zhejiang University) and Zhi-Qi Xiong (Chinese Academy of Sciences) revealed a second disease-causing gene for PKD: *TMEM151A*. By whole-exome sequencing, *TMEM151A* mutations were identified in three autosomal dominant PKD families, namely c.1275dupG (p.P426Afs*19), c.375C>A (p. C125X), and c.758T>C (p.L253P). Co-segregation analysis of the related genetic family was successful. All three of these mutations were located in the conserved region of the *TMEM151A* gene and were predicted to be pathogenic in nature. Subsequently, they detected eight *TMEM151A* mutations in PKD patients without a family history of the disease. The frequency of these 11 mutations in public databases was extremely low, or even zero, and they were absent among the 1,000 normal controls.

Few prior studies have investigated the TMEM151A protein, and its structural and functional characteristics remain poorly understood. Researchers have now discovered that TMEM151A mRNA is specifically expressed in the central nervous system, whilst its expression in other tissues is very low. During the embryonic period, TMEM151A mRNA expression is low in mice. However, it then gradually increases after birth and reaches a peak at P14, then beginning to decline again upon adulthood. This is highly consistent with the natural course of PKD.

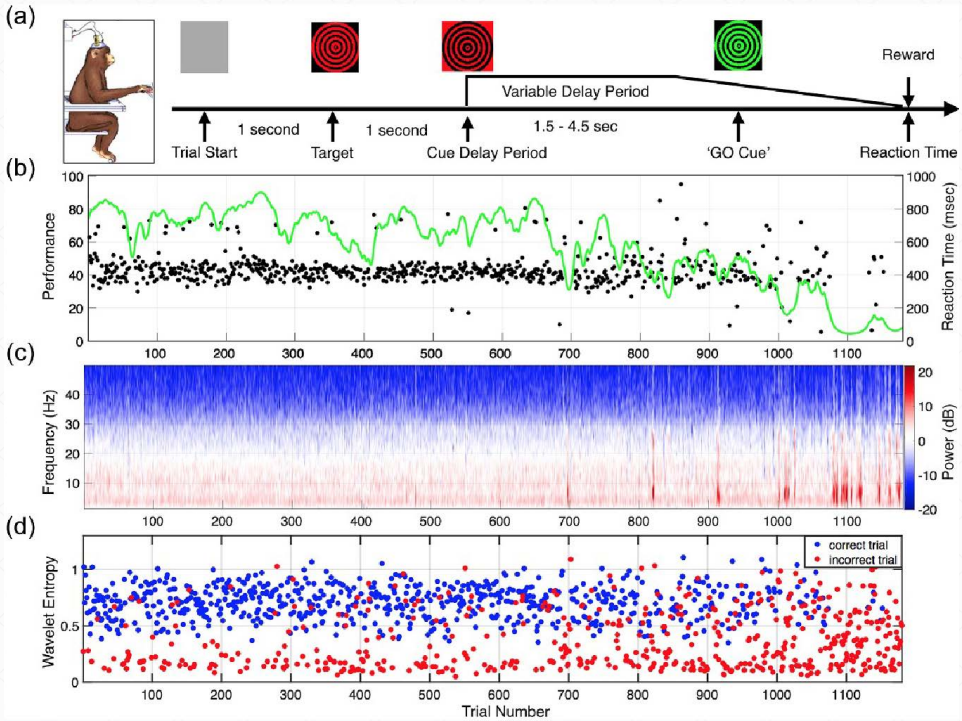
TMEM151A may be located in the endoplasmic reticulum, although it is also expressed in the axons and dendrites of primary mouse neurons. Further studies have indicated that the *TMEM151A* mutations do not affect cell localization, but lead to a significant downregulation of its protein expression. This indicates that mutations in *TMEM151A* may lead to the onset of PKD through a loss-of-function mechanism, similar to the pathogenic mechanism associated with *PRRT2* mutations.

To further explore the role of this gene in PKD, the research team conducted *in vivo* experiments using *TMEM151A* knockout mice. Among eight knockout mice, four mice exhibited spontaneous dyskinesia after exercise, with bouts ranging from 10–37 seconds in duration. This corresponded well with the clinical phenotype of PKD and further supported the hypothesis that the *TMEM151A* mutation causes PKD. In summary, after 10 years, the team led by Zhi-Ying Wu once again has discovered a new causative gene for PKD, which was of great significance for guiding the precise diagnosis and treatment of PKD.

ZHI-YING WU'S RESEARCH GROUP has been committed to the precise diagnosis and treatment of neurogenetic diseases and other difficult/rare diseases for quite some time, achieving a series of notable findings through their research. The team established the Medical Genetics Department/Rare Disease Diagnosis and Treatment Center to provide more professional diagnosis and treatment services for patients with rare diseases and genetic conditions. Zhi-Ying Wu is the Chief Physician of the Department of Neurology and the Department of Medical Genetics at the Second Affiliated Hospital of Zhejiang University School of Medicine, a winner of the National Outstanding Youth Fund, and a leader of the innovation team in key areas of the Ministry of Science and Technology Innovative Talent Promotion Program. As the corresponding author, she has published more than 150 SCI papers in international journals such as ***Nature Genetics, Brain, Neurology***, and others. She was also selected as a national candidate for the "New Century Talents Project."

The brain's "digital medicine"

Analysis of the structural code of the "pleasure neurotransmitter" receptor



EEG signal acquisition research paradigm

For individuals with suspected brain injury or chronic mental fatigue, if signs or symptoms such as decreased vigilance are noticed at a sufficiently early stage, symptomatic treatment can be carried out in combination with a closed-loop neuro-regulation strategy. In a related study, EEG signals of mental fatigue from the brain cortex in non-human primates were collected through cortical electroencephalography (ECoG) by the **Lin Yao** team at Zhejiang University. Characteristic EEG signals that could be used to distinguish mental fatigue were identified within the spectrum of electrical signals detected. The mental fatigue behaviors of different animals, or of the same animal with or without induced fatigue, were then predicted successfully. This provided a useful reference tool for further exploration of personalized therapeutic interventions for related conditions. This research was published in 2021 in the ***Journal of Neural Engineering***.

In this study, a 10-channel epidural ECoG electrode array was implanted in the brain of macaques. This enabled the signal acquisition area to cover the occipital, temporal, and prefrontal cortex of the left and right brain. The monkeys were then trained on tasks that included a random delay of 1.5 to 4.5 seconds after the cue, which increased their attention expenditure but made them more prone to "mental fatigue" and increased the failure rate for the task. Recorded data were analyzed mainly based on the ECoG signals related to either "success" or "failure" behaviors in the task.

The research team selected signals defined as higher order spectral temporal (HOST) signals using their distinct characteristices as biological indicators of mental fatigue in macaques. Indicators, such as 'wavelet entropy' (a value representing the sequence of probability distribution, with the larger the entropy value, the closer the probability distribution for the disorder), 'instantaneous amplitude', 'instantaneous frequency', and others, were used to predict the instantaneous parameters of gradient enhancement decision relating to "mental fatigue." Although there were significant differences between successful and failed power spectra, higher-order spectral feature information had natural advantages with better accuracy, sensitivity, and higher F1 scores (an indicator used to measure the accuracy of a dichotomous model) in classification results as compared with other competing techniques.

While the ECoG biomarker developed in this study proved to be a stable predictor of mental fatigue, the team noted that to apply this approach to patients with brain injury would require adjusting it to target the characteristic biomarkers of impaired cognitive function in humans. However, for the macaque training task, mental fatigue could be detected with impressive speed and efficiency, and the deep brain stimulator could be controlled to quickly rescue the mental stress state of the monkeys. This should pave the way towards the provision of a convenient and efficient treatment approach to alleviate the symptoms of human chronic mental fatigue, to achieve adaptive closed-loop regulation, and to improve any intervention effect aimed at targeting the brain's fatigued or diseased state.

LIN YAO'S RESEARCH GROUP has long been engaged in the research of non-invasive brain-computer interface (BCI), and developing digital medication based on BCI technology for older adults and adolescent ADHD patients for enhancing their attention capability. By developing sensory stimulation in BCI paradigm, we aim to enhance BCI performance and solve BCI-illiteracy problem. Main research topics include: BCI, Digital Medication, Adaptive Neuromodulation, Bio-mechatronic system etc.

Brain–computer interfaces unpacked

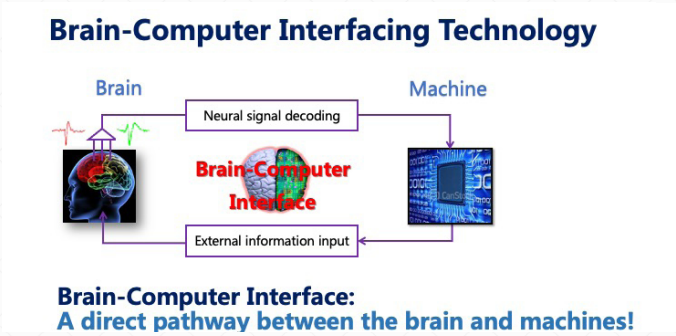
The brain-computer interface (BCI) represents a connection and information exchange pathway between the biological brain and external devices. Developing BCIs has always been a widely popular direction in the field of brain science. Over recent years things have been moving particularly fast. Many developed countries have released their plans for brain science research, cutting-edge brain technology companies have been flourishing, and various science fiction movies and novels have popularized the concept of BCIs. This has brought the subject to the forefront of public discussion. BCI technology involves multiple cutting-edge interdisciplinary fields, such as neurobiology, computer science, and mechatronic engineering. Moreover, it has promising applicability for scientific research, medical diagnosis, and many other areas. The BBMI center specially interviewed Professor Yueming Wang and Professor Lin Yao, who have been deeply involved in the field of BCI for many years, to bring you authoritative answers to questions related to brain-computer interfaces.

Question:

The structures and neural signal patterns vary from person to person, so how does the brain–computer interface deal with the differences among individuals?

Prof. Wang:

For different individuals, we can use the same overall brain-computer interface algorithm framework, and then we need to only fine-tune the detailed parameters. Similar to the face recognition problem, everyone has the same structure of the facial features, with the eyes at the top, the nose in the center, and the mouth at the bottom. This is the general framework. However, the shape of the nose and the distance between the eyes are different for each person. These are the detailed parameters. After a certain amount of training and learning, the framework algorithm can fit to the individual parameters and achieve targeted decoding optimization.



Question:

Nowadays, invasive brain–computer interfaces can help paralyzed patients reconstruct their limb functions or control robotic arms. Is this more dependent on activating the original nerve structure in the patient's brain responsible for arm–motor function, or is it equivalent to training a new set of neuron connections and processing models from scratch?

Prof. Wang:

My understanding is that a combination of these two situations occurs. If the patient's original neuro logical structure and signaling patterns are not recruited, it is difficult to derive a decoding model. However, for patients with impaired motor function, learning and training processes are still usually required to control the robotic arm. This is similar to human learning during development. Infants and young children already have the neural basis to move their fingers at birth, but they also need further learning to be able to use chopsticks well. The brain-computer interface uses digital models and machinery to replace the decoding in the organism itself. This bears a certain similarity to the original learning process. The patient and the system must undergo mutual adaptation to achieve proficiency in BCI control.

Question:

In science fiction movies and novels, the plot often focuses on using brain–computer interfaces to enhance the capability of the human body. How is this different from the current application of helping paralyzed patients to restore function in their limbs or manipulate robotic arms?

Prof. Wang:

The rehabilitation of the disabled or the treatment of related diseases mainly involves training of specific brain regions that are not well used, in combination with decoding methods. In science fiction stories, the whole human body is promoted, such as in Robocop and Avatar. In theory, the brain is "exported entirely". To do this it would be necessary to determine the circuit structure and functional connection of the whole brain to achieve such precise analysis and control. Once implemented, this could be applied without additional training. However, such research has no precedent in reality. Firstly, ethics would forbid such a harming of healthy people. Secondly, although there have been many studies on specific functions or brain regions in the field of brain science, we still lack an understanding of the whole brain as a complex network. This still requires a massive amount of research, investigation, engineering, and scientific thinking to work toward actively exploring the many unknown aspects. As we do so, this will gradually lead to the expansion of the scope and potential of brain-computer interfaces, whilst also working to improve the efficiency of the systems already in place.

CONTINUED FROM PAGE 12

Question:

The brain–computer interface not only transmits brain information to the outside but also includes feedback from external stimuli back to the brain. What progress has been made in this field?

Prof. Wang:

In September of this year, a study conducted at the University of Pittsburgh allowed paralyzed patients to feel a touch from the fingers of a robotic arm. Humans constantly adjust their movements through instant tactile feedback during the grasping process, but the mechanical arm relies only on the visual feedback of the patient, so its performance is poor. The potential to either crush something fragile or fail to sufficiently grasp something heavy would be a common issue in such cases. To solve this, for the first time researchers used a tactile sensor installed on the robotic arm to trigger a specific electrical stimulation to the patient's sensory cortex. However, it was developed using a relatively simple and direct method. Researchers first used electrical stimulation with different parameters, requesting patients to report the position and intensity of the tactile sensations. They then used this information to fine-tune the corresponding mechanical sensor.

Prof. Yueming Wang

ZJU Qiushi Academy for Advanced Studies

Deputy director of the BBMI center

The research interests of Prof. Wang's group cover brain-computer interfaces, artificial intelligence, machine learning, and computer vision. Currently, the team is working on the application of invasive brain-computer interfaces to assist the rehabilitation of patients with neurological injuries. Their primary aim is the decoding of Chinese speech and even the fine motor signals sufficient to permit patients to regain the ability of handwriting.

Question:

As a non–invasive brain–computer interface technology, what are the advantages and disadvantages of EEG compared with the invasive technology of embedded electrodes?

Prof. Yao:

The biggest advantage of EEG is its noninvasiveness. The biggest disadvantage is its relatively low signal-to-noise ratio and spatial resolution. Each EEG electrode records a large number of neuron populations and the recorded signal is susceptible to interference from noise such as eye movement or muscle electrical signals. The signals are usually vague and complicated compared to an invasive electrode which can specifically and accurately record and sum up activity from hundreds of neurons or even individual signals from each neuron. Similarly, EEGs can only read information, whereas intrusive electrodes can also write information. However, because of the noninvasive nature of EEG, it is currently more accepted by patients. We can currently apply it to attention monitoring and treatment of ADHD in children, as well as to assist stroke patients in controlling a robotic arm for active rehabilitation training. In such cases, it would be difficult to apply an invasive brain-computer interface, which would require invasive surgery.

Question:

In your opinion, what is the most important issue in the current development of non–invasive brain–computer interfaces?

Prof. Yao:

At present, the most common pursuit in the field is to greatly increase the decoding rate of neuroelectric signals. At the biological level, this requires us to understand more about the brain's mechanism for generating a control signal. At the data analysis level, we need to develop better signal-processing algorithms. The hardware would require clearer and denser signal acquisition equipment. The EEG signal is nonstationary, which means that its firing pattern is not fixed, and there is a gap between the signals obtained by subjects completing the same task at different times. Therefore, to obtain a stable decoding rate, mutual adaptation between algorithms and the brain is required. Because of limitations in the specific design of the research-purposed EEG equipment, it is difficult to track the long-term interactions between the brain-computer interface and the human nerve firing patterns. In response, the industry is constantly exploring and improving, such as by replacing the wet electrode that constantly needs to be filled with conductive paste with a dry electrode that is more convenient to wear. In addition, the overall size of the equipment is being progressively miniaturized.

Prof. Lin Yao

PI of the BBMI Center

The research interests of Prof. Yao's research group include brain-computer interfaces, neurorehabilitation, and machine learning pattern recognition. Electro-encephalogram (EEG) technology is currently being applied by his group to decode movement, tactile perception, and cognitive intention.

The headache of resolving complex dynamic brain informationin cortical motor brain–computer interfaces

"The ideal purpose of the brain-computer interface is to provide a two-way communication, - not just to read information from the brain but also to input external information to it, forming a closed loop." In this way, Professor **Yueming Wang** summarized the current developmental concept of the brain-computer interface in the lunch-time seminar on Oct 14th at the School of Medicine.

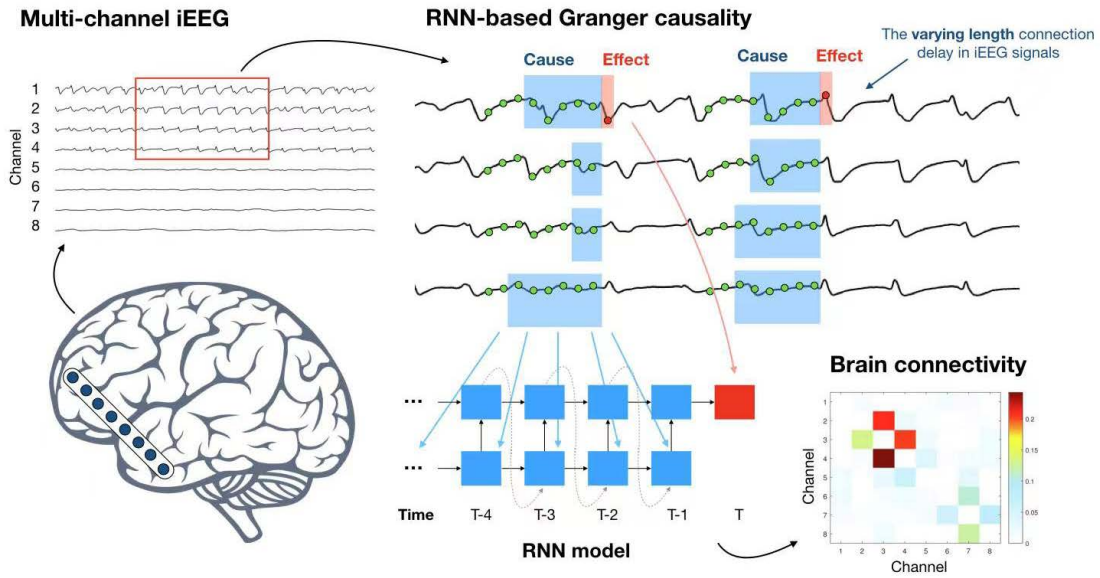
From as early as 1958, scientists began to explore the neural control of large-scale motion in experiments that would eventually lead to the concept of developing a Brain-Computer Interface (BCIs), (sometimes referred to as Brain-Machine Interfaces (BMIs)). One of the practical application focuses has been using BMIs to enable people with various disabilities, often in cases where there has been loss or damage of peripheral nerves or muscles, to communicate or to control prosthetic limbs. In such cases neural pathways could be bypassed and control could be facilitated directly via electroencephalographic activity.

Due to technological limitations, studies over the last 20 years have been mainly focusing on the analysis and control of "hand" and "arm" movements, which are relatively large-scale activities and thus easier to resolve. However, over the recent period the BMI field has been gradually shifting its research focus toward more intricate 'micro movements', such as decoding the abilities of writing or speaking through analyzing finger and mouth/face motor signals. By the 2020s, as a frontier center for interdisciplinary research, the field of brain-computer interfaces has become established as a key-player in the next round of artificial intelligence development. Such developments have had a significant 'feed-back' effect in further promoting the development of brain science. The future looks bright. Brain-computer interface systems are in the process of producing a number of disruptive technologies which are expected to take prominent roles in the emergence of new strategic industries.

However, let us not get too caught up with the big picture. The potential impacts of the technologies upon an individual life can be extremely profound. In January 2020, Prof. Yueming Wang's team, using brain-computer interface technology, helped a patient who had been paralyzed for many years to eat, drink, and shake hands with the help of a brain-controlled robotic arm. Using MRI, the researchers first localized the activation area in the primary motor cortex of the brain during the patient's imaginary movement. They then implanted two Utah microelectrode arrays (one in the handle area and one 2 mm away), adjacent to the area. Using signals acquired from a single array of 96-channel electrodes, the team proposed a novel dynamic integration method of brain network dynamic analysis with multi-model adaptive integration to achieve online decoding, thus helping patients control the robotic arm in real time.

However, the mapping of the relationship between the initial neural firing information and the desired motor parameters is not a simple process. The patterns of signaling change dynamically due to the influence of noise, tissue wrapping, neuroplasticity, and due to the divergent pathways that are employed to accomplish a movement. Such dynamic changes complicate brain information patterns primarily in two aspects. Firstly, the diversity of the many mechanisms of brain information processing leads to an equally diverse set of dynamic changes in brain connections. Secondly, comes the difficulty of navigating the instability of neural firing patterns caused by brain neuroplasticity. Both of these make it extremely difficult to develop a decoding model that would be both universal and remain effective in the long term.

To address the first problem, the research team proposed a Granger causality model based on a long- and short-term memory neural network (LSTM) to show the modeling of brain connectivity under the temporal variation of information transmission. The team used LSTM to fit the signal relationships between neural nodes, optimizing the gate mechanism. This dynamically determined how long historical time signals may remain involved in the fitting of current moment signals.



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This mechanism is driven by the data itself which automatically determines the appropriate length of the signal to be fed into the current fitting process over time. This overcomes the effect of the different transmission durations of neurons. On this basis, the research team proposed a method for analyzing the relationship of brain connectivity based on the Riemannian manifold. This demonstrates the modeling of the changing pattern of brain connectivity in a non-Euclidean vector space using a Riemannian manifold to characterize connection patterns. It then calculates a point-to-point (matrix-to-matrix) relationship in the tangent space of the Riemannian manifold. Based on the effective measures of such a connectivity matrix, traditional unsupervised clustering and temporal models can be more easily applied to model connectivity changes. Overall, the method improved the AUC performance in estimating brain information transfer sources by approximately 5%.

For the second problem regarding the difficulty of navigating the instability of neural firing patterns, the team proposed a dynamic decoding method with the adaptive integration of multiple models. The method automatically generates decoders based on different brain connections and EEG (Electroencephalography) patterns to permit adaption to current EEG patterns. This leads to higher decoding accuracy and longer sustained functioning time. The specific method involves the construction of a model pool containing a large number of decoders, which can then be flexibly combined to decode brain signals of different moments. The algorithm selects these different combinations of decoders from the pool based on integration parameters of the previous moment (prior) and observed neural signals (Bayesian likelihood) of the current moment. The combined parameters are then determined dynamically and updated in real time by both 'prior' and 'likelihood'. The larger weight a parameter has in the combination, the heavier role it plays in the current combined decoder. Compared with LSTM and the Kalman filter, the decoding performance of this model was improved by 7.6% and 6.2% respectively, and such level of performance was also maintained for longer time periods. Applying the above decoding model to brain-controlled motor systems greatly improved the performance of clinical cortical brain-computer interfaces.

Q&A Session (selected)

Q:

Currently, the neuronal clusters contacted by chip implantation are localized and random. If we can combine high–resolution scanning technology to obtain the connectivity and functional information of brain regions in advance, can we achieve more accurate implantation and simplify the computation?

A:

Yes. If the coding method and transmission knowledge of neuronal clusters are known, this is equivalent to improving the quality of the signal and providing a priori knowledge to guide the computational model. This can then effectively improve the decoding performance and simplify the computation.

Q:

Does a brain–machine interface manipulate a robotic arm to perform a series of actions such as reaching, grasping, and touching, relying on the system's analysis of a single action?

A:

No. For the arm, these are continuous movements, but each action can be reduced to motion parameters such as speed and direction. Thus, BCI control is usually achieved by relying on the establishment of the mapping of neural release to these motion parameters.

Q:

For the phenomenon in which the same movement is manipulated by different patterns of signals, suppose there are three signal patterns controlling the same movement, are these three patterns independent or linked to each other?

A:

This is a very good question and is worthy of consideration. Existing studies generally believe that the neuronal population that accomplish the same action are linked. We will study this question in detail in the next stages of our research.

Q:

This model resolves mainly signals from the motor cortex, which also receives a large amount of sensory signal input. This process is regulated by multiple brain regions such as the prefrontal lobe, and the model also mentions dynamic changes that may be related to sensory, emotional, and motivational decisions. Would it be better to integrate this information?

A:

Integrating this information would definitely be helpful; however, finding the entry point for the problem is not easy. For example, if one wants to integrate visual information, it is necessary to quantify visual information and capture neural signals in sensory areas generated by stimuli of information. It would probably require a massive amount of data to tap into a stable relationship.

Q:

Screen strike tests can simulate speed and direction, but how do you simulate force control? The force of the hand is different during grasping; how can the amount of force of the robotic arm be controlled?

A:

This is a problem related to sensory feedback. A recent ***Science*** paper published last month reported how sensory information was fed back to the brain through electrical stimulation so that the brain processed a feedback of tactile sensation from the manipulation of the robotic arm. As a simple example, the force required for a robotic arm to hold an egg is different from that required for an iron block. Having installed sensors on the robotic arm sending force and haptics signals back to the sensory cortex, the subjects may treat objects of different textures with appropriate strength when they grasp.

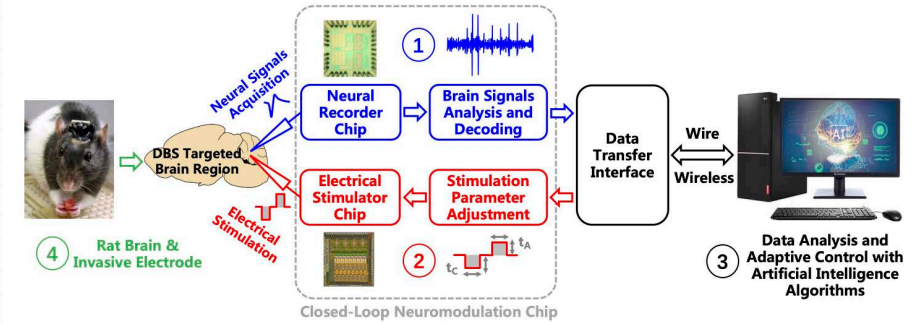
Closing the loop!

Study of a closed-loop neuromodulation microdevice for treatment-resistant depression

Over recent years, deep brain stimulation (DBS) techniques have been increasingly used for treating treatment-resistant depression (TRD). Such neurostimulation has been traditionally delivered in an open-loop system with predetermined parameters that are fairly inflexible and do not take into account the often-changeable state of the target organ. Conversely, a closed-loop neuromodulation (CLN) system represents a more responsive neurostimulation stimulation option that responds and alters its activity depending on the current state of the organ that requires modulation. Considering the individual variability of patients and the random nature of attack times, it is understood that it is necessary to increasingly explore novel DBS techniques based on these personalized and responsive CLN systems that should result in safer and more optimal treatment. For this system, the core hardware module is a closed-loop neuromodulation chip that includes a neural recording interface chip, an electrical stimulator chip, and the programming of a responsive performance optimization strategy. So far, only two companies in the world, Neuropace and Medtronic, have developed closed-loop neuromodulation products that have been approved by the FDA in the U.S., and have entered the market. However, due to export control restrictions, these products are currently unavailable for import to China.

To address this problem, Prof. **Jian Xu**'s team in cooperation with the brain-computer interface team and Prof. **Hailan Hu**'s team at Zhejiang University, have been discussing the development of a closed-loop neuromodulation system and related treatment plan for TRD (as shown in Figure 1). The specific closed-loop modulation idea is as follows. Neural signals of specific brain regions are collected, analyzed, and decoded with artificial intelligence algorithms and the potential TRD biomarkers are accurately extracted. Simultaneously, a corresponding current stimulation control signal is generated based on signal processing results. These are transmitted to the closed-loop neuromodulation chip. Thereafter, the optimal stimulation current is injected into the nerve electrodes for different depression levels, thereby realizing the required adaptive electrical stimulation intervention for the individual patient's depression. In addition, the project will conduct a series of neuromodulation experiments and analyses in animal models of depression. The team is confident that they will finally achieve a safe, reliable, novel, and efficient personalized closed-loop neuromodulation treatment program.

Jian Xu's team will focus on the development of a closed-loop neuromodulation chip for TRD treatment, including the development of a neural recording chip, an electrical stimulator chip, and a performance optimization strategy for closed-loop modulation. Initially, to develop a neural recording chip and to overcome the defects of low signal-to-noise ratio (SNR) and the poor stability of current signal recording technology, the team will explore key design technologies of ultra-low noise, ultra-low power consumption, and high SNR. The aim will be to achieve multimodal (electrical, magnetic, etc.) high-fidelity acquisition of neural signals and effectively suppress external interferences such as electrical stimulation/motion artifacts, and unwanted noise and/or interferences from either power, electrical stimulation, or electrode-chip interface sources. Secondly, in the research and development of electrical stimulation chips, the team will study key design technologies for high voltage, high current accuracy, and ultra-low charge distortion, and aim to break through the challenges related to the development of a high precision, low power consumption, and small size design. The predicted result is to achieve a high current accuracy and ultra-low charge distortion chip at low cost, which will ensure biological safety under long-term electrical stimulation and avoid the oxidation of neural electrodes. Finally, the team will develop a novel high-precision and highly robust closed-loop neuromodulation chip and bidirectional closed-loop brain-computer microdevice. This will be achieved by fusing a recording chip and an electrical stimulator chip, which will be characterized by high power efficiency, miniaturization, wireless transmission, magnetic resonance compatibility, and implantability, so as to facilitate the switching of ultra-fast stimulation-recording. In addition, using the self-developed closed-loop brain microdevice, the team will focus on the potential for related bioelectronic therapies for other major neurological diseases. They will aim to conduct timely preliminary clinical translation when the appropriate conditions are met, thus meeting urgent requirement for new technologies and methods for the diagnosis and treatment of mental/neurological diseases in China.



Schematic diagram of the closed-loop neuromodulation system for TRD treatment

Prof. Jian Xu

PI of the BBMI Center

Jian Xu's team focuses on research on high-performance biomedical chips, bidirectional closed-loop brain-computer modulation microdevices, and bioelectronic therapies for neurological diseases through brain-computer interface and bi-directional closed-loop electrical neuromodulation. The team is committed to exploring safe, reliable, and efficient personalized closed-loop neuromodulation treatment solutions which will improve the treatment and diagnosis of refractory neurological diseases in China.

'Uncle Zhang', even though paraplegic, can now play mahjong!

Dynamic adaptive neural information decoding algorithms for high-performance motor brain-computer interfaces

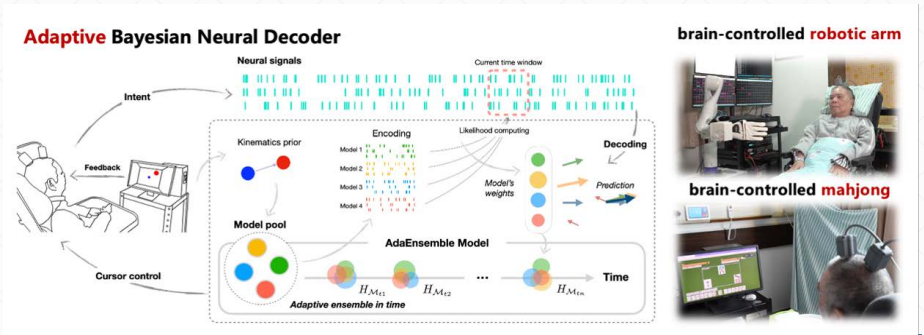
As an entirely new communication and control channel between the body and the external environment, a brain-computer interface can serve as a direct information pathway enabling interaction from the brain to external devices. Brain-computer interface technology has been gradually maturing over the past two decades. During initial development, various applications such as in the control of multidimensional robotic arms, or computer cursors to realize ideographic typing and speech synthesis, were often applied to compensate for the loss of motor functions for people with disabilities. There are now applications on the horizon that have the potential to be of profound significance to humanity as a whole, such as in the provision of barrier-free human-computer interactions. However, brain-computer interface systems still face three major challenges in terms of accuracy, stability, and robustness which represent the main barriers hindering the more immediate application of brain-computer interface technology. Professor **Yueming Wang** and **Yu Qi**'s team at Zhejiang University have proposed an innovative dynamic adaptive decoder (AdaEnsemble) based on Bayesian multi-model integration. Unlike traditional decoding methods, this new decoder can adapt its decoding model and parameters according to real-time changes in neural signaling to cope effectively with variations over time. The aim is to therefore achieve higher accuracy and a more robust online decoding of motor intention in a closed-loop brain-computer interface.

The brain's activity in motor control involves the dynamic synergy of multiple neural circuits. Modeling such joint actions among multiple pathways has always been a difficult problem. Traditional neural information decoders have been only able to use fixed mapping functions that fail to account for these dynamic processes. Naturally, this often resulted in insufficient decoding accuracy and stability. Combining the neural signal characteristics mentioned above, the research team at Zhejiang University proposed an AdaEnsemble neural decoder, which constructed multiple decoding models to capture the characteristics of different neural pathways. At each time slot, the applicability of the models was evaluated dynamically based on neural data of the moment in a Bayesian framework by establishing a likelihood function. Based on this, AdaEnsemble weighted and assembled the models into an integrated model according to the principle of "whichever works, does the job," thus realizing a dynamic adaptive decoder construction that was capable of self-adjustment. The results of closed-loop brain-controlled cursor experiments based on invasive brain-computer interfaces showed that different models in AdaEnsemble could accurately complement each other online, thus improving their decoding accuracy by 13.9%.

The innovation of dynamic adaptive neural information decoding methods was based on the first clinical trial of an invasive brain-computer interface in China that was completed by the brain-computer interface team of the Qiushi Academy for Advanced Studies in cooperation with the Department of Neurosurgery of the Second Affiliated Hospital of Zhejiang University School of Medicine. 'Uncle Zhang', the clinical volunteer, was a 74-year-old paraplegic patient. The research team obtained neuronal activity using two electrode arrays implanted in the motor cortex of the brain and then performed a motor intention prediction based on a neural decoder. Via the brain-computer interface system developed by the research team, Uncle Zhang was able to successfully utilize a series of demonstration applications such as a brain-controlled robotic arm or a computer cursor. Mahjong has been a hobby of Uncle Zhang for many years. The research team recently developed a brain-controlled mahjong game for him, allowing him to operate the mahjong tiles and perform "eat, touch, and play" operations through the brain-controlled cursor. The new decoding algorithm improved the control accuracy and cursor speed, making the mahjong operation smoother. Uncle Zhang had a lot of fun.

The dynamic Bayesian decoder proposed in this study provides a brand new model and framework for robust online neural signal decoding. The preceding paper published by the research team in NeurIPS'19, a top AI conference, was evaluated by the reviewers as "a big step forward in analyzing non-stationary neural signals". This paper provided new technical strategies and ideas for further brain-machine co-adaptation, mutual learning, and deep brain-machine fusion computing. Improving the accuracy and robustness of neural information decoding and promoting the application of brain-computer interface systems into wider applications has been a long-standing goal of the research team. It is believed that with the joint promotion of new technology and new processes, brain-computer interface technology could achieve more accurate, more

Prof. Yu Qi
PI of the BBMI Center



Accurate and robust decoding of motion intent through dynamic adaptive Bayesian decoder for brain-controlled robotic arm and brain-controlled mahjong

To achieve the goal of developing high-performance brain-machine interface algorithms and systems, Yueming Wang and Yu Qi have a multidisciplinary and interdisciplinary team with backgrounds in computer science, biomedical engineering, and information science. The main research directions of the team include 1) real-time computation and decoding of non-stationary neural signals based on machine learning methods, 2) high-performance brain-machine interface systems and their applications in motor rehabilitation, 3) brain information resolution methods for closed-loop neuromodulation.

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complex, and higher-dimensional online closed-loop control, effectively improving the quality of life of patients with neuromotor disorders such as acromegaly or paraplegia, and injecting new vitality into future medicine.

"The Darwin Mouse" brain–like computer

In the development of modern computers there has been a tendency to utilize what is known as von Neumann architecture. This concept was introduced by the famous John Von Neumann in 1945 and formed the basis of programming languages and the idea of the central processing unit (CPU). Von Neumann architecture has subsequently governed how computers store programs and utilize computer-based memory. A second principle, Moore's law, (from Gordon Moore, the co-founder of IBM, in 1965), has been equally influential in computer development. This principle relates to the increasing number of transistors in a dense integrated circuit and this has governed much of the development of modern computers and their increasing performance capabilities.

However, the time may have arrived that Moore and Neumann finally need to take a back seat. Issues such as the "memory wall" and "power wall" are becoming increasingly serious owing to the gradual failure of "Moore's Law" in modern integrated circuit technology. With the development of a new era of modern, high-performance computing, we may actually be entering a 'post-Moore era' where academia and industry need to lean toward entirely new computing models.

The brain itself can be considered as an extremely energy-efficient "computer," with features and advantages far superior to those of the von Neumann computing architecture. Indeed, with the rapid development of brain science, concepts discovered from the brain have already begun to inject translational development ideas into the field of computer science. Ultimately, the building of a brain-like computer to simulate the structure and operation of the brain's neural network, presents the opportunity of a new computing model which could overturn the traditional ideas of computing architecture. Moreover, it offers an important strategy for dealing with the inadequacies, challenges, and pitfalls of the von Neumann architecture as it relates to the development of newer and better computer systems in the post-Moore era.

A number of large-scale brain-like computers are now beginning to emerge on the international scene. The following are the most representative: 1) Pohiki Spring, a 100 million neurons brain-like computing system released by Intel in March 2020, consists of 768 Intel's self-developed neuromorphic chips (Loihi). It supports 100 million neurons and 100 billion neurosynapses with an average power consumption of less than 500 W. 2) Blue Raven, which is a brain-like computing system released by IBM in July 2018. It supports 64 million spiking neurons and 16 billion neurosynapses with a typical operating power consumption of 60 W. It has applications in several fields. 3) SpiNNaker, developed with support from the European Human Brain Project (HBP), uses a conventional 1 million ARM core to imitate 1 billion neurons. It provides a powerful simulation platform for research into brain science. However, it does not directly imitate neurons using chip hardware.

Guided by the motto of "seeking truth and innovation", Zhejiang University scholars have led the charge in another direction. The brain-like computer developed by the joint efforts of Zhejiang University and Zhijiang Laboratory is the result. It is named the "Darwin Mouse" (shown in Figure 1), and is the first brain-like computer based on independent intellectual property rights of neuromorhpic chips in China. It is also the largest brain-like computer in the world in terms of its neuron scale.

This computer integrates 792 Darwin 2 neuromorphic chips developed by Zhejiang University. It is capable of supporting 120 million spiking neurons and 72 billion synapses, a scale equivalent to the number of neurons in a mouse brain, and it has a typical operating power consumption of 350–500 W. The team has also developed an operating system specifically for the brain-like computer—Darwin Brain-like Operating System (DarwinOS) and an application development tool chain (DarwinKit).

The Darwin Mouse brain-like computer, with its

Darwin Mouse brain-like computer

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large scale, highly parallel nature, and low power consumption, represents a major breakthrough in regard to both its architecture and operating mechanisms. In terms of architecture, Darwin Mouse adopts a hierarchical architecture that is easily scalable and reconfigurable. The Darwin 2 neuromorphic chip is the smallest node, and the entire brain-like computer is integrated in a tree-like hierarchical structure by expanding the scale layerwise. The neural network connection is reconfigurable from multiple granularities to ensure application characteristics, and the interconnection channels between neurons are built at different granularity neuron scales of 100,000, millions, and tens of millions. The resources are scaled at multiple levels, making the resourse of the brain-like computer flexible and easily configured.

In terms of the operation mechanism, the team has applied several technologies to ensure the large-scale brain-like computing resources of Darwin Mouse could be cooperatively operated and remain robust. Firstly, the efficient routing and communication of spikes between neurons at multiple levels ensures real-time communication for brain-like applications. Secondly, the synchronization of brain-like computing resources is based on an asynchronous event-driven working mechanism. Practically, this ensures that different brain-like computing resources deployed on the same task can work together to increase speed and energy efficiency. Finally, the efficient error-tolerant mechanism for brain-like computing resources ensures the rapid replacement of failed neurons. In this way the brain-like computer remains robust.

The DarwinOS brain-like operating system represents a hybrid computing architecture that combines the features of the von Neumann architecture and neuromorphic architecture to unify the scheduling and management of heterogeneous computing resources. The team uses key technologies such as elastic task decomposition and dynamic resource allocation to optimize the processing of neural computing tasks, solving the resource demand problem of large-scale neural network computing tasks, improving the efficiency of the utilization of brain-like computing resources, and providing an operation and service platform for large-scale spiking neural-network computing tasks. At present, the DarwinOS-brain-like operating system can realize efficient resource management for brain-like hardware that supports billions of neurons.

In addition, with the development of DarwinKit comes an application development platform for brain-like computers that enables modeling, compiling, and debugging of spiking neural networks. Thus, developers could easily develop the application and don't need to focus on the details of the complex hardware constraints. DarwinKit consists of three main components: 1) an spiking neural network modeling engine which supports a variety of neuron models and neural-network structure library models and enables developers to conveniently build neural network models and perform simulation optimization; 2) an online debugging environment which supports brain-like computers and software model co-simulation, application downloading and debugging, and model adjustment by developers; 3) spiking neural network optimization and mapping tools for neuromorphic chips, which can reasonably allocate the limited hardware resources for applications and ensure the effective operation of network models.

The biological brain can command the organism to perform different intelligent behaviors during its interaction with the environment, including speech, visual tasks, decision making, and operational control, while consuming very low energy. Many insects, for example, despite having less than a million neurons, can perform real-time visual tracking of objects, navigation, and obstacle avoidance. The researchers are investigating intelligent tasks of brain-like computers in several related domains.

At present, the research team of the Darwin Mouse brain-like computer has realized several different types of tasks, such as 1) collaboratively controlling multiple robots in flood rescue scenarios involving the simultaneous processing of several intelligent tasks such as speech recognition, target detection, path planning, and collaboration between robots; 2) realizing memory functions in music and poetry, based on the memory model imitation of the hippocampus; 3) achieving intentional typing based on the analysis of EEG signals.

The future application areas of brain-like computing can be divided into three areas: intelligent task processing, brain science research, and brain medicine.

1) In intelligent task processing, brain-like computers have the advantages of low power consumption, high parallelism, and self-learning characteristics. This may introduce revolutionary changes to several intelligent task applications such as intelligent sensor nodes, 'few-shot' learning, and solving constraint satisfaction problems.

2) In brain science research, brain-like computers can be used as simulation tools for neuroscientists to study the brain. This provides new experimental opportunities to explore the working mechanism of the brain and can reduce the necessity of actual biological experiments, thus avoiding animal suffering, lowering research costs and improving research efficiency.

3) In medicine, brain-like computers can be used as simulation platforms to study the developmental processes of diseases, such as simulating brain development and the aging process, as well as developing technical approaches to regulate brain development and modelling differentiation to prevent developmental abnormalities.

In addition to the above, brain-like computers can also be used as processing centers for neural signals, replacing some brain area functions, for instance, acting as information processing centers for human prostheses.

Overall, it is predicted that brain-like computers will penetrate into all aspects of scientific research and daily life in the near future and will make increasingly important contributions to the development, progress, and welfare of human society.

Prof. De Ma

Associate Professor of the College of Computer Science and Technology, ZJU

Research focuses:Neuromorphic, Chips, Artificial Intelligence Chips, System on a Chip, etc.

Brain–like computing

The development of the next generation computer is facing a number of major challenges. The three principal ones are as follows: 1) The size of each transistor in a CPU is approaching the atomic limit. This sets a ceiling for the number of logic devices can be integrated in the same chip. This is referred to as the "integration density problem". 2) In the big data era, processing of vast amount of data has become the primary goal of computing. However, the physical separation of computer storage and calculation results in a data communication bottleneck between the CPU and memory, known as “the memory wall problem”. 3) An increase in integration density is accompanied by significant increase in the power consumption per unit area. This leads to a serious heat dissipation problem, referred to as the "power wall problem". In addition, there is also an artificial intelligence (AI) problem. Although AI can outperform humans in certain problems (such as the strategy game Go), its advanced cognitive abilities are still limited. At present AI is only good in perception, and a gap still exists between biological intelligence and artificial intelligence with regard to memory and learning.

The brain is still the most advanced “computing device” that effortlessly recognizes all kinds of objects presented to it, instantly recalls knowledge from its vast memory space, performs reasoning and learning, all aspects of which currently, remain beyond the reach of any AI system. On top of that, the brain only consumes a fraction of the power of a modern computer. To solve the above problems in the fields of computer science and artificial intelligence, scientists are taking direct inspiration from the brain. Qualitatively, there are a number of potential inspirations that we could harness from a brain’s computing machinery: low power consumption, low-frequency computing, integrated storage and calculation, parallel processing, self-learning and evolution. Therefore, the study of biological brains has emerged as a new avenue in the development of artificial intelligence.

Over the past few years, China, the United States, Japan, the European Union and other countries and organizations have funded billions of dollars to initiate their ‘brain projects’ in which brain-like computing is one of the core components. China’s own brain project has outlined two main developmental paths for brain-like computing research: 1) imitating the brain; where intelligence is achieved from a new computer system which emulates the biological brain; 2) brain-machine interfaces, i.e. where intelligence is achieved by connecting the brain to an external computers thus combining the potential of both brain and machine.

The development of brain-like computing research has a very long history. As early as 1948, Turing proposed a plan to build a computer with a neuron network (Figure 1). Von Neumann also contemplated simulating the brain, with the nervous system being an important reference point for his ‘von Neumann computer architecture’. In 1943, scientists proposed the McCulloch-Pitts (MCP) Neuron model as a mathematical abstraction of its biological counterpart. In the MCP model, information is binary, inputs exist as either 0 or 1, the cumulative weight is fixed, and logical operations are performed simultaneously. This laid the foundation for modern artificial neural networks. In 1957, scientists proposed the concept of the perceptron, an algorithm for the supervised learning of binary classifiers, which was then expanded, improved and implemented through hardware.

In computers, information is transmitted as numerical values, whereas in the nervous system, information is transmitted as electrical signals generated by chemical substances. The level of communication is modulated through the firing of spikes (pulses). Therefore, to develop a brain-like computer, it is first necessary to determine the electrical activity of the neurons through neural recordings, and then use a mathematical model to abstract ion movement using a dynamic circuit model described in the form of a differential equation. The equation model is the well-known Hodgkin-Huxley model proposed by Alan Hodgkin and Andrew Huxley, who won the Nobel Prize in 1963 for this achievement.

One drawback of this model is that it involves a large number of calculations. The brain-like models currently being used in practical applications are simplified models for approximate calculations, such as the leaky integrated and fire model (LIF), which enables large-scale study of spike-based neural networks using computer simulations. The transformation from numerical calculations to spike-based calculations makes brain-like calculations more biologically authentic in which spikes are generated and propagated in the nervous system through the simulated changes of a nerve cell’s membrane voltage. Building a computer in this way will completely change the computer’s architecture where the entire computer becomes a neural network that contains two main components: 1) a large group of neuronal units which then connect through; 2) a large group of synapses. The computer would then be dynamically programmed and configured through a connection model and transmit information using spikes.

The next step after solving the model problem is implementation at the hardware level. This ultimately requires the development of a specific brain-like chip. **Gang Pan**’s research group successfully developed the first-generation Darwin 1 brain-like chip in 2015, and iteratively produced the second-generation Darwin 2 brain-like chip in 2019, which contained 150,000 neurons and 10 million synapses, with a typical application power consumption of only 100 mW. By using chip level interconnections, the research team released

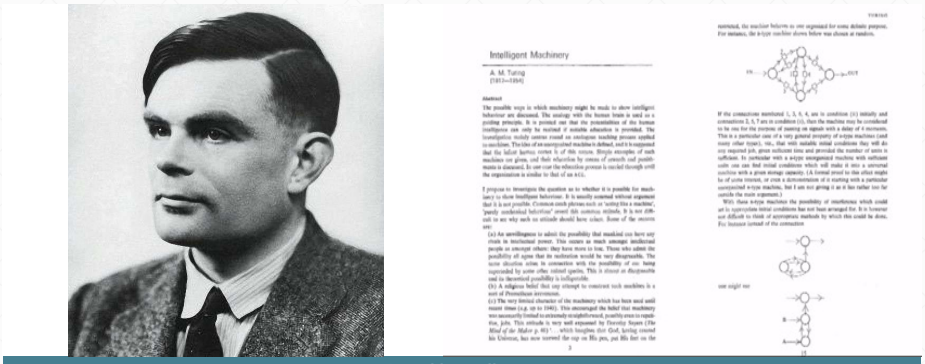

Figure 1. Turing's brain-like intelligent machinery theory

Figure 2. Darwin Mouse: a large-scale neuromorphic computer developed at Zhejiang University

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a billion-neuron scale brain-like computer in September 2020, containing 792 Darwin chips. As the number of neurons in this was comparable to those in a mouse brain, the name "Darwin Mouse" was given to this brain-like computer. After the hardware systems were built, the next technical challenge was how to achieve high computing speeds in this giant-size computer. The research group since then developed the 'DarwinOS' - a brain-like operating system to install onto the hardware. The entire system represents the state of the art of a brain-like computer in terms of scale and technical level. It is currently the world's largest brain-like computer based on its neuron count.

Professor Gang Pan's group is actively exploring a number of exciting applications for the Darwin system in the fields of robotics, neuroscience, and biomedicine. Tasks such as multi-robot cooperation, neural modeling of learning-memory functions in the hippocampus, and brain-computer interactions have already been demonstrated. The team is also collaborating with both academic and industrial partners to build up an ecosystem for the Darwin system, beyond which we could expect it to play a highly significant role in the near future for both scientific research and in practical applications.

At present, brain-like computers are still developing in the direction of spike simulations. A future research direction may be to develop brain-like systems that can, in part, authentically emulate the biological spike activities in the brain and thus establish the synchronization of brain-computer signals. This method would help to realize the fusion of computing between brains and computers. The realization of this type of fusion also requires the development of many technologies. For example, we need to establish new methods to allow for the interventions and interactions in different brain regions, through the stimulations of the biological neurons and large-scale emergent activities at a network level. In the meantime, the cerebral cortex computing model needs to be able to represent the dynamic relationship between different regions in the brain which are coordinated for most of brain functions.

Gang Pan's research group have pioneered some early studies to interact with the brain and to discover functional connections between brain regions. For example, they modeled the signals emitted from the different brain regions of monkeys and predicted the executive motion signals of the primary motor regions through the motion planning signals of the dorsal premotor region, thereby forming a neuroprosthetic model. Using such technology, brain-like computing is expected to be able to be applied to medical and clinical areas such as in tactile recovery.

Three important questions remain for the development and applications of brain-like artificial intelligence:

1) For the neural coding of the input signal, how can the numerical signal be converted into a spike code? The current coding schemes are mainly rate-of coding and temporal-coding which are not efficient.

2) How can the network structure be constructed and what kind of algorithm should be applied for learning? The current solution is to apply the most common and recognized spike timing-dependent plasticity observed in neuroscience, namely the STDP network, to the computer network. However, the attempt is still very preliminary.

3) What kind of hardware infrastructure is suitable for future brain-like computer? The current CMOS based technologies have shed light on how a billion neuron brain-like computer would perform, but there are still substantial difficulties to efficiently emulate neuronal activities through the digital medium.

The answers to these questions should all be derived from future discoveries in the interdisciplinary research field of computer science and neuroscience.

To conclude, the current development of brain-like computing is still very preliminary and relies on the co-development of artificial intelligence and brain science. This technology has many potential future applications in the diagnosis and treatment of brain diseases and in many other areas.

Prof. Gang Pan
College of Computer Science and Technology, ZJU

The research interests of Prof. Pan's team include: 1) Neural modeling and decoding; 2) High performance closed-loop brain computer interfaces; 3) Methods of brain-computer intelligence; 4) Neuromorphic chips; 5) Brain-inspired intelligence; 6) Neuromorphic computers and systems.

Academic Dynamics

In April 2021, the first annual conference of the BBMI center was held in Liangzhu. This conference covered the cutting-edge progress in neuroscience, clinical diagnosis and treatment, brain- computer interfaces, brain-like computing, and other related areas.

In May, Academician **Shumin Duan** was selected into the Elsevier's list of "2020 Highly Cited Chinese Researchers".

In Sep., Professor **Hailan Hu** won the 2022 L'Oréal-UNESCO For Women in Science International Awards.

Scientific Achivements

Focusing on the National Scientific and Technological Innovation 2030, the BBMI center has conducted a series of scientific research projects and developed new key technologies in areas of brain science, brain-inspired research and the strategic needs of the new generation of artificial intelligence. Overall, we have published 189 papers in total, including more than 20 publications in CNS and their sub-journals, with 48 project fundings received. The BBMI center has also been supporting 36 interdisciplinary research projects on the frontiers of brain science.

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 to basic and clinical brain science studies.

- We received a personal donation of RMB 1 million to establish the Dean's Scholarship.
- We received a donation of RMB 20,000 from Shenzhen Reward Life Technology Co., Ltd. to motivate and commend students who have excellent performances in academic research, scientific and technological innovation, social work and other aspects.
- We received a donation of RMB 5.5 million from Zhejiang Dongrui Industrial Co., Ltd., of which RMB 5 million was reserved for principal use, to established the "Zhejiang University School of Medicine Lizao Neuroscience Award" to reward the teachers and students in Zhejiang University for their outstanding contributions to the popularization of neuroscience and in clinical fields (including Alzheimer's disease, Parkinson's disease, gradual freezing disease, etc). The remaining proportion of the money was used for seminars, publicity, and promotion of research results in neuroscience.

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

Academic Dynamics

Dissecting neurobiological mechanisms of ASD: from genes to circuits

30th Oct. 2020

Guoping Feng

McGovern Institute for Brain Research
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology

From SARS in 2003 to COVID-19 in 2020

7th Jan. 2021

Zihe Rao

School of Medicine
Tsinghua University

Transformation of brain functional imaging from scientific research to clinical practice

25th Jan. 2021

Hesheng Liu

Department of Radiology
Massachusetts General Hospital
Harvard Medical School

Scientific research and the development of young scientific and technological talents

26th Mar. 2021

Yan Shen

Institute of Basic Medical Sciences
Chinese Academy of Medical Sciences

Research of non-pharmacological treatment for depression_from bench to bedside

7th Apr. 2021

Kwok-Fai So

Guangdong-Hongkong-Macau Institute of CNS Regeneration
Jinan University

The prospects for the co-development of brain science and brain-inspired research

18th Apr. 2021

Mu-ming Poo

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

Phase separation and the formation and function of synapses

6th May. 2021

Mingjie Zhang

School of Life Sciences
Southern University of Science and Technology

Super-resolution correlative light and electron microscopy

8th May. 2021

Tao Xu

Institute of Biophysics
Chinese Academy of Science

Brainsmatics

8th May. 2021

Qingming Luo

School of Biomedical Engineering
Hainan University

The role of maternal factors in embryonic development

17th May. 2021

Anming Meng

School of Life Sciences
Tsinghua University

Genome editing in haploid embryonic stem cells

4th Jun. 2021

Jinsong Li

Center for Excellence in Molecular Cell Science
Chinese Academy of Science

Brain network and brain machine interaction

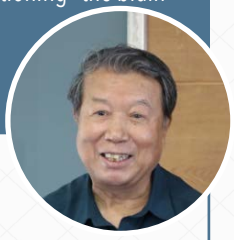
23th Jun. 2021

Dewen Hu

College of Intelligence Science and Technology
National University of Defense Technology

The intelligent road from "questioning" the universe to "questioning" the brain

24th Jun. 2021



Aike Guo

Institute of Biophysics
Chinese Academy of Science

Molecular and circuital mechanisms of memory

2rd Jul. 2021

Youming Lu

Tongji Medical College of Huazhong
University of Science & Technology

Basal ganglia and action sequencing

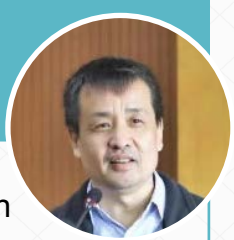
29th Sept. 2021

Xin Jin

Key Laboratory of
Brain Functional Genomics, MOE
East China Normal University

In vivo studies of synaptic plasticity and maintenance

9th Nov. 2021

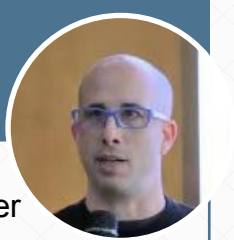


Wen-Biao Gan

Peking University Shenzhen Graduate School

Expanding mechanisms and therapeutic targets for neurodegenerative diseases

22th Nov. 2021



Aaron D. Giltler

Department of Genetics
Stanford University School of Medicine

Pattern recognition and imaging features of brain networks in mental disorders

14th Dec. 2021

Huafu Chen

School of Life Science and Technology
University of Electronic Science and
Technology of China

BBMI Quaterly Fall 2021 Letters from readers

Q In the article **"Characteristics of Whole Brain Electrical Activity of Mental Fatigue"**, why did you choose ECoG instead of other characteristics such as EEG and LFP?

A **Lin Yao:** Compared with non-intrusive EEG signals, ECoG signals have higher spatial resolution and a wider frequency spectrum (up to a frequency as high as several hundred hertz), therefore, they contain a high amount of information and favorable signal-to-noise ratio. Also, compared with the need to insert electrodes into the cortex to obtain LFP signals, in ECoG we simply attach electrodes to the surface of the cerebral cortex. This involves less damage to the brain and can achieve long-term stability for recording. This is of great significance for long-term real-time detection and decoding. Regarding spatial resolution, LFP is better than ECoG, but ECoG is better than EEG, and the same is true when you compare the other parameters of spectrum range (from wide to narrow) and damage (from most to least), respectively. Therefore, the choice of the ECoG signal can be considered a compromise, which can achieve long-term and high-precision decoding.

Q In the article **"Projection Atlas and Functional Analysis of Endocrine Neurons in the Hypothalamus-Neuropituitary System"**, what is the practical significance of analyzing the fine HNS structure for follow-up research?

A **Zhihua Gao:** Structure is the basis of function. The hypothalamo-neurohypophysis system (HNS) is an important center for neuroendocrine regulation. However, due to technical limitations, the architecture of the HNS remains unclear. Precisely dissecting the structure provides a detailed navigation map of the HNS. This allows scientists to characterize the role of different neuronal subsets in the system. For example, we found that oxytocin neuroendocrine cells collaterally project to the central brain area and the peripheral neurohypophysis. The collateral projection thus provides an anatomical basis for these cells to coordinate their peripheral and central actions. Our study also provides insights for understanding the pathological mechanisms of some mental illnesses as such patients often having a dysfunctional neuroendocrine system.

Q Human intelligence, such as synaptic plasticity, belongs to biological intelligence, whereas brain-like intelligence is machine intelligence based on the evolution of the arrangement of human neurons. In the future, is it possible for machines to evolve independently to obtain results similar to those of the human brain without the need for biological intelligence as a reference?

A **Mu-ming Poo:** It may be possible to achieve this goal, but the road towards its exploration, research, and development will be very difficult. Currently, although artificial intelligence is able to complete a wide range of difficult and high-precision tasks, there is no machine intelligence that can achieve "adaptation" without human intelligence as a reference point. In fact, the "intelligence" we refer to is still defined by human biological intelligence. However, the development of brain-like intelligence is not limited to some attempts to merely copy the human brain. Our primary goal is to understand the basic principles from living organisms and imitate the organizational structure of the brain.

To make sure that artificial intelligence can be better used in human biological intelligence, we should obtain connectivity and regularity from multiple repeated learning bouts. In short, the development of artificial intelligence and the understanding of biological intelligence should complement each other in an almost synergistic manner, rather than in an independent way, which enhances the future development directions for both brain and computer sciences.

Scholar Column

An Intro to the 2021 Nobel Prize

The ability to perceive cold and heat and the sense of touch are vital for survival. This is precisely the basis for our interaction with the world around us. In the course of our daily lives, these senses seem to be taken for granted. But have we ever stopped to think how do nerve impulses start, and how do we feel temperature or pressure? This problem has plagued scientists for quite some time.

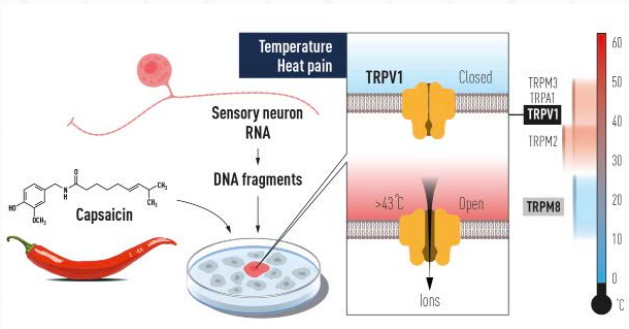
On October 4th, American physiologist David Julius and American molecular biologist Ardem Patapoutian shared the 2021 Nobel Prize in Physiology or Medicine for their discovery of receptors for temperature and touch. Professor **Shumin Duan**, chief scientist at the BBMI Center, explains how the American team finally cracked this long-standing mystery.

"The brain generally transmits information through electrical signals. To feel temperature or pressure, there must be a mechanism that converts temperature or pressure into electrical signals. However, what are the sensory receptors in the body that convert temperature and other various related mechanical stimuli into electrical nerve signals?

CONTINUED FROM PAGE 25

How do they achieve this transformation? The answers to these questions have long remained largely unanswered. Therefore, the discovery of temperature and tactile receptors was a major breakthrough in basic research. After decades of hard work, these two scientists finally identified the relevant ion channels and have since studied their structures and functional mechanisms in detail."

Professor Duan continues, **"These newly discovered ion channels are sensitive to temperature and mechanical stimuli, respectively. When stimulated by changes in temperature or mechanical force, they will open, which will increase the discharge of corresponding neurons, generate impulses, and lead to the perception of the stimulus as hot or cold, or to the perception of touch or pressure."**



Interestingly, sensations of pain and temperature rely on the same type of channel, which explains the sensation of heat we feel when we eat chili. As such, capsaicin has become a key player in unlocking the mysteries of sensory perception.

In the late 1990s, David Julius, who then worked at the University of California in San Francisco, began to analyze the burning sensation caused by the capsaicin contained in peppers. Julius and his colleagues constructed a gene bank containing millions of DNA fragments. These fragments correspond to genes expressed in sensory neurons that respond to pain, heat, and touch.

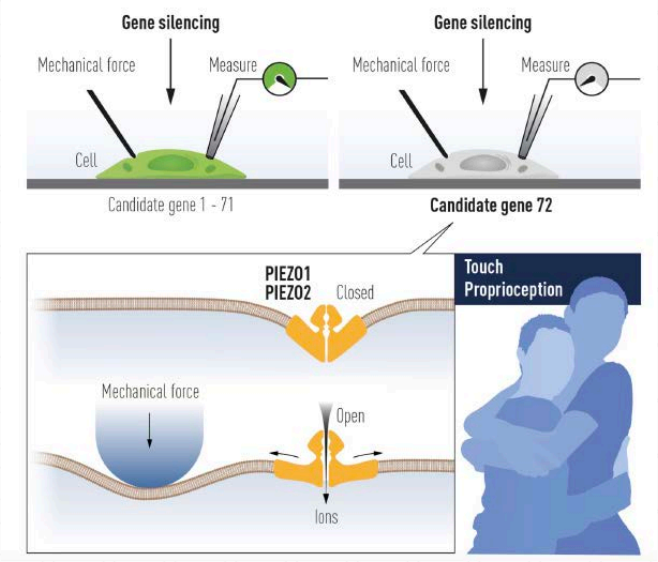
"We know that there must be certain genes in the body that can encode DNA fragments of proteins that react with capsaicin. But no one was sure about the exact genes. Thus, Julius recorded signals using the exclusion method, deleting genes from the system over the course of his experiments. When deletion of a gene resulted in non-response to pain or temperature, he knew the removed gene to be the one he was looking for." Duan noted.

After an arduous search, David Julius identified a gene that could make cells sensitive to capsaicin. Further experiments revealed that the identified gene encoded a new ion channel protein, and this newly discovered capsaicin receptor was later named TRPV1. When Julius continued to study the ability of this protein to respond to heat, he realized that he had discovered a heat-sensitive receptor that was activated when the body felt changes in temperature. Later, Julius and Patapoutian independently used a chemical menthol to identify TRPM8, a receptor that is activated by cold.

Although the mechanism underlying the sensation of temperature had been clarified, we still did not know how mechanical stimuli are transformed into tactile and pressure sensations. Nonetheless, Patapoutian had always hoped to be able to determine which receptors are activated by mechanical stimuli.

Using methods similar to those of Julius and his team, Patapoutian and colleagues identified a cell line that emitted a measurable electrical signal when a single cell was poked with a micropipette. They hypothesized that the receptors activated by mechanical forces are ion channels, and in the next step, they identified 72 candidate genes encoding possible receptors. One by one, these candidates were inactivated to identify the genes responsible for mechanical sensitivity in cells.

After many painstaking investigations, Patapoutian and his team discovered two new and completely unknown mechanically sensitive ion channels, which were designated Piezo1 and Piezo2. Further research confirmed Piezo1 and Piezo2 to be directly activated by pressure exerted on the cell membrane, which can regulate important physiological processes, including blood pressure, respiration, and bladder control. **"Pressure-sensitive ion channels are used in many parts of the human body. After identifying this type of channel, they were able to target the channel to interfere with physiological processes such as respiration, cardiovascular function, and even hearing,"** Prof. Shumin Duan explains. Studies of this nature have revealed that chronic pain, as well as allodynia associated with anxiety or depression, may be effectively controlled through these targets.



The breakthrough discoveries of TRPV1, TRPM8, and Piezo channels by David Julius and Ardem Patapoutian have allowed us to understand how heat, cold, and mechanical forces trigger nerve impulses, bridging the gap between the senses and the environment. Their findings, regarding the complex interactions involved in transmitting sensations of temperature and touch, allow us to appreciate some of the more fascinating aspects of this world such as walking barefoot across the lawn on a hot summer day, feeling every blade of grass that touches your feet, or enjoying the warm breeze surrounding you. It also opens up some key focus areas that may lead to more related discoveries or innovations from the BBMI in the near future.

PROF. HUAN MA

Independent PI for the "Hundred Talents Program" of Zhejiang University.

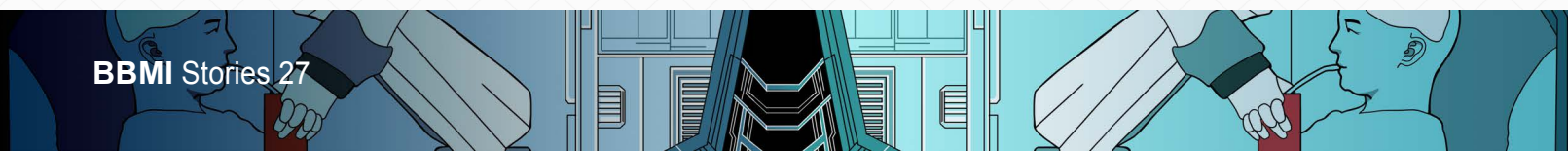
Professor Ma's research focuses primarily on the mechanisms underlying neuroplasticity, learning, and memory, as well as their relationships with brain diseases. He is the head of a number of key research and development projects for the National Natural Science Foundation of China, the Excellent Youth Project, and the Ministry of Science and Technology. As the corresponding author, he has published a series of research papers in well-known journals in the field of neuroscience, such as ***Cell*** and ***Neuron*** with related results having been given the highest evaluation of 'Exceptional' by F1000 on many occasions. Ma's research regarding the mechanisms that regulate neuroplasticity has also been published in the American neuroscience textbook ***Principles of Neurobiology.***

As the basis of cognition and emotion, learning and memory has always been a hotspot in life science research, attracting many scientists who wish to unravel its mystery. However, as Professor Huan Ma commented when introducing his research direction and interests, "Where most of the research on the brain mechanisms involved in learning and memory have focused on the plasticity of excitatory cells, relatively fewer studies have been conducted relating to the understanding of the plasticity of inhibitory cells and of neuronal networks as a whole."

At both the cellular and cognitive network levels, our brain exhibits a certain degree of plasticity. Numerous basic and clinical studies have indicated that dysregulation of neuronal plasticity or network plasticity can lead to impaired cognitive function in the brain. Given these findings, many researchers have wondered whether there is a causal association between the plasticity of nerve cells with that of neural networks involved in cognitive processes, especially learning and memory. In their research, Professor Huan Ma and his team have focused on a special molecule known as γCaMKII. Studies have shown that the coding gene *CAMK2G* is closely related to human memory and that mutations in this gene result in severe intellectual disability. With a firm grasp of this concept and in-depth investigation, Professor Ma's team revealed that γCaMKII plays a key role in mediating the plasticity of inhibitory interneurons, a result that had previously eluded the neuroscience community for many years. This research has finally clarified the mechanism by which γCaMKII mediates the plasticity of inhibitory interneurons and in turn regulates the plasticity of neural networks in the processes of learning and memory. For the first time, Professor Ma's team has evidence to suggest that there is mesoscale coupling of neuronal plasticity and neural network plasticity.

This success was by no means accidental. Indeed, it was inseparable from Professor Ma's professional thinking and planning that has stretched back to his student days. "Adequate scientific practices and learning from outstanding people are indispensable for carrying out significant research." Professor Ma explained, as he recalled some interesting moments regarding his own professional growth. He recalled his ability to move beyond living as a "free but useless soul" when he was an undergraduate student at the School of Life Sciences of Fudan University. Under the guidance of Professor Zuhang Sheng of the National Institutes of Health, he finally completed the transformation from an undergraduate who loved to play real-time strategy games, to a PhD student with great focus. Inspired by Professor Richard W Tsien at Stanford University, Hsue-shen Tsien's nephew, he then completed the transformation from a scientific researcher to a true pioneer. Under the direction of Academician Shumin Duan, Professor Hailan Hu, Professor Xiaoming Li, and Professor Jianhong Luo, he also transitioned from being primarily a learner to one of a respected and esteemed teacher.

Professor Ma has devoted himself to investigating the plasticity of nerve cells and neural networks. His hope is that his research will help identify new targets and strategies for the diagnosis and treatment of cognitive impairment using artificial intelligence. Professor Ma has expressed great enthusiasm for the establishment of the BBMI Center: **"Now, more than ever, interdisciplinarity study is important,"** he explained, **"the future of artificial intelligence research relies on advancements in an integrated understanding of human brain mechanisms. By seizing the opportunities of this era, the BBMI Center has provided researchers with an ideal platform for such a cooperation and has the potential to become a showcase international center, leading the way in this highly competitive field."**



NEW PI Message

PROF. HAOHONG LI received his Doctor of Philosophy Degree from Fudan University and performed his postdoctoral research at the Cold Spring Harbor Laboratory. In 2014, he joined the Wuhan National Laboratory for Optoelectronics, Huazhong University of Science and Technology as a team leader. He had the opportunity to work with many renowned engineers from the optical and electronic engineering fields. This experience largely changed his view on how to conduct biological research. To be closer to the clinic, he joined the BBMI center in 2020. His research team mainly uses in vitro and in vivo electrophysiology and live animal brain imaging technology, combined with animal genetic manipulation, to study the regulation mechanism of wakefulness and sleep and the neural circuits underlying brain oscillations.

> “As a researcher with an engineering background, I hope I can make use of this advantage to serve the center.”

PROF. LIN YAO received PhD degree from Shanghai Jiao Tong University, and continued his postdoc research at University of Göttingen in Germany, University of Waterloo in Canada and Cornell University in USA. Prof. Lin Yao's research expertise is in the brain-computer interface (BCI) field, which fits well with the newly developed BBMI. He wants to have a deeply collaborative relationship with talented researchers at the BBMI center, to investigate and develop new technologies for brain-machine intelligence, and to make more discoveries in the neuroscientific field using BCI technologies. The BBMI is a new home after several years of research in numerous foreign countries. He thinks he will make many friends in the BBMI center and build his career as a competitive researcher in this new platform.

> “I wish that the BBMI center will grow to be an outstanding research platform both nationally and internationally and will be a shining star in the neuroscientific and brain-machine integration field.”

PROF. JIAN XU decided to join the BBMI center because of its multidisciplinary research team in the fields of medicine, engineering, information, and science. It has built the most complete rat-primate-clinical patient brain-machine interface (BMI) research platform in China. This would provide a good working environment and academic atmosphere for cutting-edge research in brain science and brain-machine intelligence. After joining the center, he intends to independently develop high-performance bidirectional closed-loop BMIs for drug-resistant epilepsy, treatment-refractory depression, and motor dysfunction; and explore high-efficiency, safe, and reliable personalized closed-loop neuromodulation treatment methods to improve the treatment and diagnosis of refractory neurological diseases in China. In the near future, he hopes that many top talents will gather in the center, which will cultivate a number of top-notch innovative young researchers who will help in overcoming the cutthroat rivalry facing the current development of BMI in China. The ultimate goal is to place China at the forefront in terms of BMI technology.

> “The BBMI center provides a good working environment and academic atmosphere for cutting-edge research in brain science and brain-machine intelligence. It will place China at the forefront in terms of BMI technology.”

PROF. YU QI received her BS degree from the Mixed Class, Chu Kochen Honors College, Zhejiang University. She received her PhD degree at Qiushi Academy for Advanced Studies (QAAS) and the College of Computer Science, Zhejiang University where she witnessed and participated in the development of brain- computer interfaces at Zhejiang University. Thanks to training in the College of Computer Science, she received a “digital brain”; thanks to the research experience at the QAAS, she received a “neuroscience brain.” She has now joined the BBMI center with her “double brains,” to investigate how to integrate the two through brain-computer interfaces and brain-inspired computing, both of which are very exciting and frontier areas.

> “I believe the BBMI center is in an ideal situation to foster breakthrough innovations in brain-machine integration. I am excited to join the team of talented researchers here and look forward to adding my unique contributions.”

PROF. ZHIGUO MA was a former postdoctoral fellow in Prof. Marc Freeman's lab at the Oregon Health & Science University, United States. His groundbreaking work on dissecting the role of astrocytes in neural circuits revealed important implications of glial cells in neuromodulation and neurodegenerative diseases. Zhiguo is excited to join the faculty of the BBMI center. “It's always thrilling for me to think that one day we will be able to decode our brains. We could then wire some electronic chips together to improve our physical and mental health and even better understand ourselves. Scientists have made great progress towards this, but many challenges still remain. The BBMI center has pioneered the collaboration of neuroscientists, engineers, computer scientists, psychologists, and physicians to explore how our brains work, why they fail in disease, and to find cures for patients.”

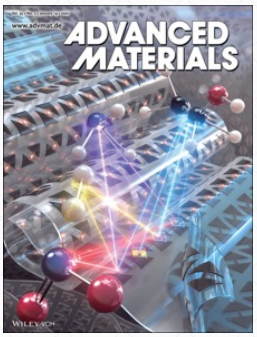
> “The BBMI center is a young and exceptional center. With the endeavors of its talented members, it should become an icon for brain science/engineering in China and globally within the next few years.”

PROF. HONGBIN YANG, received his Ph.D. from the Institute of Neurobiology at Zhejiang University (now the School of Brain Science and Brain Medicine), following which he engaged in postdoctoral research at the University of California, Berkeley. After joining the BBMI Center in September 2021, his lab adopts a multidisciplinary approach, combining electrophysiology, optogenetics, Ca^{2+}-imaging and neural circuit tracing to elucidate the organization and functions of midbrain dopamine circuits, as well as the pathological changes that occur in these circuits as a consequence of mental diseases.

> “The BBMI Center combines excellence in basic neuroscience research with other superior disciplines, such as computer science and engineering, of Zhejiang University. Under the support of the excellent research platform of the BBMI Center, our researchers can more comprehensively and deeply investigate mechanisms of major mental illnesses such as anxiety, depression, and schizophrenia, and ultimately develop effective diagnosis, prevention and treatments for these major mental diseases.”

PROF. HAITENG JIANG, received his Ph.D. from Donders Institute in the Netherlands and then completed his postdoctoral training at University of Minnesota and Carnegie Mellon University in the United States. He joined the BBMI Center in September 2021. Prof. Jiang's research mainly integrates experimental approaches and artificial intelligence with multi-modal brain imaging and neuromodulation technology to study cognition and brain diseases. His main aim is to advance system neuroscience and develop translational applications.

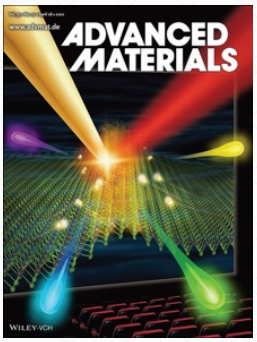
> “Under the background of the China Brain Project, we hope to utilize the outstanding research platform of the BBMI Center to develop a world-leading precise digital system that can aid in the diagnosis and treatment of mental illness by combining objective, measurable multi-dimensional biomarkers and artificial intelligence technology.”



Prof. Ruiliang Bai's Research Group

Wang J#, Jia Y#, Wang Q#, Liang Z#, Han G, Wang Z, Lee J, Zhao M, Li F, Bai R*, Ling D*. An Ultrahigh-Field-Tailored *T1-T2* Dual-Mode MRI Contrast Agent for High-Performance Vascular Imaging. ***Advanced Materials***. 2021 Jan 14; 33(2): 2004917

This study details a UHF-tailored *T1-T2* dual-mode iron oxide nanoparticle-based contrast agent (UDIOC) with extremely small core size and ultracompact hydrophilic surface modification which exhibits dually enhanced *T1-T2* contrast effect under the 7T magnetic field. UDIOC enables clear visualization of microvasculature as small as ≈140 μm in diameter under an UHF MRI, extending the detection limit of 7T MR angiography. Moreover, by virtue of high-resolution UHF MRI and the advanced design of the MRI sequence, UDIOC-based dual-mode dynamic contrast-enhanced MRI was successfully applied to detect tumor vascular permeability with extremely high sensitivity and accuracy. This provides a novel paradigm for the precise medical diagnosis of vascular-related diseases.



Prof. Lixia Gao's Research Group

Feng Z, Bai S, Qi J, Sun C, Zhang Y, Yu X, Ni H, Wu D, Fan X, Xue D, Liu S, Chen M, Gong J, Wei P, He M, Lam J W. Y., Li X, Tang BZ, Gao L, Qian J. Biologically Excretable Aggregation-Induced Emission Dots for Visualizing Through the Marmosets Intravitally: Horizons in Future Clinical Nanomedicine. ***Advanced Materials***. 2021 Mar 19; e2008123.

Superb reliability and biocompatibility equip aggregation-induced emission (AIE) dots with tremendous potential for fluorescence bioimaging. However, there is still a chronic lack of design instructions for excretable and bright AIE emitters. Here, PEGylated AIE (OTPA-BBT) dots with strong absorption and extremely high second near-infrared region (NIR-II) PLQY of 13.6% are designed, and a long-aliphatic-chain design blueprint contributing to their excretion from an animal's body is proposed. Assisted by the OTPA-BBT dots with bright fluorescence beyond 1100 nm, even up to 1500 nm (NIR-IIb), large-depth cerebral vasculature (beyond 600 μm) as well as real-time blood flow are able to be monitored through a thinned skull. Noninvasive NIR-IIb imaging with rich high-spatial-frequency information was able to give a precise presentation of the gastrointestinal tract in marmosets. Importantly, after intravenous or oral administration, the definite excretion of OTPA-BBT dots from the body was demonstrated, which provides important evidence of biosafety.

Prof. Wei Chen's Research Group

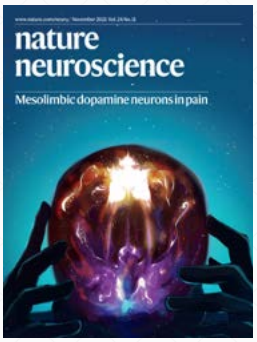
Hu W*, Zhang Y*, Fei PY*, Zhang TT*, Yao DM*, Gao YF, Liu J, Chen H, Lu Q, Mudianto T, Zhang XR, Xiao CX, Ye Y, Sun QM, Zhang J, Xie Q, Wang PH, Wang J#, Li ZH#, Lou JZ#, Chen W#. Mechanical activation of spike fosters SARS-CoV-2 viral infection. ***Cell Research***. 2021 Oct; 31(10):1047-1060.

This paper reveals that tensile force, generated by bending of the host cell membrane, strengthens spike recognition of ACE2 and accelerates the detachment of spike's S1 subunit from the S2 subunit to rapidly prime the viral fusion machinery. Mechanistically, such mechano-activation is fulfilled by force-induced opening and rotation of spike's receptor-binding domain to prolong the bond lifetime of spike/ACE2 binding to up to 4 times longer than that of SARS-S binding with ACE2 under 10 pN force application. Subsequent force-accelerated S1/S2 detachment occurred up to ~10^3 times faster than that in no-force conditions. Interestingly, the SARS2-S D614G mutant, a more infectious variant, showed 3-time stronger force-dependent ACE2 binding and 35-time faster force-induced S1/S2 detachment. This paper also reveals that an anti-S1/S2 non-RBD-blocking antibody, derived from convalescent COVID-19 patients, had potent neutralizing capability and could reduce S1/S2 detachment by 3×10^6 times under force. Our study sheds light on the mechano-chemistry of spike activation and on developing a non-RBD-blocking but S1/S2-locking therapeutic strategy to prevent SARS2 invasion.

Prof. Shumin Duan / Prof. Yijun Liu's Research Group

Liu YJ #,*, Zhang T#, Chen S, Cheng D, Wu C, Wang X, Duan D, Zhu L, Lou H, Gong Z, Wang XD*, Ho MS*, Duan S. The noncanonical role of the protease cathepsin D as a cofilin phosphatase. ***Cell Research.*** 2021 Jan 29; 31(7):801-813

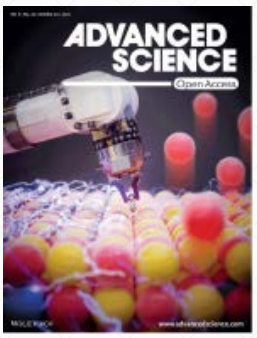
Cathepsin D is the major lysosomal protease responsible for nonspecific protein degradation. However, it also non-proteolytically promotes cell proliferation, tumorigenesis and tumor invasion, suggesting an unknown non-canonical role beyond its traditional proteolytic properties. This study reports that cathepsin D plays an unconventional role as a cofilin phosphatase, orchestrating actin remodeling. In neutral pH environments, the cathepsin D precursor directly dephosphorylates and activates actin-severing protein cofilin in a manner independent of its proteolytic activity. However, in acidic pH conditions, mature cathepsin D degrades cofilin. During development, cathD complements the canonical cofilin phosphatase slingshot and regulates the morphogenesis of actin-based structures. Moreover, suppression of cathD phosphatase activity leads to defective actin organization and cytokinesis failure. These findings identify cathepsin D as a dual-function molecule, the functional switch of which is regulated by environmental pH and its maturation state. This reveals the novel regulatory role of cathD in actin based cellular processes and also provides mechanistic insight into the mitogenicity of cathepsin D which relies on its cofilin phosphatase activity, but not canonical proteolytic activity, in promoting tumor cell proliferation in related cancers.



Prof. Hongbin Yang's Research Group

Yang HB, Johannes W. de Jong, Cerniauskas J, James R. Peck, Byung Kook Lim, H Gong, Howard L. Fields, Stephan Lammel*. Pain modulates dopamine neurons via a spinal–parabrachial–mesencephalic circuit. ***Nature Neuroscience***. 2021 Oct; 24(10):1402-1413.

This study delineates important circuits by which painful stimuli inhibit dopaminergic neurons. The researchers found that a population of neurons in the lateral parabrachial nucleus (LPB) that project to the substantia nigra pars reticulata (SNr) is critical for responses to noxious stimuli. Furthermore, the study found that the LPB→SNr pathway may dampen VTA DA activity via direct inhibition of lateral VTA DA or indirect reduction of lateral VTA DA excitatory-drive by activating the SNr projections onto LPB→VTA neurons.



Prof. Chong Liu's Research Group

Rui Liu, Yinhang Jia, Peng Guo, Wenhong Jiang, Ruiliang Bai, Chong Liu*. In Vivo Clonal Analysis Reveals Development Heterogeneity of Oligodendrocyte Precursor Cells Derived from Distinct Germinal Zones. ***Advanced Science***. 2021 Oct 21:2170131.

This study developed an *in vivo* clonal analysis approach to trace the lineages of individual neonatal Oligodendrocyte Precursor Cells (OPCs), derived from either dorsal or ventral embryonic germinal zones, and comprehensively described the landscape of their trajectories throughout development. The team was able to reveal the heterogeneity of OPCs from different germinal zones and demonstrate that their developmental origins play a role in determining OPC fate. Furthermore, this work disclosed the importance of *in vivo* clonal analysis in studying stem/progenitor cell heterogeneity.

Prof. Xuemei Song's Research Group

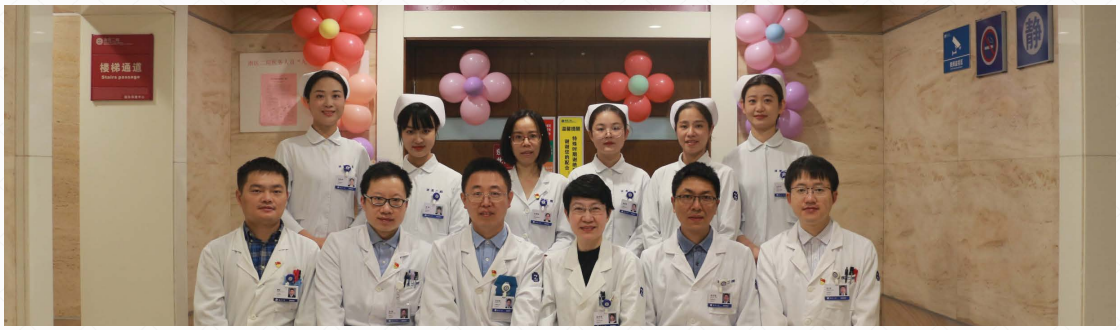
Song X, Hu X, Li Z, Gao Y, Ju X, Liu D, Wang Q, Xue C, Cai Y, Bai R, Tan Z*, Northoff G*. Reduction of higher-order occipital GABA and impaired visual perception in acute major depressive disorder. ***Molecular Psychiatry***. 2021 Apr 16.

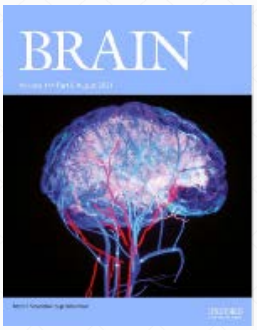
Major depressive disorder (MDD), sometimes simply referred to as clinical depression, is a complex state-dependent psychiatric illness. Its biomarkers, linked to psychophysical, biochemical and psychopathological changes, still remain elusive. Combining psychophysical investigation of visual perception with measurement of GABA concentrations in the middle temporal visual area (hMT+) in patients with MDD, the researchers observed a high degree of specific deficit in the visual system, particularly surrounding motion suppression. Importantly, the level of this deficit correlated with the severity of MDD symptoms. Using high-field 7T proton Magnetic resonance spectroscopy (1H-MRS), acute MDD subjects were seen to exhibit decreased GABA concentration in visual MT+. This study highlights the importance of the higher-order occipital cortex (MT+) in the acute depression of MDD, and includes the suggestion of its use as a candidate biomarker.

Prof. Huan Ma's Research Group

He X, Li J, Zhou G, Yang J, Sam McKenzie, Li Y, Li W, Yu J, Wang Y, Qu J, Wu Z, Hu H, Duan S, Ma H *. Gating of hippocampal rhythms and memory by synaptic plasticity in inhibitory interneurons. ***Neuron.*** 2021 Mar 17; 109(6):1013-1028.

Mental experiences can become long-term memories if the hippocampal activity patterns that encode them are broadcast during network oscillations. The activity of inhibitory neurons is essential for generating these neural oscillations. However, the molecular control of this dynamic process during learning has remained unclear. Here, Huan Ma and his group show that the hippocampal oscillatory strength positively correlates with excitatory monosynaptic drive onto inhibitory neurons (E→I). To establish a causal relationship they identified ϒCaMKII as the long-sought mediator of long-term potentiation for E→I synapses (LTPE→I), which enabled the genetic manipulation of experience-dependent E→I synaptic input/plasticity. Their data suggest that E→I synaptic plasticity, exemplified by LTPE→I, plays a gatekeeping role in tuning experience-dependent brain rhythms and mnemonic function.





Prof. Zhi-Ying Wu's Research Group

Dong HL, Ma Y, Yu H, Wei Q, Li JQ, Liu GL, Li HF, Chen L, Chen DF, Bai G, Wu ZY. Bi-allelic loss of function variants in COX20 gene cause autosomal recessive sensory neuronopathy. ***Brain***. 2021 Sep 4;144(8):2457-2470.

Zhi-Ying Wu's Lab, also the Department of Medical Genetics and Center for Rare Diseases, serves as a genetic testing center for the discovery of novel causative genes for undiagnosed diseases. Recently, Prof. Wu's team used whole exome sequencing to identify eight sensory neuronopathy families carrying a founder variant c.41A>G (p.Lys14Arg) in the *COX20* gene. All patients displayed sensory ataxia with a decrease in non-length-dependent sensory potentials, showing that the *COX20* variants had led to a loss-of-function mechanism. Loss of COX20 expression resulted in impaired assembly and activity of complex IV, which subsequently compromised the cell's spare respiratory capacity and reduced cellular proliferation. Overall, this study identified a novel causative gene for autosomal recessive sensory neuronopathy, further highlighting mitochondrial bioenergetic dysfunction as a prominent mechanism in peripheral sensory neuron disease.

Prof. Shaohua Hu's Research Group

Jing Lu#, Lifeng Ma#, Jiajun Jiang#, Bochao Huang, Tingting Mou, Tingting Huang, Yi Xu, Ming Li, Lin Zhang, Xiaoping Han*, Shaohua Hu*. Linking peripheral $CD8^+$ single-cell transcriptomic characteristics of mood disorders underlying with the pathological mechanism. ***Clin. Transl. Med***.2021; 11: e489.

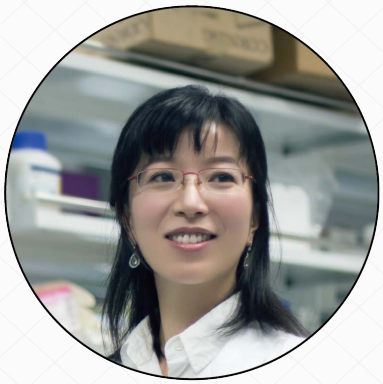
This study represents the first report of peripheral $CD8^+$ T cell mapping in mood disorders by single-cell sequencing. The researchers found that Tim-3, on the surface of $CD8^+$ T cells, participated in immune regulation by mediating cellular functions. This may be an important immune mechanism for bipolar disorders. This study provides new evidence for immune dysfunction with potential insights for immunotherapy related to mood disorders.

Prof. Yueming Wang
Professor, PhD Supervisor

Key R&D program of Zhejiang

▼ **Brain computer interface for high precision Chinese-based communication**

The development of brain-computer interfaces for language decoding is an international frontier direction that has been emerging over the past two years. As language is the most direct and efficient way of communication between people, and due to the high importance and high clinical application potential placed upon such developments, language brain-computer interfaces are predicted to become the next breakthrough in brain-computer interface technology. Real-time and high-efficiency language decoding technology, based on invasive brain-computer interfaces, is a technology yet to emerge in a Chinese language context. This project focuses on real-time high-precision language decoding technology based on invasive brain-computer interfaces. It will research Chinese language neural coding and decoding mechanisms based on the unique characteristics of Chinese in writing and pronunciation, and then develop language brain-computer interface technology based on handwriting, imagination, and pronunciation. On this basis, this project aims to develop a set of real-time high-precision and reliable Chinese language decoding brain-computer interface systems. These will have great research significance and clinical application potential.



Prof. Hailan Hu
Professor, PhD Supervisor

Key Project of the National Natural Science Foundation

▼ **Neural Circuit Basis and Emotional Effects of Social Competition**

Socially competitive behavior, as a key type of instinctive behavior common to social animals, is a primary mechanism that influences the individual's position in the social hierarchy and corresponding status, behavior, and mental fitness. Repeated social defeat may lead to depression as well as a low social status. We previously found that dmPFC is a key brain region that regulates socially competitive behaviors and that LHb burst firing mediates depression. However, several key questions remained unclear. Which are the dmPFC downstream circuits that regulate social competition? What is the core neural mechanism mediating downward-social-mobility-induced depression? What is the mechanistic foundation for the crosstalk between social mobility and psychological disorders? Based on our previous findings, we hypothesize that in a stable hierarchy, dmPFC and its downstream circuits regulate socially competitive behaviors. However, in an unstable hierarchy, downward social mobility triggers a negative social reward prediction error (RPE), which instigates increased LHb bursting firing to cause a depressive-like state and to reinforce subordination. The depressive state then also influences socially competitive behaviors via the function of LHb on dmPFC and its downstream targets. In this proposal, we aim to dissect the function of the dmPFC in its regulation of social competition, create an animal model for loss of social status, reveal the core neural mechanism mediating downward-social-mobility-induced depression, and investigate how social experiences affect emotions and behaviors by using the tube test, anterograde and retrograde tracing, activity-dependent cell-labeling technology, calcium imaging, optogenetics, and in vivo and in vitro electrophysiological techniques. We also aim to identify a reciprocal crosstalk between socially competitive behaviors and the mood state, providing potential targets for behavioral intervention for cases of depression.

Prof. Han Xu
Professor, PhD Supervisor

The National Science Fund for Distinguished Young Scholars

▼ **Neural mechanism for social interaction behavior**

Social interaction represents the cornerstone of our daily life and society. Unfortunately, social impairments are commonly observed in many neuropsychiatric disorders and can have devastating impacts on patients with such afflictions. It is therefore of great importance to decipher the neural mechanisms of social interaction or social impairment to see if treatments and/or preventions of such conditions may be possible. The present proposal aims to systematically dissect the mechanism of the neuronal circuitry of social phobia, a globally prevalent psychiatric disorder. Firstly, taking advantage of mouse models of social fear, we will identify the key brain regions, important neuronal types, and specific circuitries underlying this aberrant phenomenon. Secondly, using human brain imaging technology, we will further examine the potential structural and functional alterations associated with social anxiety in humans. Taken together, these studies will aid in the understanding of the neural substrate of social interaction behavior at the level of neural circuitry. Findings from our proposed studies should advance the development of future therapies for patients with social phobias and related disorders.

Prof. Benyan Luo
Professor, PhD Supervisor

Key R&D program of Zhejiang

▼ **Development of a multimodal fusion early warning system for Alzheimer's disease and new non-invasive neuromodulation techniques**

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Research into its early indications, allowing for timely and precise intervention, represents a critical current focus issue for modern society in China and globally. As the progress of AD is difficult to reverse once dementia symptoms have already appeared, the present search for a solution for AD has a clear goal of "shifting the window forward". How to develop early recognition or early warning technology for AD, and then use it for easy and efficient screening of the elderly, is the prerequisite for delaying the progress of AD, particularly for patients with aspects of cognitive impairment. This project intends to 1) acquire the biometric information of the subjects' peripheral modalities through the use of digital intelligence equipment, 2) further combine ERP and MRI multi-modal image data, and 3) use deep learning algorithms to construct and verify AD early warning markers to achieve early warning and diagnosis of AD. More specifically, it aims to use the key features in this multi-modal early warning model to accurately locate abnormal neural networks and nuclei that may be the precursors of dementia. On the basis of this precise positioning, we will be able to make use of the great advantages of transcranial ultrasound stimulation (TUS) and its high penetration to determine individualized therapeutic intervention prescriptions. Such analysis would enable the subsequent therapy to target the stimulation of the related cognitive network with an extremely high-degree of precision, reconstruct the abnormal brain areas and neural networks of patients, and finally achieve the aim of preventing the progression of early AD. Overall, the medical-technical team cooperation and multi-disciplinary collaborative research nature of this project aims to develop artificial intelligence (AI) algorithms based on biometric recognition, and realize the AI system of "*precision early warning- individualized TUS prescription-quantitative evaluation of therapeutic intervention effects*" for early AD diagnosis and treatment.

Prof. Dan Wu
Professor, PhD Supervisor

Outstanding Youth Project of National Natural Science

▼ Diffusion magnetic resonance imaging technique

Magnetic resonance imaging (MRI), whilst representing an extremely useful imaging technology, is rather limited by the resolution of its output images. Prof. Wu's team has endeavored to overcome this limitation by developing novel diffusion MRI techniques. These incorporate diffusion physics, imaging sequencing, and mathematical modeling perspectives, to improve the imaging resolution from macro- to meso- to micro-levels. Her team developed 3D high-resolution imaging sequences that were able to overcome the technical bottleneck of diffusion MRI at meso-scale, and achieved ultra-high resolution at the sub-millimeter or even micron level. Moreover, based on the principle of time-dependent diffusion MRI, her team designed oscillating gradient sequences to measure diffusion time-dependency and established biophysical models to reconstruct cellular microstructural properties. They also successfully translated the new microstructural imaging method into a clinically available and assessable routine by addressing several technical challenges related to oscillating gradient sequences. The imaging pulse sequences that Prof. Wu's team has developed have now been implemented into the major MRI vendor systems such as Siemens, Philips, and Bruker, and are now used in more than 20 world-renowned hospitals and research institutions. Based on time-dependent diffusion MRI, this project aims to develop new oscillating gradient sequences and microstructural models that are specifically tailored to tumor cell characteristics. These reconstructed tumor microstructural properties will be used for pathological and molecular classification of medulloblastomas, as well as to predict patient outcomes.

Prof. Zhefeng Gong
Professor, PhD Supervisor

The Pioneer Plan of the Department of Science and Technology of Zhejiang Province

▼ Robotics inspired by Drosophila larval motor control

As one of the recent 'hot spots' in the field of robotics, soft robots, as their name may suggest, are robots made mainly of soft materials. They have a number of valuable properties such as good adaptivity to the environment and provide high safety and compatibility for human-machine interactions. However, due to their almost infinite capacity for freedom of movement and high nonlinearity in deformation, modeling the kinematics and control of movement for such soft robots is very difficult. A direct way to solve this problem is to mimic the behavioral control mechanism of soft bodied animals such as *Drosophila* larva. In this project we plan to firstly perform simultaneous imaging of larval neural/muscular activity and behavior, using a high-speed light sheet system to build a dataset. We will then analyze the relationship between neural network activity, muscle activity and behavioral movements, in combination with the structural information obtained from the larval brain connectome. Using this information, we will setup a model that can generate virtual larval locomotion that is indistinguishable from the locomotion of real larva. Finally, a prototype robot maggot, that mimics real larva in both morphology and the manner of motor control, will be built. Our work will provide a biomimetrical prototype with a biologically clear internal structure and motor control mechanism, that should provide many future applications into autonomous bionic soft robot related technologies.

Prof. Tao Li
Professor, PhD Supervisor

Key R&D program of Zhejiang

▼ **Research on precision diagnosis and treatment for schizophrenia using multi-omics and multidimensional features**

Schizophrenia is a major mental disorder that involves emotional, cognitive, and behavioral abnormalities. At present, objective biomarkers for prediction, diagnosis and treatment responses are insufficient and effective approaches for early identification and intervention are rare. In order to improve early diagnosis, the objectivity of diagnosis, and the effectiveness of treatment, this project plans to 1) establish a cohort of patients with first-episode schizophrenia using standardized methods; 2) integrate clinical biological databases and research results as sourced by multiple teams involved in this project; 3) map multidimensional phenotypes, including clinical features, neurocognition, neuroelectrophysiology, and neuroimaging; 4) map multi-omics, including genomics, epigenetics, transcriptomes, proteomics, and lipid metabolomics; 5) validate positive results in independent samples and comprehensively analyze results from step 3 and 4; and 6) replicate the results in a longitudinal cohort. The project will establish a new classification system based on multi-omics and multidimensional feature spectra, benefiting disease prediction, early diagnosis, effective treatment, and prognosis, for patients with schizophrenia. Moreover, it will have the potential to be translated into a clinical guide for the precision diagnosis and treatment of schizophrenia.

Prof. Ping Wang
Professor, PhD Supervisor

Sub-project of National Science and Technology Innovation 2030 New Generation Artificial Intelligence Major Project

▼ **Research on Bionic Sensor and Brain-like Sensing System**

This project studied the sensing principle of the olfactory neural pathway and proposed a new mode of pulse coding based on the bionic olfactory bulb model. In this model, the mechanism by which the olfactory nerve pathway transmits and processes signals is studied, and a neural network based on a bionic olfactory bulb model is proposed. The effectiveness of the bionic olfactory pulse neural algorithm was then verified by the recognition of different rotten fruit odor samples. In the resulting paper, the fusion centre of auditory and olfactory stimuli and Bayesian decision theory were presented, and the behavioural analysis of auditory and olfactory stimuli under single and multiple-modes were carried out for mice. A theoretical framework based on an impulse neural network was then established and verified using biological experiments.

Within this project, a robot model integrating auditory and olfactory perception was established. Through the development of high-performance olfactory intelligent sensors and auditory speech sensors to collect odor and sound signals, respectively, odor information coding and neural coding of bionic electronic signals were able to be studied. Taking the robot as the demonstration of intelligent application, an intelligent sensory integration based on listening and smelling modes was then realized. The sensing principle of auditory receptor cells was also studied, and a bionic auditory pulse coding algorithm based on mechanical and electrical transduction of auditory receptor cells is now being proposed. Further, a bionic auditory sensor based on auditory receptor cells is planned, designed for bionic hearing.

Prof. Xuequn Chen
Professor, PhD Supervisor

Key Project of National Natural Science

▼ **Mechanism of response and adaptation to hypoxia environment in subterranean rodents**

Survival of the fittest: The blind subterranean mole rat *Myospalax baileyi* is one of the toughest and most dominant mammals in the Qinghai-Tibet Plateau, China. They live in underground caves and have to deal with hypoxia, extreme cold, and high a CO_2 environment at up to 4,000 meters above sea level. Another similar species of subterranean blind mole rats (*Spalax galili*) suffers comparable aspects of extreme low oxygen concentration and high CO_2 stress during winter flooding in Israel. Our team discovered special physiological adaptive regulation factors and adaptive genetic variations in both *M. baileyi* from China and *S. galili* from Israel. Some factors were common to both species, and others more divergent, possibly linked to their differing different adaptation mechanisms under their respective micro-environmnents. By using cellular and molecular techniques, such as CRISPR/Cas9 editing techniques and bioinformatics to mimic gain and loss functions, this project will study the environmental adaptation mechanisms of the transcription factor p53 and its negative regulators MDM2 and MDMX, in both the *Myospalax* and *Spalax* genera. We will elucidate and compare the mechanism of apoptotic responses related to p53 phosphorylation, and investigate the mechanism of MDM2 and MDMX phosphorylation and acetylation links to p53 accumulation. Further, we will demonstrate how p53 is involved in the inhibition of glycolysis and explore the DNA damage response and cell fate decisions via p53-MDM2 interactions. Through demonstrating the survival strategies of these subterranean mole rats, this project focuses on how genetic adaptation helps adaptation to extreme environments, aims to provide new insight into the environment-genetic evolutionary theory, and could result in potential clinical applications for chronic mountain sickness.

Prof. Ge Bai
Professor, PhD Supervisor

Special Project of the National Natural Science Foundation

▼ **Eliminating neuronal vulnerability by RNA granule reprogramming**

Recent studies have highlighted the important role of RNA granules and other membraneless organelles in neurodegenerative diseases. RNA granules may act as important therapeutic targets to block the pathogenic pathways of these diseases. Based on these findings, we propose to develop an innovative strategy, so called “RNA granule reprogramming”, to modify RNA granules in “vulnerable” neurons in the hope of increasing their disease-resistance. This new strategy has the potential to provide a breakthrough in the treatment of a number of neurodegenerative diseases. Based on our previous studies of RNA granules and motor neuron diseases, we will employ motor neuron RNA granules as the entry point to investigate RNA granule reprogramming strategies by using a combination of *in vitro* and *in vivo* disease models. This proposal should provide new clues for the treatment of a number of neurodegenerative diseases.

Prof. Yi Zhang
Professor, PhD Supervisor

Key R&D program of Zhejiang

▼ Novel Magnetic Resoannce CEST Imaging

Magnetic resonance chemical exchange saturation transfer (CEST) imaging is a new and rapidly developing branch of magnetic resonance imaging. Traditional magnetic resonance imaging technology can only detect the spatial distribution of water molecules in the human body, while CEST, as a new molecular magnetic resonance imaging technology, can non-invasively detect the distribution of proteins and metabolites. However, CEST imaging technology is still limited by issues such as inadequate sensitivity and slow imaging speed, which limits the application and further development of CEST imaging for routine clinical applications. The purpose of this project is to realize a novel scanning sequence and imaging method for CEST imaging that is highly sensitive, fast, and integrated with data acquisition and analysis, in order to apply CEST imaging technology to daily clinical diagnosis. Specifically, this project intends to achieve a CEST saturation pulse length of more than 2 seconds and fast three-dimensional CEST imaging of the whole brain, and integrate a CEST data analysis algorithm into the real-time magnetic resonance computing system.

2021 BBMI Selected Publications

1. Duan J#, Xu PY#, Cheng X#, Mao CY#, Croll T, He XH, Shi JJ, Luan XD, Yin WC, You EL, Liu QF, Zhang SY, Jiang HL, Zhang Y*, Jiang Y*, H. Eric Xu*. Structures of full-length glycoprotein hormone receptor signalling complexes. ***Nature***. 2021 Oct; 598(7882):688-692.

2. Ping YQ#, Mao C#, Xiao P#, Zhao RJ#, Yi Jiang#, Yang Z, An WT, Shen DD, Yang F, Zhang H, Qu C, Shen Q, Tian C, Li ZJ, Li S, Wang GY, Tao X, Wen X, Zhong YN, Yang J, Yi F, Yu X, Xu H E *, Zhang Y*, Sun JP*. Structures of the glucocorticoid-bound adhesion receptor GPR97–Go complex. ***Nature.*** 2021Jan; 589(7843):620-626.

3. Xu P #, Huang S #, Zhang H #, Mao C #, Zhou X E#, Cheng X#, Simon I. A, Shen DD, Yen HY, Robinson C V, Harpsøe K, Svensson B, Guo J, Jiang H, Gloriam D E, Melcher K, Jiang Y *, Zhang Y *, Xu H E *. Structural insights into the lipid and ligand regulation of serotonin receptors. ***Nature.*** 2021 Apr; 592(7854):469-473.

4. Shen CS#, Mao CY#, Xu CJ#, Jin N#, Zhang HB, Shen DD, Shen QY, Wang XM, Hou TJ, Chen Z, Philippe Rondard, Jean-Philippe Pin*, Zhang Y*, Liu JF*. Structural basis of GABAB receptor–Gi protein coupling. ***Nature.*** 2021 Jun; 594(7864):594-598.

5. Zhang Y #, Xu P #, Mao C #, Wang L #, Krumm B #, Zhou X E #, Huang S, Liu H, Cheng X, Huang XP, Shen DD, Xu T, Liu YF, Wang Y, Guo J, Jiang Y, Jiang H, Melcher K, Roth B L *, Zhang Y *, Zhang C *, Xu H E *. Structural insights into the human D1 and D2 dopamine receptor signaling complexes. ***Cell.*** 2021 Feb 18;184(4):931-942.e18.

6. Yang HB, Johannes W. de Jong, Cerniauskas J, James R. Peck, Byung Kook Lim, H Gong, Howard L. Fields, Stephan Lammel*. Pain modulates dopamine neurons via a spinal–parabrachial–mesencephalic circuit. ***Nature Neuroscience***. 2021 Oct; 24(10):1402-1413.

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8. He X, Li J, Zhou G, Yang J, Sam McKenzie, Li Y, Li W, Yu J, Wang Y, Qu J, Wu Z, Hu H, Duan S, Ma H *. Gating of hippocampal rhythms and memory by synaptic plasticity in inhibitory interneurons. ***Neuron***. 2021 Mar 17; 109(6):1013-1028.

9. Zhang C#, Zhu H#*, Ni Z#, Xin Q, Zhou T, Wu R, Gao G, Gao Z, Ma H, Li H, He M, Zhang J, Cheng H, Hu H*. Dynamics of a disinhibitory prefrontal microcircuit in controlling social competition. ***Neuron.*** 2021 Nov 17; S0896-6273(21)00864-3.

10. Wang J, Jia Y, Wang Q, Liang Z, Han G, Wang Z, Lee J, Zhao M, Li F, Bai R*, Ling D*. An Ultra high-Field-Tailored T1-T2 Dual-Mode MRI Contrast Agent for High-Performance Vascular Imaging. ***Advanced Materials.*** 2021 Jan 14; 33(2): 2004917.

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Our Vision

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

"Innovate 2030" Plan

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

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