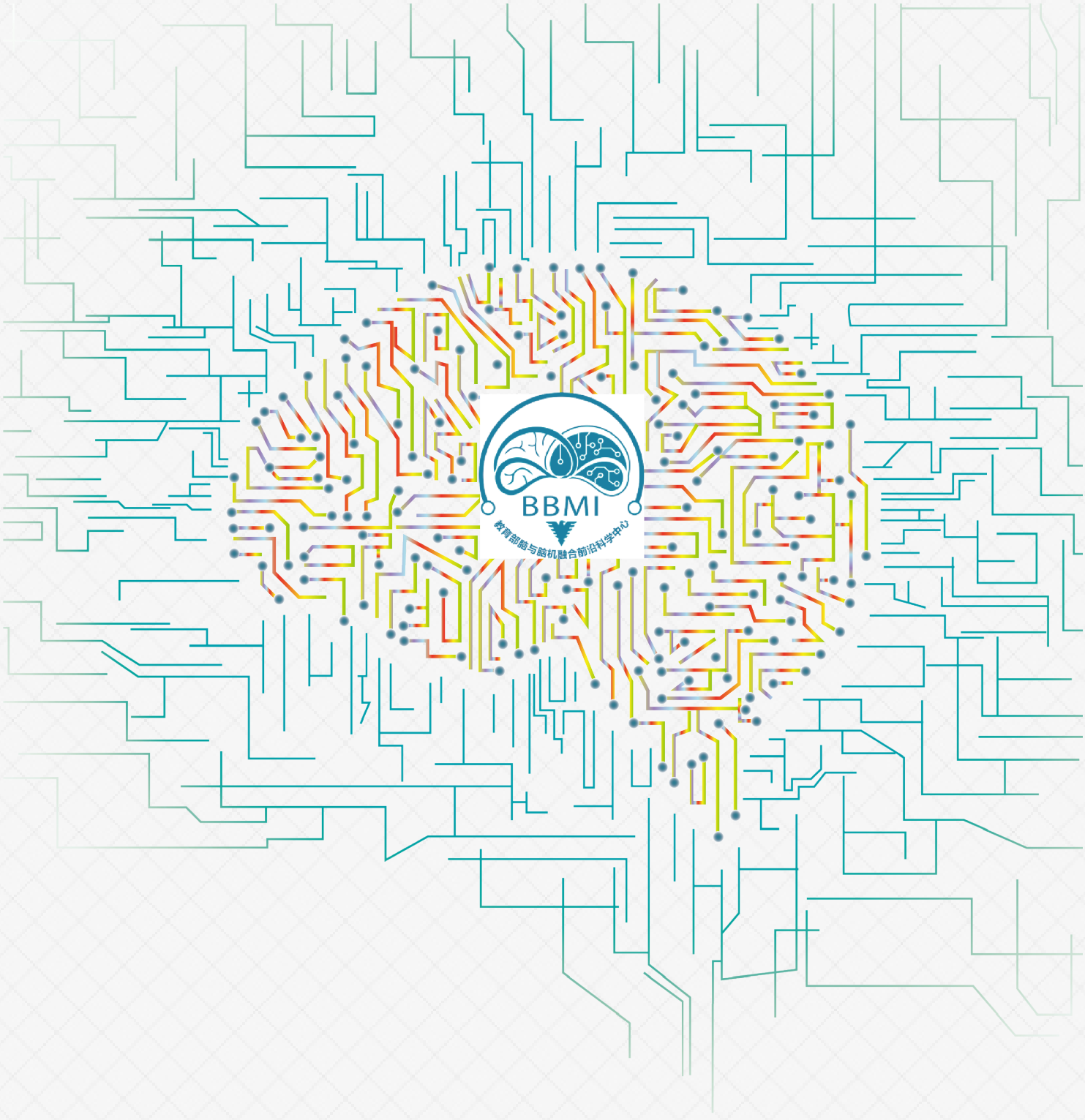
Vol.1 No. 7 2024

BBMI

First Half 2024

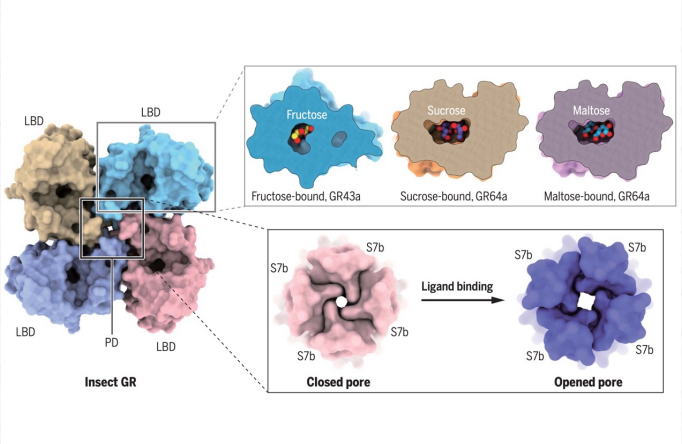

BBMI
教育部脑与脑机融合前沿科学中心

Research Progress

The Basic, Clinical and Interventional Research of Autism Spectrum Disorder

The 'Sugar radar' for sweet-toothed fruit flies!

The mechanism of sugar perception by drosophila gustatory receptors



Molecular basis for the sugar perception by insect GRs.

Taste perception in animals plays an essential role in the seeking of nutritious foods and the avoiding harmful compounds. Unlike mammals that detect sweet, umami, and bitter tastants via G-protein-coupled receptors, insects harness a large group of ligand-gated ion channels called gustatory receptors (GRs) for the perception of sweet, bitter, and other tastes. Among these, the sweet sensation is particularly important for a number of species due to its crucial role in detecting sugars and regulating carbohydrate intake. As we lack three-dimensional structural information for GRs, it remains unclear how GRs recognize tastant molecules and then responsively transit from a closed state to an open conformation.

On February 2, 2024, **Prof. Jiangtao Guo**'s research group from Zhejiang University School of Medicine, Haoxin Xu's research group from Zhejiang University School of Medicine/Liangzhu Laboratory, Minrui Fan's research group from CAS Center for Excellence in Molecular Plant Sciences, and Nannan Su's research group from the Fourth Affiliated Hospital, Zhejiang University School of Medicine, jointly published a research article in ***Science***, entitled *"Structural basis for sugar perception by Drosophila gustatory receptors"*. This study revealed how sugar molecules bind to activate insect sweet taste receptors, providing a prototypical platform for understanding how different tastants are perceived by diverse members of the insect GR family and offering accurate structural models for the rational design of attractant or repellent modulators for pest control.

Using techniques including electrophysiology and Ca^{2+} imaging researchers revealed that GR43a and GR64a are ionotropic sugar receptors with distinct sugar selectivity, where GR43a is activated by monosaccharide fructose while GR64a is activated by maltose and sucrose, two disaccharides found in the fly's food.

To uncover the sugar activation mechanisms of insect GRs, the researchers determined the cryo-EM structures of wild-type (WT) GR43a and GR64a in the apo (non-sugar-bound) and sugar-bound states. The GR43a and GR64a channels are both homotetramers composed of four symmetric subunits. Each GR subunit contains seven transmembrane helices (S1-S7) with S1-S6 forming the ligand-binding domain (LBD) and S7 contributing to the formation of the central pore domain (PD). At the cytosolic side of the GR channel, four lateral conduits between adjacent subunits act as potential ion exit routes.

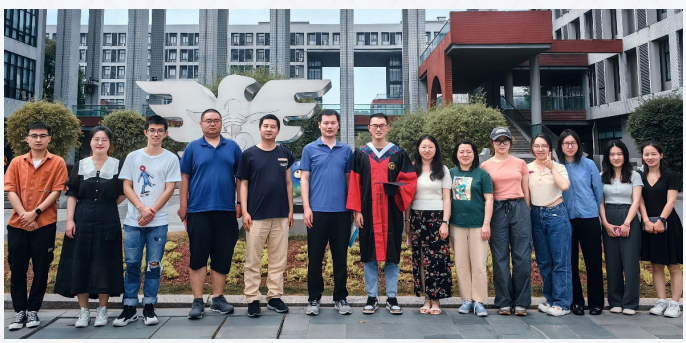
In the sugar-bound GR structures, sugars bind to the extracellular-facing pockets of LBDs via hydrogen bonds and CH-π interactions. GR43a recognizes fructose with a narrow pocket that can neither accommodate disaccharides nor optimally fit other monosaccharides such as glucose. GR64a binds disaccharides with a larger and flatter pocket that possesses structural plasticity to accommodate both sucrose and maltose, but not monosaccharides. In the apo state and sugar-bound structures of GR, the channel pores remain closed. To understand how sugar binding triggers the opening of the channel pore, the researchers identified a constitutively activated mutant GR43a-I418A and determined the structure of GR43a-I418A in an open conformation in the presence of fructose. By comparing structures of GR43a in the apo closed, fructose-bound closed, and fructose-bound open conformations, the fructose activation mechanism of GR43a was uncovered. The binding of fructose to the LBDs induces motions of S5-S6 towards the ligand binding pocket center. This then causes a bending of the pore-lining S7 to open the channel pore through hydrogen bonds and hydrophobic interactions between S5 and S7.

Thereby, as Prof. Jiangtao Guo explains, "This study elucidated the sugar binding and activation mechanisms of different GRs and may guide the development of new strategies to tune the physiology and behavior of insects, as well as to control pests".

Ma D[#], Hu M[#], Yang X[#], Liu Q[#], Ye F, Cai W, Wang Y, Xu X, Chang S, Wang R, Yang W, Ye S, Su N[*], Fan M[*], Xu H[*], Guo J[*]. Structural basis for sugar perception by Drosophila gustatory receptors. ***Science***. 2024 Feb 23;383(6685):eadj2609. doi: 10.1126/science.adj2609. Epub 2024 Feb 23. PMID: 38305684.

JIANGTAO GUO'S RESEARCH GROUP

employs a diverse array of biophysical and biochemical techniques to investigate the intricate molecular processes of ion transmembrane transport. Their research extends to the exploration of regulatory molecules and protein tools tailored for associated ion channels and transporters with a particular emphasis on understanding the structure and functionality of the ion channels and transporters that are pivotal in fundamental life processes such as perception or the regulation of cellular excitability. The lab's contributions have been recognized through publications in esteemed international journals such as ***Nature*** and ***Science***.



Is the wide distribution of sweet taste receptors on fruit flies and their ability to distinguish different sugars related to their diet? If a new pesticide is developed based on targeting such diet related receptors, would it lead to the selective pressure for the evolution of new fruit flies to become more like insects without sweet taste receptors?

The taste receptors of fruit flies are closely related to their dietary habits. Fruit flies mainly feed on rotting fruits and other sugary substances. Their sweet taste receptors can detect and differentiate various types of sugars, helping them effectively locate these food resources to optimize their food search and intake behavior.

Pesticides developed based on sweet taste receptors may exert selective pressure on the sweet taste receptors of insects, but it is unlikely that these receptors will disappear completely. Evolution is a long process that depends on various factors including environmental pressure and genetic variation. Pesticides will exert selective pressure on insects, potentially prompting them to evolve resistance or other adaptive traits. However, this evolution is primarily reflected in changes in resistance genes, not necessarily through the loss of sweet taste receptors. Some variants that reduce sensitivity to pesticides may appear, for example, fruit flies might evolve variant forms of sweet taste receptors that are no longer sensitive to pesticides. However, as sweet taste receptors are crucial for the survival and foraging of insects, their complete disappearance is unlikely. Insects are more likely to respond to the challenge of pesticides through genetic variation, behavioral adaptation, and other adaptive mechanisms.

What are some challenges encountered during the dissection of the sweet taste receptor mechanisms? How did the team overcome them?

The most challenging issue during this project was the difficulty to obtain sugar-bound open-state structure of insect taste receptors. This prevented us from deriving a mechanistic understanding of how sugar binding gates the channel. We made numerous attempts to obtain an open-state structure of GR43a. Our strategies included: (1) testing different detergents in different pHs, (2) reconstituting the proteins into lipid nanodiscs, (3) adding possible channel cofactors (e.g. PI(4,5) P_2 and Ca^{2+}) into the protein samples, and (4) introducing mutations around the extracellular gate, pore-lining, and ligand binding pocket in GR43. Finally, combined with electrophysiological analysis, we successfully identified a constitutively activated mutant GR43a-I418A and determined the structure of GR43a-I418A in an open conformation in the presence of fructose.

Sweet taste intake is beneficial for maintaining both the body energy supply and an enjoyable mood in humans, but too much sugar intake may also lead to health issues. Is there currently any small molecular medicine targeting sweet taste receptor in development?

There is indeed research being conducted on the development of small molecule drugs targeting sweet taste receptors. Researchers are exploring the use of small molecule drugs to modulate these sweet taste receptors to reduce the perception of the sweet taste and help control sugar intake. Although there are currently no small molecule drugs for sweet taste receptors that are widely used in clinical practice, this field of research is developing rapidly and more specific drugs may become available in the future.

Dissecting the functional structure of ion channels helps researchers understand the generation, delivery, and functions of complex signals. How far away are we from developing new clinical medications based on our understanding of ion channel- mechanism related diseases? What are some of the challenges?

The development of ion channel-targeted drugs requires multiple stages, including basic research, drug screening, preclinical research, and multi-stage clinical trials of Phase I, Phase II, and Phase III. This process usually takes more than ten years. If everything goes well, the new drug may then be approved for marketing.

Currently, there are many challenges from basic research to clinical application of new drugs. One is the complexity of biological mechanisms. The structure and function of ion channels are extremely complex and involve a variety of molecules and signaling pathways. The process of gaining a deep understanding of these mechanisms requires a lot of time and resources. The second is the difficulty of drug design. Drugs targeting ion channels need to be highly specific to avoid affecting other normal physiological functions. This requires precise design of drugs at the molecular level. It is a big challenge to develop drugs that can specifically target the diseased site without side effects. The third is preclinical risk assessment. Drugs must undergo strict safety evaluations before entering clinical trials, especially relating to cardiac risk assessment. Fourth is the risks of clinical trials. Drugs need to go through multiple stages of testing in clinical trials to evaluate their safety and effectiveness. There is a risk that clinical trials may fail and be terminated due to insufficient efficacy or side effects.

The blood as a whistle-blower for the brain in AD diagnosis

Alzheimer's disease early diagnostic and staging biomarkers revealed by large-scale cerebrospinal fluid and serum proteomic profiling

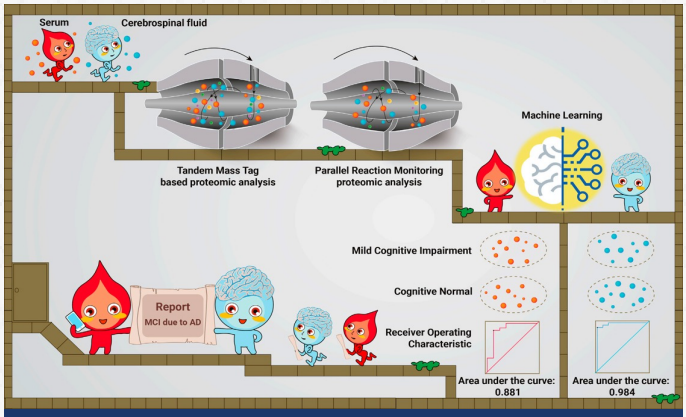
Alzheimer's disease (AD) is the most common type of neurodegenerative disease and its patients typically present with progressive cognitive decline. Its pathology is characterized by the deposition of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). One research framework defining AD on the basis of Aβ deposition, phosphorylated tau (p-tau), and neurodegeneration (ATN) was proposed in 2018. However, such diagnostic biomarkers are not AD specific, and exhibit positivity in individuals with other brain diseases in which AD pathology has been recognized as a comorbidity. Other techniques based upon cerebrospinal fluid (CSF) or positron emission tomography (PET) based biomarkers may be more specific to AD, but these suffer other limitations as first-line diagnostic strategies due to issues such as high cost, insufficient accessibility, and/or invasiveness.

If testing could be simply conducted by taking blood, this would be highly advantageous due to its comparative convenience, minimal invasiveness, and affordability. Recently, several blood-based AD biomarkers, such as the plasma Aβ42/40 ratio, p-tau, neurofilament light polypeptide (NEFL) and glial fibrillary acidic protein (GFAP), have been reported. Notably, plasma tau phosphorylated at threonine 217 (p-tau217) has been shown to be able to accurately determine AD and correlated with Aβ and p-tau pathology in the brain. Nevertheless, plasma biomarkers for Aβ and tau pathology are not currently recommended for use in clinical practice as they still require further standardization and validation. In addition, these clinical manifestations lose their correlation with both Aβ and p-tau protein levels as the disease progresses. Thus, suggests that Aβ and p-tau biomarkers are not suitable for all stages of AD.

Thankfully, converging findings indicate the presence of many additional pathological mechanisms underlying the pathogenesis of AD that are independent of Aβ and p-tau pathology and further comprehensive research is necessary to identify early diagnostic and staging biomarkers for AD.

In response to this clinically challenging issue, an article titled *"Alzheimer's Disease Early Diagnostic and Staging Biomarkers Revealed by Large-Scale Cerebrospinal Fluid and Serum Proteomic Profiling"* was recently published by Prof. **Zhi-Ying Wu**'s team in ***The Innovation journal*** in Jan. 2024.

In this study, researchers performed tandem mass tag (TMT) proteomic analysis of paired cerebrospinal fluid (CSF) and serum samples in a discovery cohort comprised of 98 participants. Candidate biomarkers were validated by parallel reaction monitoring (PRM)-based targeted proteomic assays in an independent multicenter cohort comprising 288 participants. We quantified 3238 CSF and 1702 serum proteins in the discovery cohort, identifying 171 and 860 CSF proteins and 37 and 323 serum proteins as potential early diagnostic and staging biomarkers, respectively. In the validation cohort, 58 and 21 CSF proteins, as well as 12 and 18 serum proteins, were verified as early diagnostic and staging biomarkers, respectively. Separate 19-protein CSF and an 8-protein serum biomarker panels were built by machine learning to accurately differentiate mild cognitive impairment (MCI) due to AD from normal cognition with areas under the curve of 0.984 and 0.881, respectively. The 19-protein CSF biomarker panel also effectively discriminated patients with MCI due to AD from patients with other neurodegenerative diseases. Moreover, we identified 21 CSF and 18 serum stage-associated proteins reflecting AD stages. Our findings provide a foundation for developing blood-based tests for AD screening and staging in clinical practice.



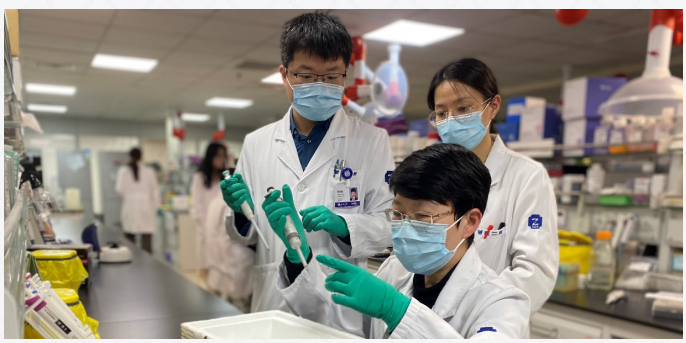
Overview of the research workflow

A proteomic workflow based on Tandem Mass Tag (TMT) was employed to discover potential early diagnostic and staging biomarkers for AD. Subsequently, a targeted proteomic workflow was applied in validation cohorts to confirm early diagnostic and staging biomarkers for AD. Finally, machine learning was utilized to identify the optimal CSF and serum biomarkers for early AD diagnosis.

Tao QQ[#], Cai X[#], Xue YY[#], Ge W[#], Yue L, Li XY, Lin RR, Peng GP, Jiang W, Li S, Zheng KM, Jiang B, Jia JP[*], Guo T[*], Wu ZY[*]. Alzheimer's disease early diagnostic and staging biomarkers revealed by large-scale cerebrospinal fluid and serum proteomic profiling. ***Innovation (Camb)***. 2024 Jan 2;5(1):100544. doi: 10.1016/j.xinn.2023.100544. PMID: 38235188; PMCID: PMC10794110.

ZHI-YING WU'S RESEARCH GROUP

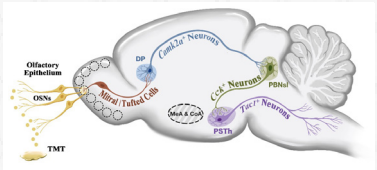
Upon global population aging, neurodegenerative diseases, as typified by Alzheimer's disease, have been increasing as significant public health challenges worldwide. The research team led by Dr. Zhi-Ying Wu focuses on optimizing the diagnosis and treatment of neurodegenerative diseases and rare neurological disorders, as well as investigating their related pathogenic mechanisms. Grounded in clinical practice, the team aims to utilize cutting-edge technologies to address clinical issues through research conducted across multiple levels including population cohorts, animal models, and both cellular and molecular studies. Their work has been published in top international journals including ***Nature Genetics***.



A novel neural pathway from forebrain to hindbrain co-mediating fear and anxiety

Excessive or repetitive fear are important factors leading to anxiety disorders. Whilst the amygdala has been identified as the core brain region related to fear, clinical studies have found that patients with bilateral amygdala damage can still feel and express fear. This suggests the existence of redundant non amygdala located neural mechanisms that can mediate fear responses. However, any such neural mechanisms co-mediating fear along with the amygdala have yet to be clarified.

On February 12, 2024, **Prof. Xiaoming Li**'s team from Zhejiang University School of Medicine published a study in ***Nature Neuroscience***. In this they detail their discovery of the importance of the main olfactory bulb-dorsal peduncular cortex-lateral parabrachial nucleus-parasubthalamic nucleus pathway in expressing fear and anxiety.



Connections of the main olfactory bulb-dorsal peduncular cortex-lateral parabrachial nucleus-parasubthalamic nucleus pathway

The dorsal peduncular cortex cooperates with the amygdala to mediate olfactory mediated innate fear

The olfactory pathway is a common pathway for inducing innate fear in animals. Using 2,4,5-trimethyl-3-thiazoline (TMT), a component similar to fox feces, as a fear stimulus, researchers have shown that mice with apoptosis of cortical amygdala and medial amygdala neurons exhibit significantly reduced aversion and freezing behavior induced by TMT. However, such an amygdala disfunction did not completely block the mice's fear response and had no significant effect on their fear-induced escape behavior. Thus attention was turned to which other brain area might mediate odor-driven innate fear-induced escape behavior.

Our researchers performed whole-brain Fos immunohistochemistry in mice after TMT stimulation and found a significant increase in Fos expression in the dorsal peduncular cortex (DP). The DP was seen to receive specific inputs from the main olfactory bulb (MOB). The MOB-DP neural circuit was then observed to exhibit significantly increased activity after TMT stimulation. By using apoptosis virus to inhibit DP neuron function, researchers then found that mice did not show obvious escape behavior in response to TMT stimulation, with aversion and freezing behavior also significantly decreased. Conversely, optogenetic activation of DP neurons induced escape behavior in mice and led to fear-like responses such as pupil dilation. Conversely, in mice with localized amygdala damage combined with optogenetic inhibition of DP neuron function, the escape behavior induced by TMT almost disappeared with aversion and freezing behavior also further decreasing. Anatomical evidence further showed that the mitral or tufted cells in the MOB projecting to DP and amygdala are segregated. These functional and structural results suggest that DP can co-mediate odor-driven innate fear along with the amygdala.

Tetra-synaptic "relay" mediating fear and anxiety

Using viral tracing and other techniques, our researchers found that DP can form excitatory synaptic connections with cholecystokinin (Cck) positive neurons in the anterior superficial lateral parabrachial nucleus (PBNsl). PBNslCck+ positive neurons can then continue to descend and dominate the tachykinin 1 (Tac1) positive neurons in the parasubthalamic nucleus (PSTh), together outlining a tetra-synaptic neural circuit with molecularly specific markers of $MOB^{Slc17a7+}$→$DP^{Camk2a+}$→anterior $PBNsl^{Cck+}$→$PSTh^{Tac1+}$.

So, does such a tetra-synaptic neural circuit mediate olfactory innate fear? Researchers further discovered that the pathway was significantly activated in TMT-induced escape behavior. Optogenetic inhibition of the pathway significantly reduced escape behavior and rescued innate fear-like behavior. In mice with combined cortical and medial amygdala damage, activation of this pathway still induced escape behavior and could simulate innate fear-like autonomic nervous changes. These research results indicate that the drawn neural circuit from the forebrain to the hindbrain can co-mediate olfactory innate fear along with the amygdala.

As repeated or excessive fear stimuli can lead to anxiety disorders and other mental illnesses, researchers studied the role of this pathway in anxiety and found that continuous optogenetic activation for 3 days, 1 hour per day, resulted in very obvious anxiety-like behavioral phenotypes in mice. However, in mice with acute restraint stress-induced anxiety-like models, inhibition of this pathway significantly reversed anxiety-like behavior, indicating that the pathway can regulate anxiety bidirectionally.

Wang H#, Wang Q#, Cui L#, Feng X#, Dong P, Tan L, Lin L, Lian H, Cao S, Huang H, Cao P, Li XM*. A molecularly defined amygdala-independent tetra-synaptic forebrain-to-hindbrain pathway for odor-driven innate fear and anxiety. ***Nature Neuroscience***. 2024 Mar;27(3):514-526. doi: 10.1038/s41593-023-01562-7. Epub 2024 Feb 12. PMID: 38347199.

XIAOMING LI'S RESEARCH GROUP

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

Recent advances in neuromorphic chips

Darwin3: a large-scale neuromorphic chip supporting a novel ISA and on-chip learning

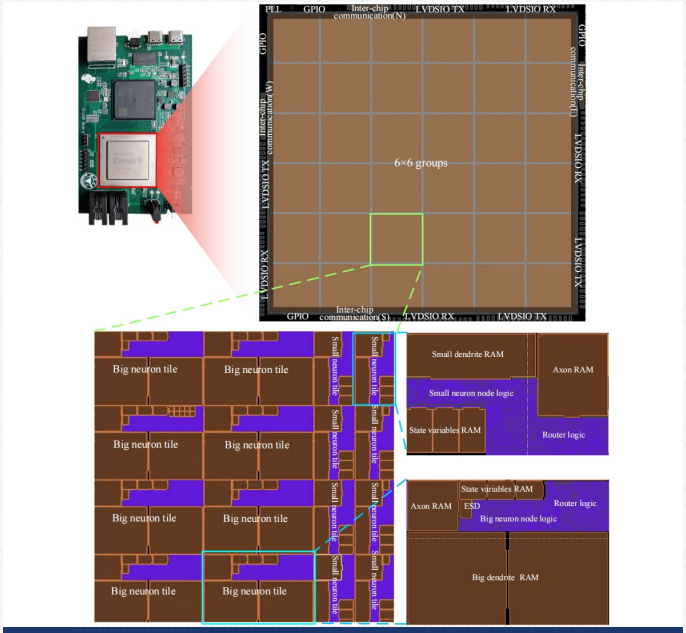
Spiking Neural Networks (SNNs) are computational models. Inspired by the communication methods of neurons in the brain they utilize brief pulses or spikes. Unlike conventional Artificial Neural Networks (ANNs) that operate on continuous signals and focus primarily on weighted sums of inputs, SNNs place significant emphasis on the timing and propagation of these spikes. They process information in an event-driven manner where spikes act as discrete events triggered by inputs that surpass a specific threshold. SNNs strive for biological plausibility by closely mimicking various aspects of brain function including neuron firing rates, synaptic delays, and the dynamic interplay of neural processes. Crucially, the timing and sequence of spikes are pivotal in SNNs, enabling them to capture intricate temporal patterns and dynamics more effectively than their traditional ANN counterparts.

Specialized neuromorphic computing chips are now also being developed to better leverage the benefits of SNNs . These chips represent a departure from traditional computing architecture, offering a promising solution to storage and power constraints in the post-Moore era. However, to fully realize the potential of SNNs researchers face several challenges. Firstly, they must ensure the flexibility of neural models to accurately capture the brain's diverse behaviors. Secondly, they need to address the scalability and density of synaptic connections to effectively support large neural networks. Finally, achieving on-chip learning capabilities is essential for these chips to adapt and improve themselves, like actual brains.

Considering these challenges, Prof. **Gang Pan**'s team at Zhejiang University collaborated with the Zhejiang Lab to develop the Darwin3 neuromorphic chip, the latest version of the Darwin series. A review of their work was recently published in the ***National Science Review***. The team examined numerous neuron and synapse models, analyzed how they work, and identified their key computational aspects. Based on their findings, they proposed a new aspect of instruction set architecture (ISA) specifically for neuromorphic computing. This ISA allows for rapid state updates and parameter loading, enabling efficient construction of various models and learning rules.

Moreover, the research team also developed an effective connection mechanism that enhances on-chip storage efficiency, supporting over 2 million neurons and 100 million synapses on a single chip. This achievement is significant, especially when considering the complex interconnectedness seen in biological neural networks. In the human brain, neurons form connections with thousands of other neurons on average, creating an intricate network crucial for cognitive processes. The proposed connection mechanism provides a strong hardware foundation for building neural networks at scales approaching those of the human brain, ultimately improving computational capacity.

The research team has also made significant advancements in on-chip learning capabilities for Darwin 3, enabling it to smoothly manage new information and dynamic environments within spiking neural networks. Darwin3 therefore excels in supporting Spike-Timing-Dependent Plasticity (STDP) and learning related rules efficiently,



The top left shows a photo of the system test board, with a red box indicating Darwin3. The top right displays the top-level view of the chip layout, while the lower section provides layout details of the main modules. The chip's structure is organized into a grid of 6*6 groups, each consisting of 4*4 tiles. Each tile comprises a node connected to a router. Except for the RISC-V node, all nodes on the chip are neuron cores, collectively driving their computational functions. There are two distinct tile types, differing mainly in the size of their axon-in memory.

while demonstrating flexibility and ease in effortlessly implementing other learning mechanisms. This capability allows Darwin3 to adjust synaptic weights based on the precise timing of spikes between neurons, thus facilitating robust learning processes. Furthermore, Darwin3's versatility extends to accommodating diverse learning paradigms, empowering it to handle complex computational tasks effectively in artificial intelligence applications. These advancements have enhanced Darwin3's adaptability and user-friendliness, demonstrating exceptional performance in demanding scenarios.

In conclusion, multiple sets of experimental results demonstrate Darwin3's impressive capabilities of on-chip learning with the ability to support kinds of SNNs, distinguishing it from other neuromorphic chips. The development of the Darwin3 marks a significant milestone in neuromorphic computing, promising to advance artificial intelligence capabilities.

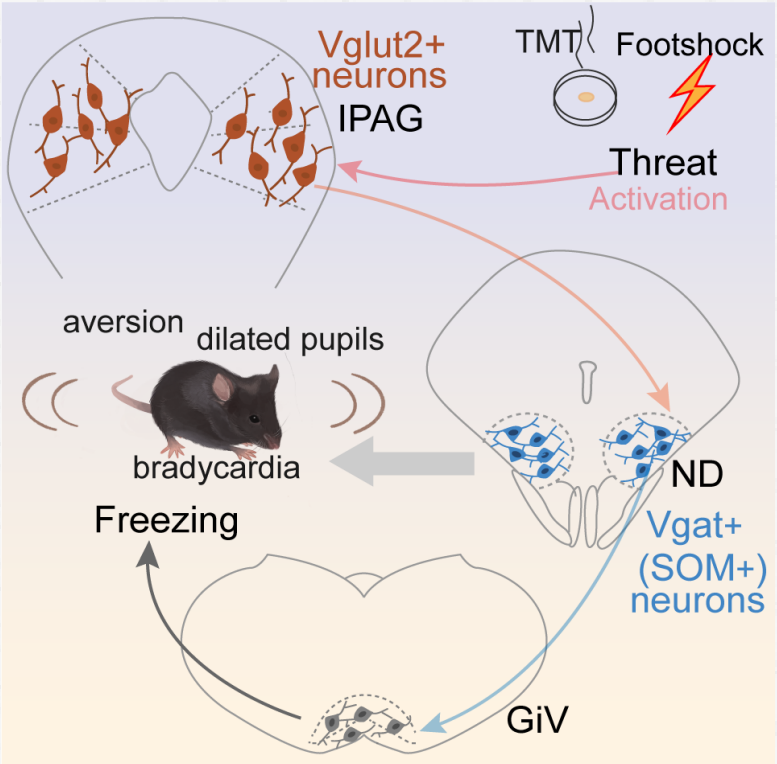
Ma D, Jin X, Sun S, Li Y, Wu X, Hu Y, Yang F, Tang H, Zhu X, Lin P, Pan G. . Darwin3: A Large-scale Neuromorphic Chip With a Novel ISA and On-Chip Learning. ***National Science Review***, 2024 Mar 18;11(5):nwae102. doi: 10.1093/nsr/nwae102. PMID: 38689713; PMCID: PMC11060491.

GANG PAN'S RESEARCH GROUP

The group primarily focuses on critical aspects of brain-machine interaction, fusion, simulation, and enhancement. It includes the study of spiking neural networks, brain-inspired intelligence, neuromorphic devices, neuromorphic computing chips and architectures, neural decoding methods and behavioral control, new brain-machine interfaces and fusion enhancement, human-machine symbiotic intelligence, foundational theories, and key technologies in these areas. They aim to develop new computing models, intelligent forms, and hardware/software architectures.

A novel relay underlying defensive behaviors

Control of defensive behavior via the nucleus of Darkschewitsch GABAergic neurons



NDGABA neurons relay threat information from PAG to the medulla

Threatening situations, such as the presence of a predator, or exposure to other stimuli that may suggest or provoke the perception of imminent danger, evoke the evolutionarily conserved brain state of fear. This then triggers defensive behaviors to avoid or reduce potential harm. Defensive behaviors triggered in response to perceived threat thereby play a fundamental role in survival.

The research team led by Prof. **Yan-qin Yu** has recently published an article titled "*Control of defensive behavior by the nucleus of Darkschewitsch GABAergic neurons*" in ***National Science Review*** on Mar 5th. This research identifies a previously unrecognized role for the $lPAG_{Glu}$-ND_{GABA}-GiV_{Glu} pathway in controlling defensive behaviors.

Over the past few decades, several brain areas including the periaqueductal gray, amygdala, and hypothalamus have been implicated in with involvement in defensive behaviors. The periaqueductal gray (PAG) is noted as a particularly common governor of such defensive behaviors, noted to control a number of its key aspects. Yet, accumulating evidence suggests that the circuitry that mediates fear responses is complex and demonstrates that multiple independent circuits are involved, some of which process different types of fear. However, how the fear response output center selectively generates distinct defensive responses such as freezing, flight, or hiding, remains largely unknown. Many of the nuclei important for defensive behaviors clearly remain to be discovered.

The nucleus of Darkschewitsch (ND), named after the Russian neurologist L. O. Darkshevich, was first described in 1889 as an accessory oculomotor nucleus. It was implicated in the control of eye movement . The ND is mainly composed of GABAergic neurons. However, there has long been a paucity of research on the anatomical outputs and inputs and the physiological functions of GABAergic neurons of the ND. The functional contribution of ND GABAergic neurons (ND_{GABA}) in animal behavior also remains largely unknown.

Here, we show that ND_{GABA} neurons are selectively activated by different types of fear stimuli, such as predator odor and foot-shock. Optogenetic and chemogenetic manipulations reveal that NDGABA neurons mediate freezing behavior. Moreover, using circuit-based optogenetic and neuroanatomical tracing methods, we identified an excitatory pathway from the lateral periaqueductal grey (lPAG) to the ND that induces freezing by exciting ND inhibitory outputs to the gigantocellular reticular nucleus, ventral part (GiV). Interestingly, GABAergic neurons expressing somatostatin (SOM), rather than parvalbumin (PV), were found to be crucial in controlling freezing behavior.

Together, these findings indicate the ND_{GABA} population as a novel hub for controlling defensive responses by relaying fearful information from lPAG to GiV, a mechanism critical for understanding how the freezing behavior is encoded in the mammalian brain. Our results advance the current understanding of how threats selectively trigger freezing as a specific defensive response, via the $lPAG_{Glu}$-ND_{GABA}-GiV_{Glu} circuitry and provide precise anatomical and functional information that is important for the discovery and development of new therapeutic interventions for mood disorders.

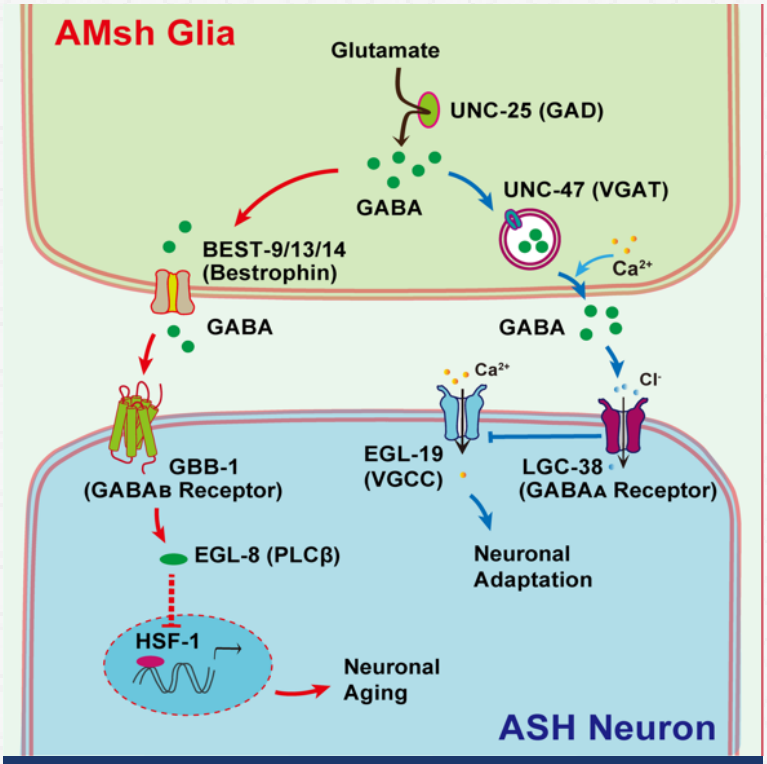
Zhao H#, Liu J#, Shao Y#, Feng X, Zhao B, Sun L, Liu Y, Zeng L, Li XM, Yang H*, Duan S*, Yu YQ*, Control of defensive behavior by the nucleus of Darkschewitsch GABAergic neurons, ***National Science Review***, 2024,11 (4), nwae082. PMID: 38686177; PMCID: PMC11057443.

YANQIN YU'S RESEARCH GROUP

dedicated to understanding the neural basis and mechanisms of innate behaviors including sleepiness, aggression, and fear behavior. Their numerous original research papers have been disseminated in reputable journals, including ***Neuron, eLife, Current Biology*** and ***National Science Review***.

Glia regulate neuronal adaptation and aging

AMsh glial cells modulate olfactory adaptation and neuronal aging through two distinct GABA signaling pathways



Phasic/tonic glial GABA differentially transduce for olfactory adaptation and neuronal aging

Glia play crucial roles in the development, function, and health of the nervous system and brain. In species ranging from *C. elegans* and *Drosophila* to zebrafish, mice, and humans, the origin, structure, and function of glia is noted as highly conserved.

On March 5, 2024, **Lijun Kang** and his team published a research article entitled *"Phasic/Tonic Glial GABA Differentially Transduce for Olfactory Adaptation and Neuronal Aging"* in the journal ***Neuron***. They discovered that AMsh glia regulate real-time olfactory adaptation and long-term neuronal aging through two distinct GABA signaling pathways.

The observation that neurons decrease their activity in response to prolonged stimulation, a process termed adaptation, is one of the fundamental characteristics of the nervous system. Lijun Kang's team had previously revealed that the sheath-like glial cells known as AMsh glia sense odorants via G-protein coupled receptors (GPCRs) in the chemosensory organ of *C. elegans*. These glial cells could release GABA, which acts on the $GABA_A$ receptor LGC-38 in ASH sensory neurons, leading to the inhibition of their activity and thereby promoting olfactory adaptation. This work proposed a dual receptor model involving glial cells and neurons for olfactory sensation, emphasizing the essential role of glial cells as driving forces behind neuronal adaptation (***Neuron*** 2020).

In their recent publication in Neuron, Lijun Kang's team have now demonstrated that AMsh glia elevate cytoplasmic calcium levels upon sensing odorants. This elevation triggers the secretion of GABA from vesicles, a process dependent on the vesicular GABA transporter UNC-47/VGAT. The released GABA then acts on ASH sensory neurons to facilitate olfactory adaptation. Additionally, at resting calcium levels, AMsh glial cells can gradually release GABA through bestrophin ion channels (Best-9/-13/-14), which activates the $GABA_B$ receptor GBB-1 on ASH sensory neurons and regulates the activity of the transcription factor HSF-1 via the PLCβ signaling pathway. This mechanism acts to slow down the aging process of ASH neurons.

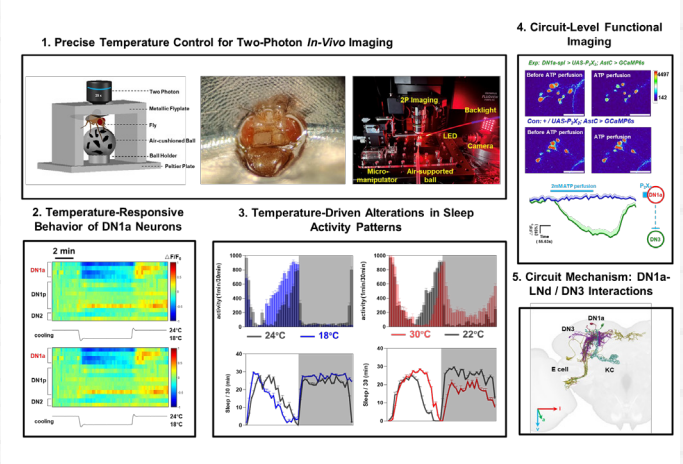
This research has revealed two distinct GABA signaling pathways within the local circuitry involving AMsh glia and ASH sensory neurons: (1) The UNC-47/VGAT--LGC-38/$GABA_A$ fast signaling pathway where the key gene UNC-47 is predominantly expressed in the soma and proximal processes of AMsh glial cells, whilst LGC-38 is localized to the soma and axons of ASH neurons. (2) The Bestrophin channels--GBB-1/$GABA_B$ slow signaling pathway, where the critical proteins, namely the bestrophin channels and GBB-1, are extensively expressed in AMsh glia and ASH neurons, respectively. Notably, UNC-47/VGAT-dependent GABA release is triggered by high calcium levels, whereas bestrophin channels can release GABA under low calcium conditions. Furthermore, GBB-1/$GABA_B$ receptor exhibits higher affinity for GABA compared to the LGC-38/$GABA_A$ receptor. These findings underscore the fundamental significance of glial GABA in maintaining healthy aging and neuronal stability.

Cheng H#, Chen D#, Li X#, Al-Sheikh U, Duan D, Fan Y, Zhu L, Zeng W, Hu Z, Tong X, Zhao G, Zhang Y, Zou W, Duan S, Kang L. Phasic/tonic glial GABA differentially transduce for olfactory adaptation and neuronal aging. ***Neuron***. 2024 May 1;112(9):1473-1486.e6. doi: 10.1016/j.neuron.2024.02.006. Epub 2024 Mar 5. PMID: 38447577.

LIJUN KANG'S RESEARCH GROUP

Employing an interdisciplinary strategy that integrates molecular genetics, optogenetics, calcium imaging, electrophysiology, and behavioral tracking, research carried out in the Kang laboratory is dedicated to unravel the complex molecular mechanisms governing sensory perception, including olfaction, hearing, and tactile sensation. Utilizing *C. elegans* and various other model organisms, the laboratory delves into the physiological roles and mechanisms of glia in regulating sensory circuits. The laboratory also seeks to investigate pharmaceutical approaches for mitigating sensory dysfunctions stemming from genetic anomalies, aging, and other influential factors.

The neural regulatory mechanism behind seasonal sleep patterns



Regulation of temperature-dependent sleep activity by DN1a and its downstream circuits

It is often said that "spring makes you sleepy, fall makes you tired, summer nights are sleepless, and winter is the season of heavy sleep". This leads to the question, "why do our sleep patterns change with the seasons?" Conventional wisdom attributes this to temperature changes. So how exactly does temperature affect the circadian mechanism of sleep activity in animals? On April 2, 2024, Professor **Guo Fang**'s research group from the Institute of Brain Sciences and Brain Medicine at Zhejiang University published a landmark study titled "*Dynamic encoding of temperature in the central circadian circuit coordinates physiological activities*" in the journal ***Nature Communications.***

Among many model organisms, Drosophila has emerged as an ideal model for uncovering the mechanisms of circadian rhythm due to its unique physiological characteristics. Research on the fly's biological clock was recognized with the 2017 Nobel Prize in Physiology or Medicine (received by the laureate Michael Rosbash who also mentored this study). In the fly brain, a neural circuit composed of about 75 pairs of circadian neurons coordinate to orchestrate various feeding, movement, sleep, and wakefulness behaviors at different times of the day. Previous studies have uncovered certain temperature responsive neurons. These include DN1a noted as responsive to low temperatures in the fly brain (Alpert et al., 2020), and DN1p neurons being associated with the physiological activity of flies under temperature changes (Yadlapalli et al., 2018, Jin et al., 2021). However, the core regulator of temperature within the central circadian neural circuit has remained an elusive.

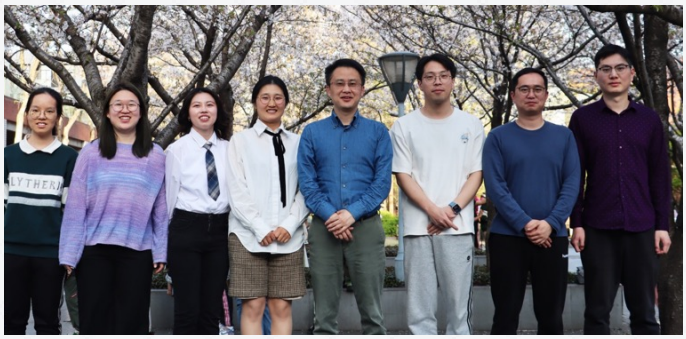
In this study, Professor Guo Fang's team used a custom-built precise temperature control system and in vivo two-photon calcium imaging technology to discover that DN1a neurons are inhibited by low temperatures and excited by high temperatures. In addition, they demonstrated that the response of DN1a to temperature exhibits a rhythmic change - weak during the day and strong at night. Further molecular level studies then revealed the circadian mechanism of the DN1a response to temperature to be controlled by the internal biological clock. Specifically, through RNAi screening they uncovered that the biological clock (circadian protein) regulates the oscillation of the circadian neuron calcium signal through the SERCA calcium pump protein on endoplasmic reticulum. This finding provided important insights into how the biological clock regulates neuronal calcium levels. In addition, the study discovered that, depending on environmental temperature information, DN1a neurons target different circadian neurons. In this LNd was targeted by DN1 to regulate the early evening activities of the fruit fly at cold temperatures (DN1a-LNd), whereas this switched to DN3 which acted to increase in nocturnal activities at higher temperatures (DN1a-DN3).

This study provided crucial insights into the impact of temperature on sleep activity. In the context of global warming, such studies could be highly significant, enabling the mapping of responsive changes in the physiological activities of animals. For example, the incidences of sleep disturbance and anorexia in animals is noted to be increased in high-temperature environments (Siegel, 2022, Gutiérrez et al., 2002). This suggests that global warming may affect physiological activities and disease occurrence in humans and most animals. Although we do not yet fully understand the specific mechanisms by which temperature affects physiological activities in animals, *Drosophila*, as a classic model organism for studying biological circadian rhythms, provides a wealth of genetic tools that will help us to further reveal the conserved signaling pathways and neural mechanisms of physiological activity changes under different temperature environments. By studying the circadian mechanisms of model organisms such as these flies in detail, we can gain valuable clues and insights into the physiological responses of humans and other animals to environmental change.

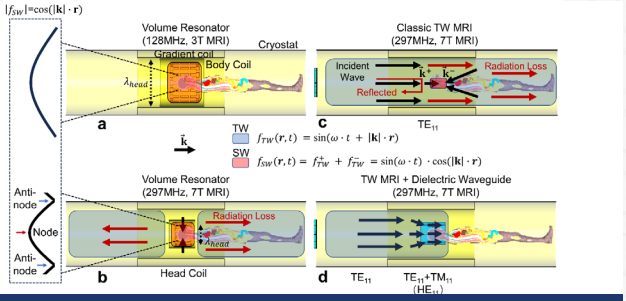
Li H, Li Z, Yuan X, Tian Y, Ye W, Zeng P, Li XM, Guo F. Dynamic encoding of temperature in the central circadian circuit coordinates physiological activities. ***Nat Commun.*** 2024 Apr 2;15(1):2834. doi: 10.1038/s41467-024-47278-5. PMID: 38565846; PMCID: PMC10987497.

FANG GUO'S RESEARCH GROUP

has long been dedicated to elucidating the neural regulatory mechanisms of circadian rhythms and sleep regulation. Their research results have been published in top international journals such as ***Nature***, ***Neuron*** (2018, 2022), ***Nature Communications*** (2024), ***PNAS***, and ***Elife***. The group is currently recruiting postdoctoral fellows, and those interested in the above aspects of neuroscience research are encouraged to contact Professor Guo Fang (email: gfang@zju.edu.cn).



Subwavelength dielectric waveguide for efficient travelling-wave magnetic resonance imaging at ultra-high fields



The schematic diagram of radio-frequency electromagnetic transmission system in 3T and 7T MRI

Uniform excitation of nuclei spins (a concept relating to the movement of atomic nuclei as aligned with or against an external magnetic field) through a B1 magnetic field, (the circular-polarized transverse component of a radio-frequency magnetic field), is the basic principle used for generating unbiased tissue contrasts in magnetic resonance imaging (MRI). Establishing good uniformity is paramount for clinical diagnosis, ensuring accurate and reliable imaging results. However, as we venture into ultra-high field (UHF, 7T and above) MRI systems, (where standard clinical MRI systems typically operate at only 1.5T or 3T), the task becomes increasingly challenging. This is because the 'electrically large' human body, coupled with elevated B1 working frequency demanded by these high-field systems, poses significant difficulties in maintaining B1 homogeneity. This complexity is further compounded by the inherent limitations of existing technologies. While the travelling-wave (TW) system, which utilizes an MRI-embedded waveguide, has shown promise towards improving and solving this issue and enabling large-coverage excitation, its practical application has been hindered by low power transmission efficiency.

On March 14, 2024, Dr. **Xiaotong Zhang**'s research team published an article in ***Nature Communications***, titled *"Subwavelength Dielectric Waveguide for Efficient Travelling-Wave Magnetic Resonance Imaging"*. This study presented a novel approach towards tackling above challenges. Via designing and implementing a subwavelength dielectric waveguide insert, they successfully enhanced both B1 homogeneity and power transmission efficiency at 7T. This technology not only facilitated more uniform excitation but also improves the overall performance of the UHF MRI system.

In the process of its development, the team initially conducted a thorough investigation into the characteristics of dielectric waveguides, focusing on mode conversion, wave impedance matching, energy focusing, and phase velocity matching. Based on these findings, they then carefully designed a hollow dielectric waveguide structure capable of tightly wrapping around electrically large imaging objects, while achieving a transition from a transverse electric mode to transverse magnetic mode within the imaging region. This unique method of mode conversion served to maximize the transverse magnetic field component required for magnetic resonance spin excitation, thereby significantly improving transmission efficiency. Additionally, the team utilized materials with high-dielectric constants to reduce the local wave impedance within the hollow waveguide. This approach was targeted to achieve wave impedance matching and local energy focusing within the waveguide transmission system. This not only enhanced the uniformity and transmission efficiency of B1, but also effectively addressed the challenge of the unevenness of B1 within electrically large objects. Furthermore, the team took full advantage of the continuity of tangential field components at the lossless dielectric boundary. This effectively mitigated the phase velocity mismatch at the dielectric-air interface, providing solid technical support for achieving a more uniform B1 distribution.

After a series of electromagnetic numerical modeling simulations and 7T MRI experiments on human brains, the research team optimized the traditional travelling wave transmission method by integrating the dielectric waveguide structure into the MRI transmission system. Experimental results showed that the MRI signal strength for the human head had increased by more than 114%, while maintaining transmission efficiency comparable to that of the classic resonator (birdcage coil) method. Additionally, this approach effectively suppressed the "center-brightening" phenomenon caused by the standing wave effect, improving the uniformity of MRI signals by more than 22% compared to traditional commercial transmission coils. This improvement not only enhanced the image quality of UHF MRI but also boosted its accuracy.

This study marks a milestone in the advancement of MRI technology, paving the way for more accurate and efficient clinical diagnosis. By overcoming the limitations of traditional systems, Xiaotong Zhang's team has opened new possibilities for human MRI at UHF, bringing us closer to the goal of unbiased tissue imaging and enhanced diagnostic capabilities at 7T.

Gao, Y.*, Liu, T., Hong, T., Fang, Y., Jiang, W. and Zhang, X.* Subwavelength dielectric waveguide for efficient travelling-wave magnetic resonance imaging. ***Nat Commun***. 2024 Mar 14;15(1):2298. doi: 10.1038/s41467-024-46638-5. PMID: 38485742; PMCID: PMC10940709.

XIAOTONG ZHANG'S RESEARCH GROUP

focuses on cutting-edge electrical engineering theories, bioelectromagnetic technologies, and the construction of medical imaging and brain-computer intelligent devices/systems. Over recent years, major progress has been made in their exploration of magnetic resonance radio-frequency engineering (***Nature Communications*** 2024), electromagnetic detection of brain function (***Nature Neuroscience*** 2024; ***IEEE TMI*** 2022, 2018), and electromagnetic neuromodulation (***Science Advances*** 2019).

Neural circuitry underlying social behavioral maladaptation

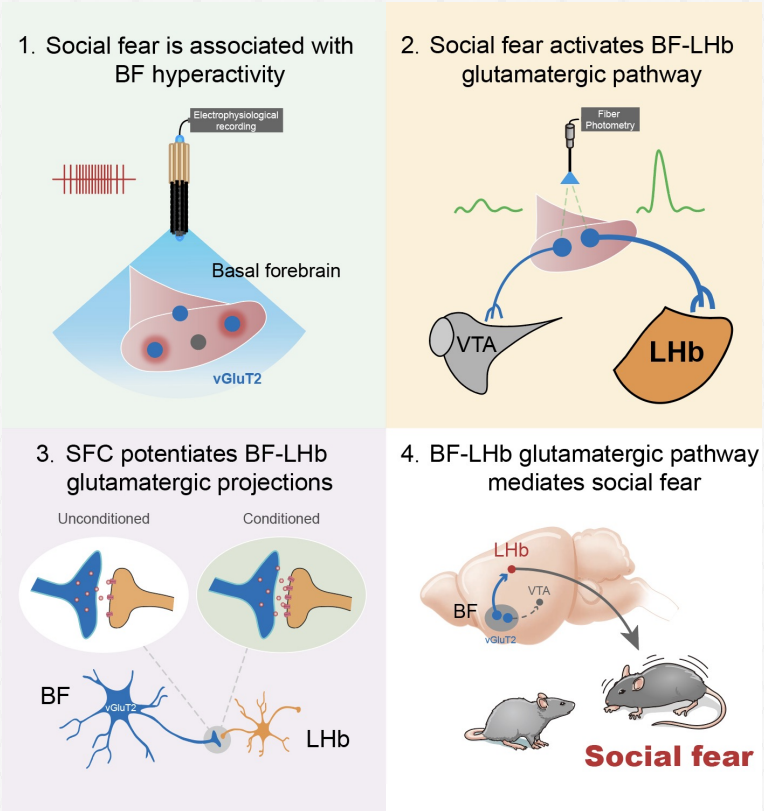
Fear and avoidance responses to social stimuli are typical behavioral symptoms of social phobia, affecting both patients' physical, mental health and social function. Adverse social experiences are significant contributors to the development of social fear. However, the precise mechanisms through which these negative social experiences impact brain function and ultimately lead to social fear behavior remain unclear.

The research team led by Prof. **Han Xu** has recently published an article entitled "*The basal forebrain to lateral habenula circuitry mediates social behavioral maladaptation*" in ***Nature Communications*** online on May 13, 2024. In this research they discovered a novel neural circuit mechanism of glutamatergic neurons in the basal forebrain (BF) mediating social behavioral maladaptation through their projection to the lateral habenula (LHb).

The BF is well-known to be enriched with cholinergic projection neurons, but the functions of the other two main neuron types within the BF—GABAergic and glutamatergic neurons—remain largely unknown. A prior study by Prof. Han Xu's team in 2021 revealed for the first time that a subpopulation of SST-expressing GABAergic neurons in the BF can modulate pro-social behaviors. This finding suggests that the BF receives socially relevant information input and then plays a crucial role in the regulation of social behaviors. However, whether and how the BF directly contributes to social fear behavior remains an important but unresolved question.

In the study of Prof. Han Xu's research team, they first induced social fear behavior in mice using conditioned social fear conditioning (SFC). *In vivo* multichannel electrophysiology and fiber photometry revealed that a large number of vGluT2-expressing glutamatergic neurons in the BF were activated during social fear expression, whereas cholinergic and GABAergic neurons showed no significant changes in their activity. Using neuron type-specific manipulation approaches, they found that inhibition of vGluT2 neurons, but not cholinergic or GABAergic neurons, dramatically attenuated social fear behavior, suggesting that BF glutamatergic neurons play an essential and particular role in the expression of social fear.

This result led the team to further question which downstream targets BF vGluT2 neurons mediate social fear. They first used viral tracing and brain slice patch-clamp recordings to reveal that vGluT2 neurons have close anatomical connectivity and monosynaptic functional links with both the ventral tegmental area (VTA) and lateral habenula (LHb). Interestingly, BF vGluT2→LHb projections were selectively activated during social fear behaviors. Specific inhibition of the BF vGluT2→LHb projection significantly reduced social fear in mice, while inhibition of BF vGluT2→VTA projections failed to alter social fear behaviors. Finally, using brain slice patch clamp techniques, they found that social fear conditioning enhanced the glutamatergic synaptic connections from the BF to the LH. This may serve as a potential synaptic mechanism underlying social fear modulation via this neural circuit.



This study proposes a novel mechanism of social fear expression that centers on the BF at the circuit and cellular level. This sheds light on our understanding of the neural basis of social anxiety disorders and may provide new targets for the treatment of social fear-related neuropsychiatric disorders in the future.

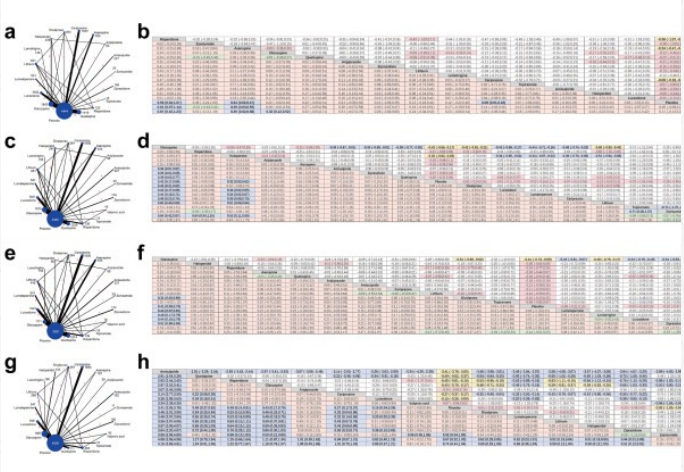
Wang J#*, Yang Q#, Liu X#, Li J#, Wen YL, Hu YZ, Xu TL, Duan SM, Xu H*. The basal forebrain to lateral habenula circuitry mediates social behavioral maladaptation. ***Nature Communications***. 2024 May 13;15(1):4013. doi: 10.1038/s41467-024-48378-y. PMID: 38740778; PMCID: PMC11091113.

HAN XU'S RESEARCH GROUP

Social dysfunction is a common symptom of many neuropsychiatric disorders such as anxiety disorders, depression, autism, etc. It seriously affects the patients' daily life and work and imposes a heavy mental and economic burden on the patients' families and society. Prof. Han Xu's team focuses on neuronal circuits underlying social interaction behavior and social deficits associated with neuropsychiatric disorders.

Baseline demographic characteristics may influence clinical decision-making

The effect of antipsychotics and mood stabilizers on themetabolism of patients with bipolar disorder



Network maps and league tables presenting head-to-head comparisons of fasting serum glucose, total cholesterol, total triglyceride, and body weight.

Bipolar disorder (BD), characterized by fluctuating mood and behavior, is a serious psychiatric disorder with adverse outcomes and poor long-term prognosis if untreated. Current pharmacotherapies for BD are mainly second-generation antipsychotics and mood stabilizers. However, metabolic abnormalities are often observed in BD patients treated with these drugs which may eventually progress to obesity, type II diabetes, and/or coronary heart disease. However, to date, no studies have systematically analyzed and ranked these interventions by their effect on metabolism.

In March, 2024, The research team of Prof. **Shaohua Hu** from the First Affiliated Hospital of Zhejiang University School of Medicine published a network meta-analysis based on Bayesian theory online in ***eClinicalMedicine***, a subsidiary journal of Lancet. The study ranked 17 commonly-used antipsychotics and mood stabilizers (Lithium, Valproic Acid, Divalproex, Lamotrigine, Topiramate, Zonisamide, Quetiapine, Lurasidone, Aripiprazole, Ziprasidone, Risperidone, Olanzapine, Haloperidol, Asenapine, Cariprazine, Lumateperone, and Amisulpride) for 12 metabolic indicators. Subgroup analyses were performed for age range, sex ratio, race, current episode, intervention duration, and baseline medication.

A total of 41 published randomized-controlled trials (RCTS) were included in the network meta-analysis after a detailed search of 6 literature databases. The possibility of high publication bias was additionally assessed for 4 studies. Comprehensive analysis showed that antipsychotics generally displayed stronger metabolic effect than mood stabilizers, while mood stabilizers were generally ranked after placebo.

Comprehensive ranking was also performed based on SUCRA and ranking results of five representative indicators (fasting blood glucose, total cholesterol, total triglyceride, low-density lipoprotein, and body weight) provided. Olanzapine was recognized as having the most adverse effects on metabolism, while Lumateperone, a recently-approved antipsychotic, showed relatively mild effects on metabolism. No notable alternations were observed before and after the sensitivity check.

Subgroup analysis suggested that Quetiapine was more likely to affect glucose metabolism among male BD patients with current manic/hypomanic or mixed status and with baseline medication, while long-term Lurasidone treatment (over 6 weeks) tended to affect glucose metabolism among female BD patients with current depressive episodes. Lurasidone might have greater effects on glucose metabolism on adults than adolescents. In addition, for adolescent patients under 18 years old, Divalproex tended to have a greater affect upon glucose metabolism, while lithium showed a more pronounced effect on lipid metabolism. Subgroup differences in the use of Risperidone were also observed.

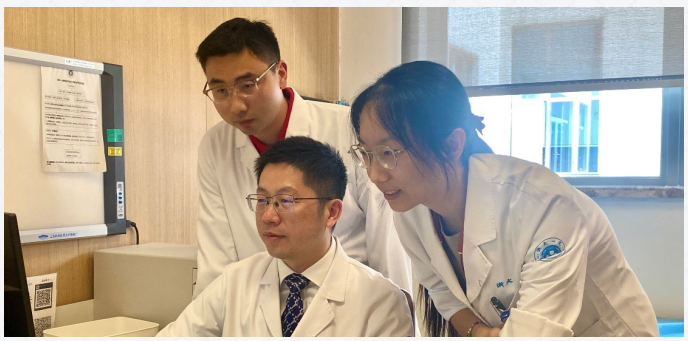
Based on the applicable data, a binary meta-analysis of efficacy and tolerability was also performed. The observed indicators were response rate, remission rate, and dropout rate. Combined effect size was expressed as a binary variable. It was found that most antipsychotics were more effective than placebo and were similarly tolerated. However, Olanzapine was less tolerated than placebo. No between-group difference was noted between mood stabilizers and placebo.

Although limitations exist for the relatively small amount of included studies and interventions, the results of this study still put forward evidence-based information in support of the need for further research into personalized pharmacotherapy and towards deeper insight into BD mechanisms. Larger cohort studies and corresponding pre-clinical studies are also in demand to further elucidate drug-induced metabolic dysregulation occurring in stages of psychiatric disorders.

Kong L[#], Wang H[#], Yan N, Xu C, Chen Y, Zeng Y, Guo X, Lu J[*], Hu S[*]. Effect of antipsychotics and mood stabilisers on metabolism in bipolar disorder: a network meta-analysis of randomised-controlled trials. ***EClinicalMedicine***. 2024 Apr 5;71:102581. doi: 10.1016/j.eclinm.2024.102581. PMID: 38618207; PMCID: PMC11015341.

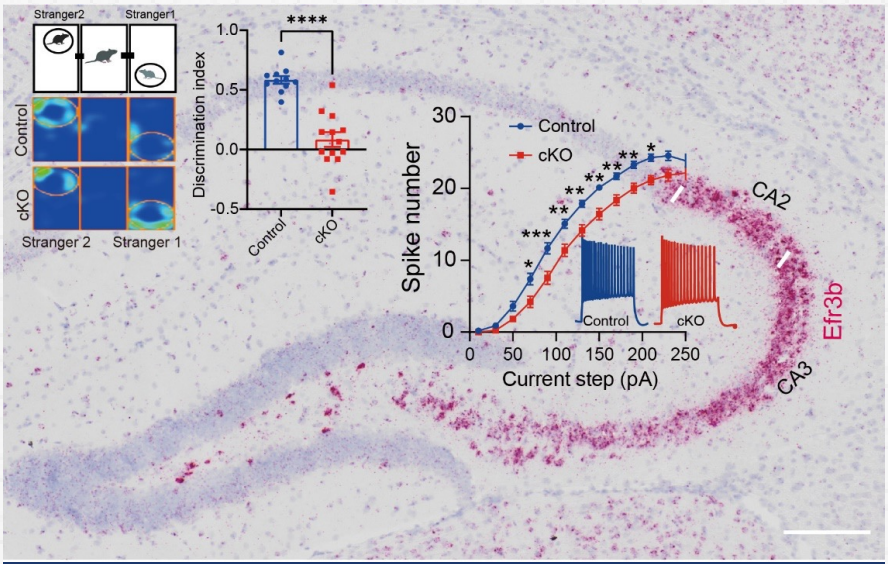
SHAOHUA HU'S RESEARCH GROUP

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



Have I met you before?

Exploring the mechanisms underlying the effects of the excitability of CA2 pyramidal neurons on social recognition of mice



Efr3b is highly enriched in the fields of CA2 and CA3, and deficiency of Efr3b may lead to social deficits by reducing the excitability of CA2 PNs.

Social behaviors such as social interaction, social recognition, or social memory, are essential for daily life in both social animals and humans. Conversely, social disorders such as social withdrawal, social anxiety, or social isolation, are associated with different types of neurological and psychiatric diseases. Investigation of the molecular, cellular, and circuitry mechanisms of social behaviors could lead to greater understanding of, and potential treatments for, such conditions.

We have long known that the anterior cingulate cortex (ACC) plays a key role in social behavior. However, more recent reports have indicated that CA2 pyramidal neurons (PNs) are also important for regulating social recognition. However, the detailed mechanisms for both cases remain to be further elucidated.

Recently, an article entitled *"Efr3b is essential in social recognition by regulating the excitability of CA2 pyramidal neurons"* was published in ***PNAS***. Its authors were from the laboratory of Dr. **Binggui Sun** at Zhejiang University School of Brain Science and Brain Medicine.

Eighty-five requiring 3 (Efr3) is the yeast and mammalian homologue of rolling blackout (RBO) in *Drosophila*. RBO has been reported to be an integral plasma membrane lipase which is essential for phototransduction in Drosophila and required for bulk endocytosis and synaptic vesicle exocytosis. Mammalian Efr3 includes two isoforms, Efr3a and Efr3b. Previous studies using quantitative PCR revealed both Efr3a and Efr3b to be highly expressed in brain. However, any related physiological functions for these two isoforms remained obscure.

In their study, Wei et al performed RNAscope for detection and quantification of these isoforms. They found that Efr3b was highly enriched in the hippocampal CA2/CA3 area. They then crossed Nestin-Cre mice with Efr3b$^{f/f}$ mice to delete Efr3b in the brain. Behavioral tests showed that deleting Efr3b in the brain significantly impaired social novelty recognition without affecting social interaction, spatial learning and memory, anxiety or the fear memory of mice. Deleting Efr3b in the brain also reduced the excitability of CA2 PNs. This suggested that deficiency of Efr3b may result in social deficits via decreasing the excitability of CA2 PNs.

To further characterize the function of Efr3b, Wei et al knocked down the expression of Efr3b specifically in CA2 PNs of C57BL/6J mice. Their results showed that reducing Efr3b in CA2 PNs leads to deficits of social novelty recognition and hypoexcitability of CA2 PNs. More interestingly, restoring the expression of Efr3b in CA2 PNs enhances the excitability and improves social novelty recognition in Efr3b-deficient mice. Direct activation of CA2 PNs with chemogenetics also improves social behaviors in Efr3b-deficient mice. Together, their data suggest that Efr3b is essential for social novelty recognition by modulating the excitability of CA2 PNs.

This important study provides evidence that Efr3b is important in maintaining the excitability of CA2 PNs. Dysregulation of Efr3b may affect the excitability of CA2 PNs then leading to deficits in social behavior.

Wei X#, Wang J#, Yang E, Zhang Y, Qian Q, Li X, Huang F, Sun B*. Efr3b is essential for social recognition by modulating the excitability of CA2 pyramidal neurons. ***Proceedings of the National Academy of Sciences***. 2024 Jan 16;121(3):e2314557121. doi: 10.1073/pnas.2314557121. Epub 2024 Jan 8. PMID: 38190534; PMCID: PMC10801834.

BINGGUI SUN'S RESEARCH GROUP

Dr. Binggui Sun's laboratory is working on the study of multiple aspects of Alzheimer's disease. Currently, they are applying multiple approaches such as electrophysiology, fiber photometry, chemogetic and optogenetic modulation, cellular and molecular biology, and behavioral tests, to investigate the mechanisms underlying the aberrant activity/excitability of hippocampal neurons in mouse models of Alzheimer's disease.

The 2023 Zhejiang University "Brain and Brain-Machine Project" Academic Annual Meeting and the 277th West Lake Academic Forum and Annual Commendation Ceremony

The conference format includes conference reports, young doctoral forums, graduate poster exhibitions, and annual commendation ceremonies. Notably, Professor Shengxi Wu from the Air Force Medical University was invited to deliver a special report. The Brain Institute and BBMI will continue to focus on the researches in two core areas—human brain and machine brain—aligned with national strategic priorities. Leveraging high-level platforms as a foundation, major fundamental scientific questions as a guide, and interdisciplinary research as a hallmark, they will continue to advance the convergence of brain science and artificial intelligence through interactive exploration and integrated innovation, striving to reach new heights in science and technology.

2024 FRONTIERS IN NEUROSCIENCE

The conference focused on cutting-edge topics in brain science and explored the latest research advancements in basic neuroscience, clinical treatments, and translational applications. This forum invited 24 experts and scholars from China and abroad to give academic reports. The Neuroscience Frontier Forum is part of a series of events commemorating the fifth anniversary of the School of Brain Science and Brain Medicine at Zhejiang University. It serves as an academic platform for dialogue on cutting-edge neuroscience topics and aims to foster international collaboration and exchange in the field.

- **Academician Guoping Feng**
  Massachusetts Institute of Technology
- **Prof. Tara Keck**
  University College London, School of Life Sciences
- **Prof. Lasana Harris**
  University College London, School of Brain Sciences
- **Prof. James Cox**
  University College London, Institute of Mental Health
- **Prof. Alexander Gourine**
  University College London, Department of Neurophysiology
- **Prof. Stefan Trapp**
  University College London, Department of Neurophysiology
- **Prof. Mala Shah**
  University College London, Department of Neurophysiology
- **Researcher Ian Harrison**
  University College London, Department of Imaging
- **Researcher Sarah White**
  University College London, Institute of Neurocognition
- **Associate Prof. Simon Beggs**
  University College London, Department of Neurobiology
- **Lecturer Jeremy Skipper**
  University College London, Department of Experimental Psychology
- **Dr. Ceci Qing Cai**
  University College London, Institute of Neurocognition

2023 Most Cited Chinese Researchers

Hailan Hu • Biology

Shumin Duan • Basic Medicine

Tao Li • Clinical Medicine

Second Prize of National Natural Science Award

The project

"*Research on the brain mechanism of depression caused by negative emotions and social competition*"

won the second prize of National Natural Science Award

Prof. Hailan Hu

Research group of Hailan Hu

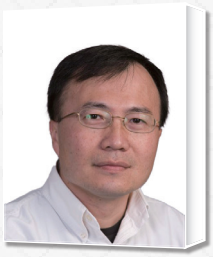
The BBMI Academic Reports

Prof. Shengxi Wu
Air Force Medical University
Jan. 22nd, 2024
Synaptic Homeostasis in the Anterior Cingulate Cortex: A Convergence of Genetic and Environmental Factors in Social Dysfunction

Prof. Peng Xie
NHC Key Laboratory of Diagnosis and Treatment on Brain Functional Diseases
Apr. 23rd, 2024
Exploring the gut-brain Axis: Potential therapeutic impact on Major depressive disorder

Prof. Volker Haucke
Freie Universität Berlin
Apr. 30th, 2024
Lipid switches in cell physiology: From nutrient signals to disease

Prof. Zhenyu Yue
Icahn School of Medicine at Mount Sinai
May 9th, 2024
The Landscape of Autophagy in the Brain, Neurological Disorders, and Beyond



Prof. Jing Wang
University of California, San Diego
May 13th, 2024
The Hierarchical Organization of Needs and The Gut's Influence

Decoding the neural mechanisms of autism

An Interview with Professor Jianhong Luo

Autism is strongly influenced by genetic factors with numerous autism-related genes having been now identified. How do these different gene mutations lead to similar pathologies? Is there a common downstream mechanism underlying these varied genetic mutations?

Jianhong Luo: Autism is a spectrum disorder characterized by significant clinical heterogeneity. Its diagnosis is based on two common clinical symptoms, firstly disturbances in social interaction and communication, and secondly stereotypical repetitive behaviors. Autism is strongly associated with heredity, where literature reports heritability rates ranging from 60% to 90%, higher than those for schizophrenia. However, large-scale sequencing studies has confirmed that autism is predominantly sporadic, characterizing it as a disease with a multi-gene background and often accompanied by novel mutations. Approximately one thousand risk genes have been identified, many of which lack phenotypic expression and do not exhibit sufficient similarities in mouse models. However, a small number, about three dozen risk genes, have been identified in the population whose phenotypes are observable in genetically modified mouse models. These genes are considered to be single-gene pathogenic genes. We hypothesize that these gene defects may share a common neuropathological mechanism that ultimately leads to a common phenotypic risk of autism.

These autism risk genes are classified into two functional categories: those involved in synaptic function and those involved in the regulation of gene transcriptional expression. From the perspective of biochemical and cellular function, these two types of genes primarily affect the function of neurons and synaptic transmission. Although a few synapse-related receptors and ion channels have also been identified as risk genes, most risk genes are associated with scaffold proteins and adhesion proteins involved in synaptic transmission structures. Therefore, when these genes are mutated they often impact the function of synaptic receptors and presynaptic vesicle release, thereby altering synaptic transmission function. Current research has focused on the general damage to synaptic plasticity and neurons caused by autism-related risk genes. Building on this, we aim to explore whether mutations in these risk genes affect specific neural circuits at the neural network level. For example, the dorsal striatum and its downstream pallidum, which are part of the direct and indirect pathways that control motor functions, are directly associated with repetitive and stereotypical behaviors. We also focus on the prefrontal cortex (PFC), as damage to this region is common in both autistic patients and mouse models. Such damage may be associated with impairments in social behavior. Our previous work utilized neurolinker (NL3) mutated mice and revealed that NL3 is essential for the maturation of the prefrontal cortex (PFC). We recently published a study in "***Molecular Psychiatry***" demonstrating that dysfunction in the PFC-nucleus accumbens circuit and midbrain-limbic dopamine modulation in this mouse model leads to impaired cognitive flexibility, a characteristic seen in various psychiatric disorders including autism and schizophrenia.

Therefore, we believe that common pathological mechanisms exist in autism and can be identified at the circuit level. However, significant complexity arises from the unique phenotype of each individual where, in humans, the phenotype of each individual is highly heterogeneous. Although we broadly categorize manifestations into either social dysfunction or stereotypical repetitive behaviors, specific manifestations vary for each patient. In contrast, the observable behavioral phenotype in mouse models remains relatively simple, making it a significant challenge to extrapolate findings to the understanding of human behavior.

What are your thoughts on the various animal models used in basic research, and what recommendations do you have for the future direction of basic research on autism?

Jianhong Luo: If a monogenic pathogenicity mouse model develops autism-like social impairments it may have damage to a broad neural network. In this case specific genes may affect different circuits. For example, we have recently developed a mutant model of CHD8, an important molecule for chromatin remodeling and transcriptional regulation. CHD8 influences the expression of a range of proteins in neurons making it critical for neurodevelopment. Mice with the CHD8 mutation exhibit macrocephaly and a typical autism phenotypes. Further investigation of the mPFC microcircuit revealed significant differences compared to the circuit affected by another widely studied mutation, Shank3. Therefore, while different gene mutations can cause similar impairments in socially related behaviors, the underlying neural circuits affected by these mutations may differ considerably. To date, no two mutated genes have been found to affect neural circuits in a completely consistent manner. By contrast, at the synaptic level, different gene mutations share certain commonalities. For example, NMDA receptors, which are crucial for synaptic plasticity, are also particularly vulnerable in autism. We found that NL3 mutations lead to the downregulation of NMDA receptor expression and function in the mPFC, impairing synaptic plasticity and causing social deficits. However, in some models, NMDA receptor expression is upregulated. Therefore, studying the mechanisms by which different gene mutations contribute to the autism phenotype remains a significant challenge, particularly in identifying common mechanisms through single-gene models.

I believe a more straightforward path is to discover the optimal therapeutic target through single-gene research which emphasizes the advantage of using non-human primate models where such studies can contribute effectively to the development of gene therapy. In this regard, I prefer to begin with some of the most significant single-gene mutations with high incidence, such as those associated with Shank3 and CHD8, which together account for about 8% of the entire autism spectrum. Yet how do we translate ongoing studies into clinical value? This is crucial for autism research. While other drugs are being developed, I believe that for autism, drug development should not only aim for broad coverage but should also be closely aligned with specific genetic mutations. Because autism spectrum disorders represent a highly heterogeneous population, potential adaptive autism subgroups need to be re-evaluated when conducting relevant clinical trials. In fact, existing interventions, including physical regulation through intestinal microecological modulation, NMDA receptor agonists, and related clinical trials, have been less effective due to poor categorization and sample selection of autism spectrum disorders. The development of drugs for autism spectrum disorders therefore differs from that in many other diseases. It should be subdivided based on genetic background, clinical phenotype, and functional imaging results, and further combined with basic research. Subsequently, drug development should be tailored for each subgroup.

How do brain computer interfaces and other aspects such as physical therapy contribute to the field of autism treatment?

Jianhong Luo: I believe that for mental diseases, particularly those without effective corresponding medicine, therapy through physical modulation remains an exciting and promising direction. Currently, there are two main methods. One is a new approach based on traditional rehabilitation training, which primarily involves the incorporation of closed-loop stimulation. This method trains specific neural activities using VR and other techniques while simultaneously monitoring neural activities through EEG recordings and other methods to evaluate the training effect. This then allows for further adjustments to the training mode. Second, transcranial magnetic stimulation technology, developed over recent years, has shown positive progress in some clinical trials. However, it still requires time to accumulate sufficient data, primarily due to the high heterogeneity of autism spectrum disorders. Individual patients may have varying degrees of damage in different brain regions. In the future, there might be hope to combine the abovementioned technology with MRI to achieve more precise treatment.

What is the current focus of societal and governmental attention on the autism spectrum, and what are the support policies for patients and their families?

Jianhong Luo: Currently, many improvements in the support of disabled people in China are developed rapidly. Once children with autism are diagnosed they can receive government support through the Disabled Persons' Federation. This support primarily focuses on rehabilitation and includes access to rehabilitation institutions and special schools. Overall, there is a steady increase in societal attention and support for autism. For example, the Zhejiang Foundation for Disabled Persons has established a special research project on autism, with funds donated by entrepreneurs. Despite substantial social support, the impact and burden of autism on the entire family remain significant. There is much more that needs to be done to meet the needs of children and families affected by autism. Autism is not a rare disease; it affects 1% to 2% of the population, which constitutes a sizable group requiring considerable attention and support.

Jianhong Luo

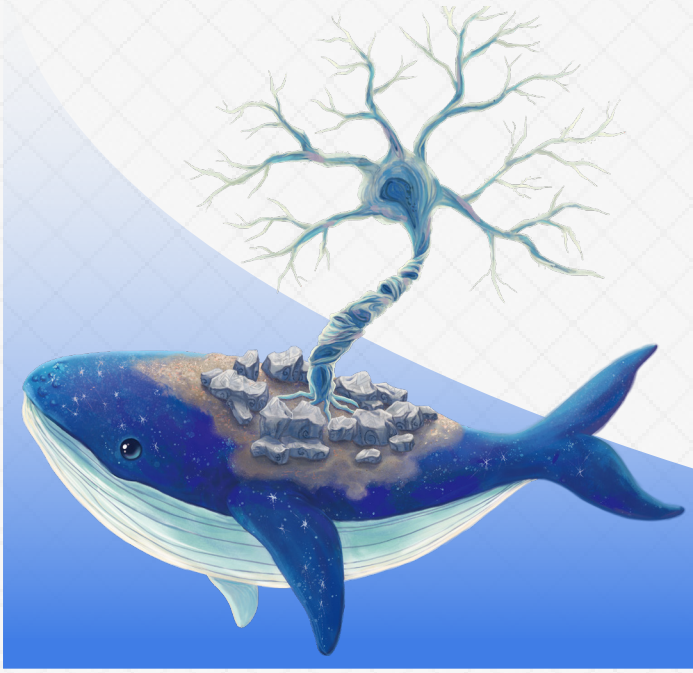
Jianhong Luo is a professor at the Department of Brain Science and Brain Medicine, Zhejiang University School of Medicine. Recently, his lab focuses on molecular, synaptic, and circuitry mechanisms for social deficits, abnormal aggression, and behavioral inflexibility in mouse models of autism by using in vivo electrophysiological recording and fiber photometry, genetic and pharmacological manipulation, and various in vitro procedures, and explores potential therapeutic targets for these annoying symptoms.

Under your initiative, the Zhejiang Neuroscience Society established the Autism Committee. What role has this committee played in the diagnosis, treatment, and basic research of autism?

Jianhong Luo: Throughout my tenure in autism research, I have encountered numerous colleagues dedicated to the diagnosis and rehabilitation of autism. Additionally, I spearheaded a significant project focused on the diagnosis and treatment of autism in Guangdong Province. Through this experience I have come to realize the urgent need for a platform that bridges basic research with clinical diagnosis. Currently, numerous institutions are involved in autism rehabilitation within society, many of which have emerged in recent years. However, the professional standards of these institutions require enhancement. Some emerging technology companies, particularly those focused on digital rehabilitation, have developed numerous computer-assisted and even AI-assisted assessment tools to aid in rehabilitation. This prompted my belief in the necessity of such a platform, which has now been established and has received a positive response. Now in its fourth year, the platform encompasses a broad spectrum of activities ranging from basic research to a wide array of autism-related social organizations which include numerous parents of children with autism. Its primary advantage lies in facilitating communication and collaboration among diverse stakeholders dedicated to autism advocacy and support. Through the research and efforts of various groups we can enhance our understanding of autism, gain insights into the progress of research, and explore emerging rehabilitation methods such as advancements in neural regulation and drug development. Additionally, researchers can acquire a deeper understanding of the real-life experiences of autistic children and their families.

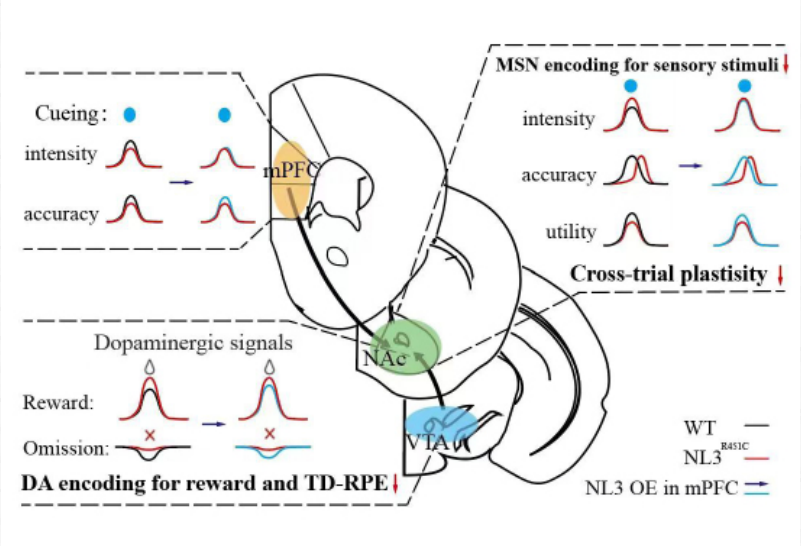
How do you envision the BBMI contributing to autism research or benefiting the patient community?

Jianhong Luo: The BBMI is advancing both basic research and brain-computer interface development. Alongside our lab, other researchers focus on the relationship between environmental factors and autism. For instance, Professor Yudong Zhou investigates the connection between infection, immunity, and the pathogenesis of autism. Many researchers, including Professors Hailan Hu and Han Xu, have investigated the neural mechanisms underlying social behavior, encompassing both physiological and pathological aspects, thereby enhancing our understanding of autism's neural mechanisms. I believe, in this way, the BBMI provides fertile ground for studying the neurobiological mechanisms of various neuropsychiatric disorders. Furthermore, the development of neuroregulatory technologies is a promising direction. Autism serves as a particularly valuable starting point, especially in regulating specific brain wave oscillations which may then be applied to interventions targeting complex behaviors such as social functioning. A prior study within our group indicated that enhancing gamma oscillations in the prefrontal lobe could improve social behavior. I am confident that the interdisciplinary collaboration and innovation fostered by the BBMI will undoubtedly shed new light on autism research and treatment.



Dysfunction of prefronto-striatal circuitry underlies cognitive inflexibility in NL3 R451C mouse model of autism

Cognitive flexibility, essential for executive functions, enables individuals to adapt to changing environments and make appropriate decisions. This capability is particularly compromised in individuals with Autism Spectrum Disorder (ASD), a complex neurodevelopmental condition characterized by social deficits, repetitive behaviors, and restricted interests. Despite the prevalence of cognitive flexibility deficits in ASD, the underlying neural mechanisms have remained elusive.



The PFC-Striatum Mechanism of Cognitive Inflexibility in ASD

On March 8, 2024, Prof. **Jianhong Luo**'s team from Zhejiang University's Institute of Brain Science and Brain Medicine published a paper titled *"Frontostriatal Circuit Dysfunction Leads to Cognitive Inflexibility in Neuroligin-3 R451C Knockin Mice"* in ***Molecular Psychiatry***. This study uncovered the dysfunction in the prefrontal-striatal circuit leading to cognitive inflexibility in the NL3R451C autism mouse model, offering new directions for potential interventions.

The Neuroligin-3 (NL3) gene, crucial for synapse formation and function, has been linked to ASD through the R451C missense mutation. The team developed the NL3R451C knock-in (KI) mouse model, which exhibits autism-like social behaviors. A choice selection task revealed that NL3R451C mice had lower correction rates, increased repetitive errors, and prolonged response times. This indicated deficits in response to changing task demands that mirror the cognitive flexibility challenges observed in individuals with ASD.

Central to the study was the examination of the nucleus accumbens (NAc), a key region involved in behavioral selection and a primary target of the midbrain dopamine system in reinforcement learning. Through innovative in vivo single-neuron recording and computational neuroscience methods, the research team assessed the response intensity, discrimination accuracy, and information utilization efficiency of NAc medium spiny neurons (pMSNs). Results showed that while NL3R451C mice had enhanced responses to cues, the accuracy and efficiency of their neural encoding were significantly diminished. This nuanced analysis provided a deeper understanding of the abnormal stimulus responses in autism, challenging previous assumptions based solely on discharge intensity as a measure of neural encoding strength.

The research further examined anticipatory encoding, a fundamental element of decision-making involved in reinforcement learning. The study demonstrated that excessive reliance on previous choices significantly impaired the flexibility of anticipatory encoding in NAc pMSNs in NL3R451C mice. This suggests reduced experience-dependent neural plasticity, leading to rigidity in anticipatory encoding, a characteristic often seen in ASD.

Additionally, the study explored the dynamics of midbrain-limbic dopamine (DA) signaling regarding reward and reward prediction error (RPE). It was found that DA responses in NL3R451C mice during reward acquisition or omission were markedly different from those in wild-type mice, particularly during reward omission. This seems to indicate a disruption in DA signals and RPE. This disruption could hinder the acquisition of new strategies and impair cognitive flexibility.

Another pivotal aspect of the research was the examination of the medial prefrontal cortex (mPFC)-NAc circuit. Optogenetic calcium signal recording revealed impaired activity in this circuit in NL3R451C mice. Remarkably, re-expressing wild-type NL3 in the mPFC not only rescued the behavioral phenotype but also improved cue encoding precision in the mPFC-NAc circuit and the accuracy of NAc MSN encoding for cue stimuli. This highlighted the critical role of the mPFC in the cognitive flexibility deficits observed in NL3R451C mice.

This comprehensive study elucidates the dysfunctional relationship between the prefrontal cortex-striatal circuit and the midbrain-limbic dopamine system in NL3R451C mice, underscoring the etiological role of the prefrontal cortex in impaired cognitive flexibility. It significantly advances our understanding of the neural mechanisms behind cognitive flexibility deficits in ASD. By shedding light on these complex neural pathways, the study opens new avenues for developing targeted interventions, offering hope for improving the lives of individuals with ASD.

Lin S[#*], Fan C[#], Wang H[#], Li X, Zeng J, Lan P, Li H, Zhang B, Hu C, Xu J[*], Luo J[*]. Frontostriatal circuit dysfunction leads to cognitive inflexibility in neuroligin-3 R451C knockin mice. ***Molecular Psychiatry***. 2024 Mar 8. doi: 10.1038/s41380-024-02505-9. Epub ahead of print. Erratum in: Mol Psychiatry. 2024 Jul 23. doi: 10.1038/s41380-024-02658-7. PMID: 38459194.

JIANHONG LUO'S RESEARCH GROUP

focuses on molecular, synaptic, and circuitry mechanisms for social deficits, abnormal aggression, and behavioral inflexibility in mouse models of autism. Using in vivo electrophysiological recording and fiber photometry, genetic and pharmacological manipulation, and various in vitro procedures, the lab explores potential therapeutic targets for these symptoms.

Kindness with professionalism opens the hearts of autistic children

An Interview with Professor Zhiwei Zhu

What constitutes the clinical definition of autism from the perspective of it being a neural developmental disorder? What are the primary clinical symptons and underlying causes of autism?

Zhiwei Zhu: Autism is a recognized neurodevelopmental disorder characterized by abnormalities occurring during development relating to the structure and function of the nervous system. It particularly affects social brain function and the development of social-related neural circuits. Autism typically originates in the early stages of neurodevelopment, with symptoms gradually emerging during childhood. Without timely intervention, these symptoms persist and significantly impair various aspects of the patient's daily life, including learning, work, and social functioning.

The clinical features of typical autism include varying degrees of social interaction disorders, restricted interests, and stereotyped behavior patterns, all of which exist in a "spectrum". Despite these challenges, most individuals with autism have the capacity for normal cognitive function. According to the latest data from the Centers for Disease Control and Prevention (CDC), the prevalence of autism in the United States is approximately 1 in 36. However, only about one-third of children with autism spectrum disorder (ASD) for whom cognitive ability information is available are classified as having an intellectual disability. It is noteworthy that most children with autism are not born with intellectual disabilities. However, as they grow, they often begin to exhibit a widening cognitive development gap compared to their peers. This disparity is largely due to their limited social interactions and lack of engagement in learning from others. This is largely because their preference often is to remain within their own world. Children normally learn primarily from interactions with people in their environment, with the environment significantly influencing the efficiency and scope of their learning. In this way much of learning has a social context and so sociability plays a primary role in this process. Thus children with autism, who grow up with limited social interactions, tend to show increasing differences in cognitive development compared to their peers. Consequently, early medical attention and intervention with a focus on enhancing social functions are emphasized as a key focus area to address these developmental disparities.

Additionally, the autistic population is highly heterogeneous and may exhibit various degrees of comorbidities including sensory perception issues, limb coordination difficulties, fine motor abnormalities, attention deficits, learning disabilities, and epilepsy. Children who grow up unable to understand or be understood by the outside world often experience conflicts with society. They may then seek clinical help in adolescence or adulthood due to mental disorders such as anxiety and depression, which can lead to a diagnosis of autism.

The exact cause of autism remains unclear. Numerous factors, including biological and environmental influences, collectively shape early brain development, thereby impacting an individual's cognitive, emotional, and social abilities. Hundreds of autism-related genes have been identified, which are also present in healthy individuals. However, in adverse environments (such as poor maternal nutrition during pregnancy, suboptimal living conditions,

and psychological stress), these genes can induce abnormal brain development, resulting in autism symptoms. Autism, stemming from mutations in core genes, frequently correlates with intellectual disability, although this association applies to only a minority of cases. For instance, Rett syndrome, once classified as a subtype of autism, is attributed to a random mutation or deletion in the MECP2 gene located on the X chromosome. However, in the fifth edition of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Rett syndrome is no longer classified within the autism spectrum. The prevailing view among many clinicians is that developmental disorders solely attributed to genetic mutations, such as Fragile X syndrome, are often excluded from the autism spectrum.

What are the efficacious clinical screening methods and the evidential criteria employed by hospitals for diagnosing autism?

Zhiwei Zhu: Routine examinations typically involve electroencephalography, nuclear magnetic resonance imaging, and assessments of hearing function. Structural magnetic resonance imaging is commonly conducted in clinical settings, primarily during children's resting states, to identify early signs of brain damage. However, due to factors such as young age and emotional states, conducting long-term functional magnetic resonance imaging is challenging linked to such children's limited ability to cooperate. Regarding genetic screening, it is insufficient to draw definitive conclusions based solely on these technical means unless mutations in core genes such as SHANK3, FMR1, CDH8, etc., are detected.

Autism is characterized by distinct diagnostic criteria that necessitate clinicians' patience in observing core symptoms. This includes challenges in social communication, repetitive behaviors, and restricted interests. Strict adherence to specific diagnostic criteria in each module is essential as patients exhibit varying clinical manifestations based on their age group. For example, infants up to 3 years old present different clinical features to school-aged children.

In children under 3 years of age, the "5 not" method is often utilized, which involves observing behaviors such as not making eye contact, not pointing at objects in response to prompts (e.g., when asked "where is Dad" or "where is Mom"), not responding when called by name, speaking minimally, engaging in self-directed speech instead of interactive communication, and/or exhibiting repetitive behaviors like spinning in circles, running back and forth, or arranging objects in a specific order.

Due to the spectrum nature of autism, the behavior of affected children can transition gradually from typical to mildly critical states. To prevent missed or incorrect diagnoses, physicians must possess ample experience, have encountered a diverse range of patients, and integrate theoretical knowledge with practical insights to make informed judgments. When autism symptoms are atypical, additional diagnostic evaluations are necessary. In certain cases involving older children, parents are queried about patients' past between the ages of 3 to 5, a period when autism symptoms typically manifest more clearly.

Autism disorders are significantly more prevalent in males than in females. Is this gender disparity also reflected in the ratio of males to females in clinical consultations for autism spectrum disorders? What are the potential explanations for this phenomenon?

Zhiwei Zhu: Indeed, clinical observations indicate a male-to-female patient ratio approaching 4:1. A study I encountered suggested a link between the Y chromosome and brain systemization. This study posited that, compared to females, the greater brain systemization males exhibit, the weaker the functional brain networks associated with sociality, empathy, and emotion. This neurological profile in males may contribute to a higher susceptibility to autism.

What medications are currently available for the treatment of autism?

Zhiwei Zhu: Pharmacological interventions primarily target associated or comorbid symptoms rather than the core symptoms of autism. For instance, as individuals with autism reach school age and adolescence, they may experience attention deficit hyperactivity disorder (ADHD), anxiety disorders, and sleep problems. In such cases, doctors can prescribe medications tailored to these specific conditions.

In some cases, addressing comorbidities can also improve the core symptoms of autism. Our team has conducted clinical studies on autism patients with intestinal microecological issues. These patients often have a limited diet, displaying aversions to foods with certain textures, smells, shapes, or colors, leading to nutrient deficiencies. We found that administering probiotic metabolites is highly effective in this subset of children. Additionally, our collaborators have demonstrated through animal studies that improving gut microbiota balance can ameliorate autistic behavioral deficits.

What are the commonly used clinical rehabilitation therapies for autism?

Zhiwei Zhu: Autism is a neurodevelopmental disorder for which there is currently no technology capable of altering neural network connections in the brain, nor is there a specific medication that can cure the core symptoms. Behavioral interventions are regarded as the most effective treatment for these core symptoms. Special education training and behavioral intervention can enhance children's daily living skills, cognitive abilities, social interactions, and overall adaptation to society.

Applied Behavior Analysis (ABA) has been a widely used intervention method throughout the 20th century. In this patients are rewarded for correct responses to encourage the development of skills like verbal communication. In Discrete Trial Training (DTT), a decomposition

task training based on ABA, patients completed tasks for snack rewards, but the over structuralized nature of the training and its dependence on conditioning reinforcement can be too rigid and limited for real world needs. Even if the patients can match and express themselves in established training topics, they often failed to cultivate flexibility to deal with the changing scenes in social life. Additionally, children often do not experience the positive aspects of interpersonal relationships during interactions with rehabilitation therapists in such training. Instead, they may feel fear, tension, and coercion when faced with tasks, leading to resistance to rehabilitation training. Despite these issues, DTT remains widely used in many grassroots institutions due to its low requirements for therapists.

Over the past one or two decades, clinical practice has shifted more attention toward interventions based on having a more natural environment context. This approach focuses on interactions with people in everyday settings, encouraging family involvement, understanding children's needs, guiding them to express their emotional experiences, and helping them enjoy social interactions. Our department utilizes the Play and Language for Autistic Youngsters (PLAY Project) intervention program for young patients. This method fosters effective interaction with autistic children through play, improving behavioral problems and reducing autism symptoms. For example, it encourages parents to engage their children with various stimuli—hearing, seeing, tasting, touching, crawling, and running—so they can experience the world with all their senses. Encouraging children to perceive the world as vibrant and social interactions as joyful can facilitate the natural establishment of connections within their social environment. This, in turn, promotes more orderly development of the social brain. However, achieving recovery from autism remains a global challenge. The evolving nature of behavioral intervention therapies reflects a deepening understanding of autism and ongoing improvements in treatment methods.

Clinical behavioral intervention typically follows a one-year cycle, necessitating regular follow-up visits, assessments, and adjustments. Through suitable intervention and education, certain individuals with autism can attain higher education, secure employment, and live an independent, happy life, just like to their neurotypical peers.

What roles do hospitals, families, and rehabilitation institutions play in the intervention and treatment of individuals with autism in China?

Zhiwei Zhu: The primary role of hospitals is to diagnose and evaluate, as well as to guide families in intervention strategies. Given the large patient population and the limited medical resources and personnel in hospitals, it is crucial to consider the varying economic situations, learning capacities, and levels of commitment among families when planning and implementing interventions.

After a diagnosis is made in the hospital, doctors need to provide tailored support programs based on each family's unique circumstances. We primarily advocate for family intervention, as the family environment is the most natural setting for the child, fostering greater adaptability and increasing the likelihood of the child leading a typical life in the future.

Program development must consider the unique conditions and needs of children and families at different stages. Doctors and families need to collaborate to create personalized intervention plans. Some hospital rehabilitation departments provide intervention programs. However, for parents who seek treatment in different locations and cannot attend long-term regular follow-ups, we recommend local hospitals or rehabilitation institutions for ongoing training.

Zhiwei Zhu

Zhu Zhiwei is the director of Developmental & Behavioral Pediatrics department. She focuses on diagnosis, assessment and treatment of neurodevelopmental disorders, autism spectrum disorders, attention deficit/hyperactivity disorder, developmental delays, learning disabilities, intellectual development disorders, feeding difficulties, eating behavior problems, etc. Also, she is interested in children's behavior problems and neurodevelopmental disorders, includes the etiology, pathological mechanism, intestinal microecology, behavior intervention and treatment of autism spectrum disorders, learning disabilities, intellectual disabilities, and attention deficit hyperactivity disorder.

Cross Border Round Table Talk

The Basic, Clinical and Interventional Research of Autism Spectrum Disorder

Lusha Tong (Host)

Chief Physician
Department of Neurology
Zhejiang University Second Hospital

Today's discussion will focus on the fundamental, clinical, and interventional research related to autism. We are privileged to have invited experts from various fields to engage in an interdisciplinary dialogue and who will address the critical challenges in autism diagnosis and treatment while exploring potential research directions. To begin, could each of you briefly introduce your respective fields of expertise?

Jianhong Luo

Qiushi Distinguished Professor
Department of Brain Science and Brain Medicine
School of Medicine

For nearly a decade, our research group has been dedicated to studying the neural mechanisms underlying social, cognitive, and emotional disorders using mouse models. Given that social disorders are among the most characteristic symptoms of autism, we have focused on investigating the neural mechanisms of a series of autism-related proteins, particularly within the medial prefrontal cortex, a core brain region involved in social interaction.

Yuqi You

ZJU 100 Young Professor
Department of Psychology and Behavioral Sciences

We primarily employ MRI, EEG, and other techniques to study sensory integration disorders in children with autism. Our research confirms the presence of significant sensory integration abnormalities in these children and reveals considerable heterogeneity in these abnormalities. By identifying distinct patterns of sensory abnormalities, we aim to predict the symptoms and developmental trajectories of children with autism.

Jun Liu

Director
Hangzhou Carnation Gongshu Campus
Director
Houpu Technology

I have extensive experience working in a frontline rehabilitation institution and have collaborated with the Disabled Persons' Federation to provide external training and develop specialized teaching aids for children with autism. Additionally, we try to enhance the quality of life for children with autism by fostering better communication and understanding between parents, doctors, and the children themselves.

Yudong Zhou

Vice Dean
Department of Brain Science and Brain Medicine
School of Medicine

Our research group investigates the impact of environmental factors on autism, with a particular focus on infections during pregnancy and delivery. Previous retrospective studies have shown a strong association between severe infections during pregnancy and an increased risk of autism in the fetus. This includes the potential role of vaccines in neurodevelopment. We hypothesize that immune responses occurring during critical periods of neurodevelopment may significantly influence neurological outcomes. Indeed, in our maternal immune activation model in mice, we have observed typical autism phenotypes in the resulting offspring.

Jun Hu

Dean
the Institute of Art and Travel Studies
Hangzhou Normal University

My research primarily focuses on art-based methodologies, and I have proposed the "three-realm space" theoretical hypothesis. This hypothesis posits that human cognition is rooted in spatial cognition, which encompasses three distinct realms: inner (emotional) space, physical space, and virtual space (such as the internet), referred to as the "body realm," "perimeter realm," and "benevolence realm," respectively. These realms are typically disconnected from one another, with art serving as the bridge that links them. The "three-realm space" hypothesis suggests that the social barriers exhibited by children with autism may, to some extent, result from deviations in the cognition of these three spaces. Therefore, we explore the use of art to develop new cognitive approaches as a means of intervening in autism. For example, we have employed mosaic animation to alleviate social barriers and artificial intelligence-driven light dance to enhance self-cognition, both of which have yielded promising results.

Peng Zhou

Tenured Professor
School of Foreign Languages

Our research group specializes in the language and cognitive development of both typical and atypical children, with a particular emphasis on the disorders caused by developmental and behavioral conditions. Over the past decade, we have focused primarily on studying preschool children (ages 0-6) with autism. Utilizing eye-tracking technology, we have developed an objective method to assess the language and cognitive development of these children. Our research findings indicate that children with autism do not exhibit significant deficits in core language comprehension; their challenges are primarily centered around social communication. Additionally, we have identified unique social patterns within the autistic community, underscoring the need for a more nuanced perspective in understanding these children. Within the framework of neurodiversity, we advocate for viewing the differences between autistic and typical children as variations rather than disorders. To support this approach, we have collaborated with multiple teams to explore ways to create environments that guide and encourage autistic children to express themselves, build confidence in communication, and enhance their social communication skills.

Chao Song

Associate Chief Physician
Developmental and Behavioral Pediatrics
Children's Hospital Affiliated to Medical College

My primary work is in the clinical field, focusing on the diagnosis and intervention of autism. Given the high heterogeneity of autism, our goal is to accurately classify patients to enable precise and informed intervention decisions. Additionally, we emphasize the integration of medicine and education. Many children with autism experience challenges in adapting to school life, yet attending mainstream schools is often crucial for their development. Therefore, we advocate for a more diverse, equitable, and inclusive campus and social environment to better support the integration of autistic children into society. Moreover, we aim to improve the overall quality of life for children with autism, addressing aspects such as diet and sleep.

Lusha Tong
(Host)

It appears that the number of children diagnosed with autism is increasing. **Could this trend be related to the characteristics of modern society?**

Jun Liu

Based on experience, a lack of social interaction may have certain impact. During the two years of staying at home due to the pandemic of COVID19, combined with the widespread use of electronic devices and the internet, many parents have inadvertently neglected their children. As a result, the children's social environments became monotonous, which may have contributed to more severe social disorders in children with autism.

Yuqi You

There may be a correlation between the use of electronic devices and social disorders, but the causal relationship between the two requires further investigation. One possibility is that individuals with autism may be more inclined to invest significant time in electronic products. Another potential factor contributing to the rise in autism cases in modern society is the increase in maternal age, late childbearing being a known risk factor. Additionally, the expansion of the DSM (Diagnostic and Statistical Manual of Mental Disorders) to include conditions such as Asperger's syndrome within the autism spectrum has broadened the definition of autism. Lastly, improvements in detection rates have also contributed to the observed increase.

Jianhong Luo

The primary cause of autism is still believed to be genetic, with a relatively well-established environmental risk factor being exposure to harmful conditions during the perinatal period, such as premature birth, infections, and toxic chemicals. Environmental factors related to postnatal upbringing may also contribute, resulting from a complex interplay between genetics, environment, and epigenetics. Research into the environmental or upbringing factors leading to autism is challenging and necessitates large-scale cohort studies with long-term follow-up. The role of social contact in autism remains difficult to ascertain as autism is intuitively believed to be rooted in genetic factors. It is possible that environmental triggers interact with the genetic background, suggesting that quantifying environmental factors may be necessary to further elucidate their role. It is important to recognize that autism is a spectrum disorder characterized by high heterogeneity among individuals. Discussions often focus on a subset of individuals with specific conditions which do not represent the entire spectrum (for example, those with severe intellectual disabilities are often excluded from studies because they cannot participate in treatments). I believe that the observed increase in autism prevalence is primarily due to changes in diagnostic criteria. The contribution of environmental factors remains a topic for further exploration. However, the shift in social patterns in modern urban life is indeed a significant environmental factor. Socializing has become a source of stress in modern life, a pressure that was traditionally less prevalent in rural settings. For modern children, from the family environment to school and other unfamiliar settings, they encounter considerable social pressure. Interestingly, in animal models, we also observe the dual nature of socialization: while animals have an innate tendency to socialize, they also experience stress as a result.

What is the impact of the modern social environment on autism?

Peng Zhou

Our research has identified age three as a critical time point for the development of social communication skills. From 0 to 3 years old, the methods of expressing emotions are relatively similar between typically developing children and those with autism. However, after age three, typically developing children show significant improvement in their ability to integrate social information, while children with autism exhibit a completely different developmental trajectory. In this process, environmental factors are not the decisive element - the environment needs to interact with genes to exert its effects. We conducted an experiment in which we asked typical and autistic children aged 3 to 5 years old to reach for a high object that was out of their reach. By age three, typical children were already able to seek help from others to reach the object, whereas autistic children displayed a different pattern, avoiding seeking assistance from others.

Jianhong Luo

This finding suggests that social interaction may act as a stressor for individuals with autism. Is it possible that people with autism tend to evaluate social interactions negatively. **This leads to their inability to seek assistance from other people to complete tasks?**

Yudong Zhou

I believe this also relates to the varying thresholds for social interaction among different groups. In the field of energy metabolism, there is a concept called "energy stress," which refers to excessive energy intake potentially leading to "metabolic inflammation" and resulting in obesity. A similar concept may apply to individuals with autism. Their social homeostasis may be more easily disrupted, making them more susceptible to stress in unfamiliar environments. If this is the case, treating social disorders in individuals with autism would require careful strategic considerations, as excessive social exposure could be detrimental to them. Prof. Hu's "Three Realms Space" theory mentions the importance of space for sensory cognition, which is very inspiring. People need spatial representation in nature, and the impact on the skin and body will also be projected onto the cortex to form self-awareness. The parietal cortex plays an important role in sensory integration. Prof. Hu believes that art can communicate different levels of cognition, which in fact corresponds to sensory integration training in the treatment of autism.

Jianhong Luo

The brain abnormalities in autism are likely concentrated in the cortex, particularly the neocortex. The structural changes involved may be minimal, primarily occurring at the level of synaptic connections. Human prosocial behavior is a product of the evolution and development of the cerebral cortex. Our recent work has shown that in a transgenic mouse model with cognitive flexibility defects, normal behavior can be restored by re-expressing key genes in the prefrontal cortex, even when the corresponding genes in subcortical regions remain absent. This finding underscores the critical role of the cortex in cognitive flexibility. Additionally, the prefrontal cortex plays a key role in regulating social and emotional development, as well as in controlling repetitive stereotyped behaviors. From an evolutionary perspective, the development of the prefrontal cortex is the most distinctive feature of modern humans. However, across all mammals, the prefrontal cortex is the last to mature and is the most vulnerable, making it especially crucial for the study of children's psychological development.

Lusha Tong
(Host)

What impact do genes from human evolutionary history have on autism?

Neanderthals, who once existed in history, had larger brains than Homo sapiens, but with the larger areas largely restricted to the visual and auditory cortices. It is hypothesized that while their sensory perception was more acute, their social and teamwork abilities were weaker. **Modern humans are said to retain 2-3% of Neanderthal genes. Could this genetic inheritance be related to phenomena such as autism?**

Jianhong Luo

From an evolutionary perspective, a well-developed prefrontal cortex is a defining characteristic of humans, supporting advanced cognition, social interaction, and emotional regulation. As the last brain region to mature, the prefrontal cortex offers a critical window for individuals to learn and adapt to societal norms, but it also renders them vulnerable to environmental and social influences. In individuals with autism, impaired prefrontal cortex function is often linked to cognitive and social deficits.

Yudong Zhou

Primates have undergone 3 major brain expansions during the evolution of their nervous systems, with the last being the expansion of the prefrontal cortex. It has been suggested that Neanderthal genes may contribute to social-related disorders, and the hypersensitivity to certain stimuli such as sound, as observed in some autistic children, could also be linked to these Neanderthal genes.

Jun Hu

There is an interesting connection to consider. Art emerged around 70,000 to 80,000 years ago, and Neanderthals did not leave behind any murals. Could this suggest that art is also a product of the development of the prefrontal cortex? The emergence of art may have served as a means to compensate for the fragility of neuronal connections in the prefrontal cortex.

Peng Zhou

One theory suggests that Homo sapiens and Neanderthals began to diverge around 200,000 years ago, with the prefrontal cortex of Homo sapiens developing between 80,000 and 100,000 years ago, leading to the emergence of language and social interaction. The structures that evolved later became more fragile and susceptible to genetic mutations, which is an intriguing hypothesis.

Yuqi You

The well-known "Intense World Theory" posits that children with autism experience hypersensitivity to sensory input. This heightened sensory perception overwhelms their ability to effectively integrate the information, resulting in the behavioral disorders commonly associated with autism.

Lusha Tong
(Host)

Clinical diagnosis, treatment, and rehabilitation practices for autism

According to the 2021 Blue Book of the Child Development Disorder Rehabilitation Industry, over 70% of children with autism aged 0-6 receive institutional rehabilitation for fewer than 12 hours per week, a number significantly below the recommended standard. Additionally, autism is among the most challenging developmental disorders to diagnose, with experienced diagnosticians unevenly distributed across China. **This raises important questions about the common clinical manifestations of autism in children and the current treatment approaches available.**

Chao Song

From a clinical perspective, we oppose interventions that impose excessive emotional stress on both parents and children. Parents of children with autism often experience significant pressure and are at risk for poor mental health, including anxiety and depression. Additionally, some parents may distance themselves from healthcare professionals who are unable to prescribe medication for autism, leading to reluctance in accepting an autism diagnosis for their child. There is now a perspective that suggests a shift from 'intervention' to 'parenting.' The term 'intervention' may imply an overly goal-oriented approach, whereas a focus on parenting emphasizes the importance of understanding the child and allowing them to thrive within a supportive comfort zone. Within this context, small, carefully calibrated stimuli can be introduced to encourage development, but these should be administered with caution to avoid excessive pressure.

Jun Liu

In frontline education, a more segmented and detailed approach is often adopted. For instance, the process of preparing to enter the school gate may be broken down into more than a dozen individual steps, which children are guided through progressively to help them acclimate to the environment.

Chao Song

Clinically, we have observed that many cases of autism are accompanied by behavioral comorbidities, such as body twitching and blinking, which may involve subcortical brain regions. Professor Luo recently highlighted that genetic repair of the cortex in animal models can lead to improvements, which may hold significant clinical implications.

Jianhong Luo

Some comorbidities of autism are linked to epilepsy risk genes. Autism is frequently comorbid with various neurological disorders, such as attention deficit hyperactivity disorder (ADHD), and many mouse models of autism exhibit increased levels of hyperactivity.

Chao Song

Clinical experience indicates that more than half of children with autism exhibit symptoms of hyperactivity and inattention.

Peng Zhou

From a rehabilitation perspective, many institutions focus on sensory integration training and behavioral interventions, which can enhance certain behavioral abilities. However, their impact on higher-level functions, such as social interaction, remains limited. Effective interventions may need to be stratified according to different functional levels. We may first need to determine whether autistic children perceive social activities or social information as positive or negative, and then assess their willingness to engage with this information. It is important to distinguish between these two aspects. Additionally, we have observed that communication patterns differ between interactions within the autistic group and with those outside it. Future research should systematically investigate these communication patterns to identify both similarities and differences in interactions within and outside the group.

The importance of a friendly and inclusive social environment for children with autism.

Lusha Tong
(Host)

Although public awareness of autism is gradually increasing, in reality autistic children and their families often still face discrimination and exclusion. This makes it challenging for them to integrate into society and access education. **What are the common misconceptions about autism in society? How can we enhance awareness and education about autism to improve public acceptance of autistic individuals? Are there effective solutions to address these issues?**

Jun Hu

We conducted an art therapy project where autistic children collaborated to create a "silhouette animation". Contrary to the belief of international art therapy experts that autistic children cannot cooperate, we found that they worked together exceptionally well. They have their own unique ways of cooperating, which develop naturally, so it is important not to judge their collaboration by conventional standards. At that time, 3 children were unable to participate in the "silhouette animation" project due to their stereotyped behavior traits, but they excelled in another project called "Mosaic Animation". Applied behavioral analysis often uses the standards of typical individuals to assess the autistic population, labeling them as having disabilities. However, these children, who spontaneously formed teams, were sometimes able to perform certain tasks even better than typical children. For instance, in mosaic animation, where two colors of dots are repeatedly combined to form straight lines-a task that may seem monotonous to most people, some children with stereotyped behaviors found enjoyment and success.

Jianhong Luo

If we can further subdivide the groups of children with autism in this experiment, as Professor Peng Zhou has suggested, it may facilitate the connection of various targeted intervention methods which will be crucial for future rehabilitation practices. Basic research on neural synchronization could be employed to explore the brain states of these different autism groups during cooperative activities. In fact, a precedent already exists in mouse experiments, where two electrodes are placed in the brains of two mice simultaneously to record their brain activity during interactions.

Yuqi You

Children with autism often exhibit indifference toward social information. While they may not have negative experiences with social interactions, they tend to have emotional deficits. For instance, they may be entirely insensitive to cues such as eye contact and facial expressions, and they particularly struggle to recognize expressions of emotions like disgust, fear, and anger.

Peng Zhou

Many autistic children do not lack functional abilities, but rather differ in their breadth of interests. We have found that combining music and painting can enhance their attention and communication. Fostering their interests, identifying their strengths, and creating a supportive environment tailored to their needs should be central to intervention strategies.

Jun Hu

I will share a recent example. There was a child in the third grade who had not yet started school and could not communicate normally with others. However, I noticed that this child had a desire for emotional connection, so I recommended that the parents enroll him in a regular school, starting in the first grade. The children in the class had no prior knowledge of autism, so the teacher explained that the child was a "little angel" and encouraged the entire class to support him in his growth, making his progress their greatest joy. This created a very positive class atmosphere. In less than 6 months, the child's language and cognitive abilities improved rapidly. He began to speak more at home and developed a strong interest in playing the drums. The parents were overjoyed, feeling that their lives had transformed from hell to heaven. This example illustrates that for some children with autism, treatment may not always be necessary. When the social environment changes, they can develop naturally. Changes in social cognition significantly impact individual development, and an improved social environment can greatly enhance their well-being.

Yuqi You

The stigma surrounding autism is deeply entrenched. A harsh reality is that many parents in mainstream schools band together to exclude autistic children from their classes, fearing that their presence may lead to behavioral issues in their own children. However, this concern is entirely unfounded. In fact, the experience of interacting with and caring for autistic peers can be beneficial to the psychological growth and development of typically developing children.

Jun Liu

In practice, when implementing integration projects that bring together autistic and typically developing children, we often avoid extensive publicity to parents. This is because such publicity might develop resistance. Instead, by quietly integrating the children without drawing attention, we find that parents are less likely to object once they observe that no issues arise.

Chao Song

The social integration of children with autism presents a significant challenge for parents. They must learn to manage pressure from school teachers, communicate effectively, seek understanding, and sometimes employ specific "communication strategies". Some parents face frequent calls from teachers throughout the day. I advise them to respond by saying, "I have consulted a specialist who has provided some recommendations. We are actively addressing the situation and working to support the child."

Jianhong Luo

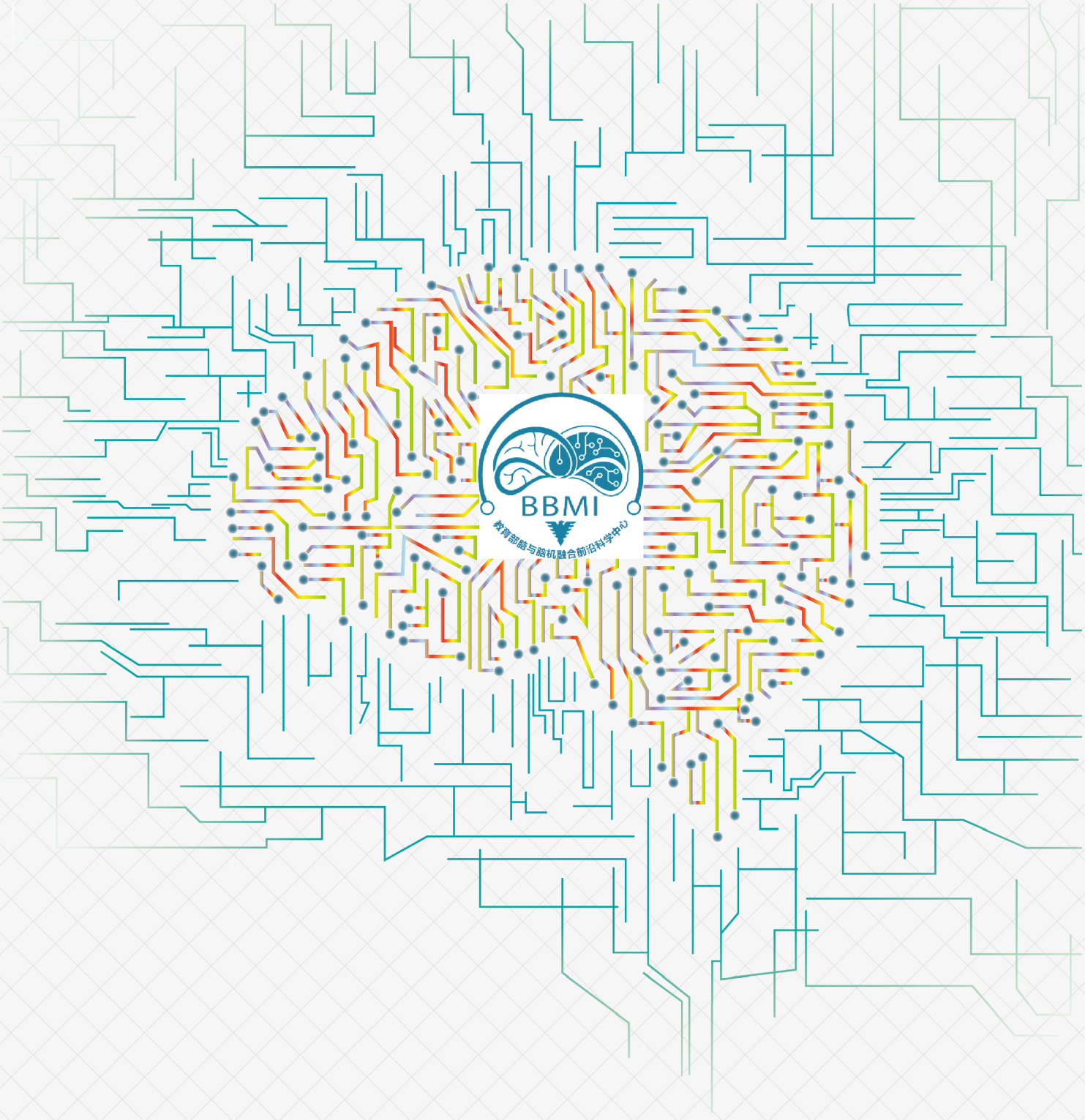
We should begin by understanding the unique characteristics of each child, acknowledging individual differences, and selecting appropriate educational methods accordingly. Individuals labeled as "socially challenged" by the standardized norms of a modern industrialized society may not have been considered problematic in the past. On the contrary, many of these individuals possessed unique talents and leadership qualities. With the advancement of AI technology, many traditional jobs that rely heavily on human experience and repetitive tasks, such as doctors' visual recognition of skin diseases, can now be automated. This shift presents an opportunity to rethink basic education. Can we find a way to develop individuals' potential based on their unique qualities, rather than adhering to a one-size-fits-all standard? Such an approach may be more conducive to the overall development of humanity.

Peng Zhou

I believe this presents a valuable idea: we should shift our perspective. Rather than expecting autistic individuals to adapt to society, we should focus on helping society better accept and accommodate them. Additionally, schools and parents should recognize that autistic children have their own strengths and unique qualities.

Jun Hu

The art world can not only open new windows for these special children, but also offer us a fresh perspective on art. If society refrains from treating them as patients, provides them with enough space, and reduces the pressure they face, it can help them develop a positive self-awareness and cultivate unique skills in creative expression.


BBMI
教育部脑与脑机融合前沿科学中心

Our Vision

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

"Innovate 2030" Plan

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

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