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## Brain Functional Connectivity Atlas and Brain-Inspired Intelligence Research Postprint

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### Abstract

The human brain is the most exquisite, complex, elegant, and successful organ produced by nature through a long evolutionary process. Brain science is the science that studies the essence and laws of cognition and intelligence in humans, animals, and machines. The nature of intelligence, the source of creativity, as well as rationality, memory and forgetting, personality, humanity, and decision-making mechanisms are all core issues of brain science. Understanding these issues will be the scientific foundation for effectively predicting, intervening in, and delaying brain aging, as well as creating artificial intelligence systems with self-learning capabilities. Brain science research will expand human understanding of nature and themselves; it will have tremendous radiating effects on human knowledge innovation, health and well-being, as well as information science and artificial intelligence, cultural science, social science, education, linguistics, and other fields, and have profound impacts on the progress of human society and economic development. Deciphering brain function requires analyzing the connection patterns and rules of brain network systems at multiple levels, ultimately obtaining a ‘circuit diagram’ of brain network structure and its function, which is the strategic high ground of brain science. To explore this major issue of brain network mapping, the Chinese Academy of Sciences launched the Strategic Priority Research Program (Category B) ‘Brain Functional Connection Mapping Project’ (abbreviated as ‘Brain Functional Mapping’) in 2012. In 2015, under the coordinated deployment of the Chinese Academy of Sciences, the brain-inspired intelligence research field was added to this program, and the expanded program was renamed ‘Brain Functional Connection Mapping and Brain-Inspired Intelligence Research’, achieving, for the first time internationally, the substantive integration of brain science and intelligent technology fields, and laying a solid foundation for the development of brain-intelligence science and the launch of China’s Brain Project.

## Full Text

# Strategic Priority Research Program (Category B) of the Chinese Academy of Sciences: Brain Functional Connectivity Map and Brain-Inspired Intelligence Research (ChinaXiv Partner Journal)

## 1. Background and Significance

The human brain represents nature's most exquisite, complex, elegant, and successful product of evolution. Brain science investigates the fundamental nature and principles of cognition and intelligence across humans, animals, and machines. Core questions in this field encompass the essence of intelligence, the origins of creativity, and the mechanisms underlying rationality, memory, forgetting, personality, human nature, and decision-making. Understanding these issues will provide the scientific foundation for effectively predicting, intervening in, and delaying brain aging, as well as for creating artificial intelligence systems with self-learning capabilities. Brain science research will expand humanity's understanding of both nature and ourselves, exerting profound radiating effects on knowledge innovation, health and well-being, information science and artificial intelligence, cultural science, social science, education, and linguistics, thereby significantly influencing social progress and economic development. Deciphering brain function requires analyzing the connectivity patterns and rules of brain network systems across multiple hierarchical levels, ultimately obtaining a "circuit diagram" of brain network structure and function—this represents the strategic high ground of brain science.

To address this major challenge of brain network mapping, the Chinese Academy of Sciences launched the Strategic Priority Research Program (Category B) "Brain Functional Connectivity Map Initiative" (abbreviated as "Brain Function Map" ) in 2012. In 2015, under the Academy's coordinated deployment, the field of brain-inspired intelligence research was incorporated into this program, and the expanded initiative was renamed "Brain Functional Connectivity Map and Brain-Inspired Intelligence Research." This represented the first substantive integration of brain science and intelligent technology internationally, laying a solid foundation for the development of brain-intelligence science and the launch of China's Brain Initiative.

## 2. Major Advances

### 2.1 Development, Function, and Disease of Sensory Neural Circuits

Research has revealed the regulatory mechanisms of fibroblast growth factor 13 (FGF13) in sensory perception and other functions, demonstrating that FGF13 is a crucial gene regulating brain development and intelligence. FGF13 knockout mice exhibited abnormal structural development in the cerebral cortex and hippocampus, with significantly impaired learning and memory capabilities. These

findings were published in *Cell* and highlighted by *Neuron* as one of the major advances since 1999 in understanding the molecular mechanisms of cerebral cortical development and disease. Additionally, studies demonstrated that androstadienone and estratetraene can effectively transmit gender information between individuals, providing compelling evidence for the existence of human pheromones. Published in *Current Biology*, this work attracted widespread media attention, with in-depth coverage by *Science*, *Scientific American*, *Time*, and other renowned international outlets. The article achieved an Altmetric score of 266, ranking 26th among all articles ever published in that journal and within the top 1% across all published articles.

## 2.2 Neural Circuit Mechanisms of Visual-Auditory Processing and Innate Fear Behavior

Researchers discovered a gating mechanism controlling visually evoked escape responses, revealing that behavioral selection can occur at the stage where visual signals are converted into motor signals. A functional module composed of dopaminergic neurons and inhibitory neurons controls behavioral choice in animals, and the characteristic of neuromodulatory systems responding to sensory stimuli may represent a universal neural mechanism in the human brain—namely, that neuromodulatory systems process the behavioral significance carried by sensory stimuli and subsequently regulate sensory-motor neural pathways to help animals make appropriate behavioral choices. These results were published as a featured article in *Neuron*. Furthermore, the study first identified the lateral amygdala-auditory cortex projection pathway as crucial in auditory fear memory and revealed the learning-related specific reorganization of this pathway. This research provides a new method for studying pathway-specific structural plasticity, represents an important complement to neural circuit studies of conditioned fear learning, and suggests fundamental rules for new synapse formation in the adult brain [Figure 1: see original paper].

## 2.3 Neural Circuit Encoding Mechanisms of Emotion

By exploiting the temporal differences in mRNA and protein expression of the neuronal activity marker c-Fos, researchers mapped a neural “atlas” of emotional value, observing for the first time in multiple brain regions the representation patterns and interactions corresponding to different emotions, including segregated, overlapping, and interleaved encoding modes. Additionally, the study elucidated the molecular and neural circuit mechanisms of the habenula in the development of depression. Overactivation of the habenula and the resulting excessive inhibition of dopaminergic neurons in the VTA (ventral tegmental area) can explain the core symptom of anhedonia in depression. In depressive states, the transcription and expression of CaMKII, a member of the calcium/calmodulin-dependent protein kinase family, were significantly upregulated in the habenula, and this protein level change could be reversed by antidepressant treatment. These findings suggest potential gene therapy approaches

for controlling and treating psychiatric disorders such as depression.

## **2.4 Mechanisms of Brain Diseases Including Addiction and Depression**

Melatonin was found to block CDK5-mediated autophagy and  $\alpha$ -synuclein aggregation, thereby preventing MPTP-induced neurotoxicity and Parkinson's disease (PD) symptoms, suggesting potential for early intervention in Parkinson's disease. A novel mechanism of dopamine "reuptake" and its relationship with cocaine addiction was discovered, revealing the important role of the GDNF signaling pathway component Vav2 in cocaine addiction formation. The brain network mechanism of the antidepressant ketamine was dissected, providing new perspectives and molecular targets for understanding depression pathogenesis and treatment. Additionally, a brain network atlas of depression was constructed, offering a novel research tool for both basic and clinical neuroscience studies.

## **2.5 Neural Basis of Self-Awareness**

For the first time, rhesus monkeys were demonstrated to possess the ability to recognize themselves in mirrors, indicating that their brains contain the neural mechanisms for self-awareness. The established rhesus monkey model can be used to investigate the neural basis of self-awareness and provides useful clues for clinical treatment of self-awareness deficits. This work fills a previous gap in the evolution of animal cognitive functions and opens new frontiers for exploring the neurobiology of self-awareness. Published in *Current Biology* and featured as a highlight, the article was reported and republished by over one hundred domestic and international mainstream science magazines and media outlets, including *Nature*, *Science*, ABC News, CBS News, Reuters, Discovery News, Xinhua News Agency, *China Science Daily*, and ScienceNet.

## **3. Original Innovations**

### **3.1 Gene Editing Technology and Non-Human Primate Models of Brain Diseases**

To address the major obstacle of long sexual maturation periods in non-human primate models for brain cognition and disease research, researchers transplanted monkey testicular tissue onto the backs of castrated nude mice. After 10 months of growth, they injected the resulting sperm into cynomolgus monkey oocytes through intracytoplasmic sperm injection, then transferred the fertilized eggs into pseudopregnant recipients, successfully obtaining two wild-type and four F1 generation MeCP2 transgenic cynomolgus monkeys. This work accelerates spermatogenesis and shortens the reproductive cycle in cynomolgus monkeys, representing significant progress for non-human primate model applications and offering guidance for preserving fertility in prepubertal male cancer patients. Furthermore, the first stably inherited transgenic autism

cynomolgus monkey model was established. Through transgenic and knockout approaches targeting the MeCP2 and FMR1 genes, researchers obtained cynomolgus monkey models related to neurodevelopmental disorders such as autism. MeCP2 transgenic monkeys exhibited symptoms similar to human autism patients [Figure 2: see original paper]. As the world's first non-human primate model of autism, this study provides a crucial foundation for in-depth investigation of autism pathology and potential therapeutic interventions. Published in *Nature*, the research received immediate coverage from major international news outlets including *The New York Times*, *The Wall Street Journal*, CNN, *The Daily Telegraph*, and BBC, as well as extensive reporting and exclusive interviews from domestic media such as Xinhua News Agency and CCTV.

### **3.2 Novel Technologies and Applications for Neuronal Classification and Functional Analysis**

A new classification framework for somatosensory neurons was established through single-cell RNA sequencing and functional analysis. By developing high-coverage single-cell transcriptome detection combined with in vivo electrophysiological recording and type identification, researchers identified 10 neuronal types [Figure 3: see original paper] and 14 subtypes, discovering 4 new neuronal types and 14 new subtypes, and preliminarily determining the sensory functions of these neuronal types. Additionally, a CRISPR/Cas9-mediated gene knock-in technology was established in zebrafish, enabling specific labeling, activity recording, and functional manipulation of different neuronal types, laying the foundation for studying the role of neurons in behavior. A carbon fiber electrode-based electrochemical method for detecting dopamine release was also developed in zebrafish, providing a tool for investigating the function of dopaminergic neurons and their circuit basis.

### **3.3 Development of Novel Dual-Color Calcium Imaging Methods**

A functional connectome of individual neurons in the *Drosophila* mushroom body was mapped using a new dual-color calcium imaging approach. By combining optical microscopy with electron microscopy, researchers investigated how the response properties of mushroom body neurons are transformed from upstream projection neurons. This work provides a novel strategy for mapping the functional connectome of single neurons and offers a fresh perspective on information transmission and integration processes in the *Drosophila* mushroom body.

### **3.4 Development of Neurotropic Virus-Based Tools for Neural Circuit Structure and Function Research**

A systematic library of genetically recombinant neurotropic viruses was established, including pseudorabies virus (PRV), herpes simplex virus (HSV), rabies virus (RV), and vesicular stomatitis virus (VSV) [Figure 4: see original paper],

along with a series of helper viruses for specific labeling of neural circuits. The transmission mechanism of PRV was also investigated. In terms of microscopic imaging, a new method and device based on scanned light-sheet illumination was developed. Conventional STORM (stochastic optical reconstruction microscopy) methods are limited to samples thinner than 1  $\mu\text{m}$  due to sensitivity to background noise. To overcome this limitation, the newly developed method enables super-resolution fluorescence imaging of tissue samples ranging from hundreds of micrometers to several millimeters, with feasibility initially verified in *C. elegans*.

## 4. Industrial Significance

### 4.1 Deep Neural Network Chip Development

The world's first instruction set for intelligent processors was proposed, and the world's first low-power neural network processor chip capable of "deep learning" was designed and implemented, passing all functional tests in its preliminary stage. This breakthrough addresses performance and energy consumption challenges at the component level, enabling operation of mainstream deep learning algorithms (MLP/CNN/DNN) with a hundredfold improvement in performance-to-power ratio compared to traditional CPUs.

### 4.2 Resource Libraries and Platform Construction

Multiple resource libraries have been established, including optogenetic viral resource libraries, transgenic animal resource libraries, monoclonal antibody libraries for synapse-related proteins, optogenetic and probe tools based on gene-targeted knock-in, Cre-dependent and independent AAV vectors expressing TVA and different fluorescent proteins, and tracer tool viruses for neural circuit labeling. Preliminary construction of macroscopic and microscopic imaging platforms [Figure 5: see original paper], optogenetics technology platforms, viral tracing platforms, and efficient genetic manipulation platforms has been completed. The iBrain big data cloud computing platform has been launched to facilitate sharing and computation of various brain science data types. By integrating and sharing data from different sources and enabling remote operation and computation, this platform will accelerate brain science development.

## 5. Recommendations for Future Deployment in Disciplinary Development, Industrial Advancement, and Talent Cultivation

The core questions of brain science concern the nature of human cognition, intelligence, creativity, and the origins of consciousness, while artificial intelligence aims to simulate, extend, and expand human intelligence. Brain science and intelligent technology research represent hotspots and focal points of competition in the international scientific community for years to come. The key to

seizing the international high ground lies in integrating interdisciplinary forces to promote deep fusion between brain science and intelligent technology. We must fully leverage the Chinese Academy of Sciences' strengths across relevant disciplines, employ top-level design to develop novel research technologies and systems based on specific research needs in brain science and intelligent technology, establish interdisciplinary and cross-institutional dual-degree programs to cultivate interdisciplinary talent in brain science and intelligent technology for future technological development, and advance artificial intelligence technology through deciphering the high-intelligence and high-energy-efficiency working mechanisms of the human brain. Under continued stable support from the CAS Strategic Priority Research Program for "Brain Functional Connectivity Map and Brain-Inspired Intelligence Research," we should further consolidate objectives, conduct sustained research and technology development based on existing progress, and actively promote translation of scientific achievements to facilitate industrialization of brain disease diagnosis and treatment technologies as well as intelligent technologies.

(Undertaken by: Shanghai Institutes for Biological Sciences, CAS; Institute of Automation, CAS)

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It is well known that understanding the neural basis of human cognition, thought, and consciousness represents the ultimate challenge in humanity's quest to comprehend nature and ourselves. In today's research landscape, brain science has evolved into a frontier interdisciplinary field that is leading a new round of scientific, technological, and industrial revolutions, promoting human health and sustainable economic and social development. Research on brain functional connectivity maps and brain-inspired intelligence constitutes the strategic high ground of brain science. The Chinese Academy of Sciences' launch of this strategic priority research program demonstrates its strong commitment to brain science and its timely grasp of major global research trends. Over the past four years, CAS has achieved remarkable breakthroughs in multiple major brain science research directions, generating significant domestic and international impact in areas such as neural circuits for sensory information processing and subcortical pathways, neural circuits and brain regions for emotion and depression, non-human primate models of neurological diseases, and artificial intelligence technologies like deep neural network chips. CAS has also published numerous influential papers in authoritative international journals including *Nature*, *Science*, *Cell*, *Nature Neuroscience*, and *Neuron*, demonstrating not only its world-class strength in brain science research but also setting a positive example for other domestic research institutions and generating beneficial societal impact. Based on years of accumulated research and technological development, brain science is poised for major breakthroughs in both basic and applied domains. Consequently, the United States, European Union, Japan, and other nations have launched national-level brain initiatives, prioritizing brain science as a paramount frontier field. With its outstanding scientific

achievements in brain science establishing its international leadership position and its extensive experience in policy formulation, CAS is well-positioned to provide a solid foundation for China' s upcoming Brain Initiative.

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The establishment of the Strategic Priority Research Program “Brain Functional Connectivity Map Initiative” in 2012 reflects the strategic vision and capacity to grasp international frontier scientific questions among CAS leadership and scientists. Over its four-year implementation, the program has achieved excellence across various research directions. While the U.S. BRAIN Initiative initially focused on developing new tools, the “Brain Functional Connectivity Map Initiative” has already made important progress in establishing key technology platforms including viral tracing tools, non-human primate genetic manipulation models, novel imaging recording tools, and big data analytics. Based on these established platforms, several important achievements have been made: (1) the first non-human primate transgenic autism model; (2) discovery of brain functional connectivity evidence supporting a topological definition of basic units for visual cognition; (3) mapping of a neural “atlas” of emotional value; (4) identification of human sex hormones that potentially influence gender perception; (5) first demonstration of self-recognition capability in rhesus monkeys; (6) revelation of neural circuits related to fear responses; (7) discovery of novel molecular mechanisms in depression and new pathways for seizure onset; and (8) identification of genes regulating development of brain regions related to human intelligence.

Through further consolidation of research directions and team collaboration, this strategic priority program will lay a solid foundation for China' s Brain Initiative. It is also recommended that university researchers be incorporated into the team. The current Brain Functional Connectivity Map Initiative focuses exclusively on brain science research, whereas the United States has recently renewed its emphasis on systems physiology research, particularly interactions between the nervous system and peripheral tissues, such as brain-gut and neuro-immune interactions. I personally believe that this holistic mind-body communication aligns with traditional Chinese medicine concepts and should be prioritized as a future direction for China' s Brain Initiative.

—Yu Tian Wang, Fellow of the Royal Society of Canada, Canada Research Chair in Molecular Medicine, Professor at the University of British Columbia

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The Chinese Academy of Sciences demonstrated remarkable foresight in launching the Strategic Priority Research Program “Brain Functional Connectivity Map Initiative” in 2012. Over four years of implementation, the program has achieved outstanding results across different research directions. While the U.S. BRAIN Initiative initially emphasized tool development, the “Brain Functional Connectivity Map Initiative” has already made significant progress in establishing critical technology platforms for viral tracing, non-human primate genetic

manipulation models, novel imaging tools, and big data analytics. Building upon these platforms, the program has yielded several major achievements: (1) establishment of the first non-human primate transgenic autism model; (2) discovery of brain functional connectivity evidence supporting topological definitions of basic units for visual cognition; (3) mapping of emotional value neural “atlases” ; (4) confirmation of human sex hormones that influence gender perception; (5) first demonstration of self-recognition in rhesus monkeys; (6) revelation of fear response-related neural circuits; (7) discovery of novel depression-related molecular mechanisms and new epileptic seizure pathways; and (8) identification of genes regulating development of brain regions associated with human intelligence.

Through further direction consolidation and team collaboration, this strategic program will establish a robust foundation for China’s Brain Initiative. Additionally, I recommend incorporating university researchers into the team. Currently, the Brain Functional Connectivity Map Initiative focuses solely on brain science, whereas the U.S. has recently emphasized systems physiology research, particularly interactions between the nervous system and peripheral tissues, such as brain-gut and neuro-immune interactions. I believe this holistic mind-body communication aligns with traditional Chinese medicine principles and should be a priority for China’ s future Brain Initiative.

—Qiufu Ma, Professor of Neurobiology, Harvard Medical School

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Qiufu Ma is a Professor of Neurobiology at Harvard Medical School. He graduated from Fudan University in 1987 and earned his Ph.D. from UCLA in 1994. After postdoctoral research in David Anderson’ s laboratory at Caltech, he joined the Department of Neurobiology at Harvard Medical School and Dana-Farber Cancer Institute as an Assistant Professor, becoming a full Professor in 2011. He was a Pew Scholar (2000–2004). His laboratory previously identified key transcription factors regulating somatosensory neural circuit formation, and has recently made important progress in understanding spinal microcircuit mechanisms underlying pain and itch, providing crucial evidence for the gate control theory of somatosensory information processing.

*Note: Figure translations are in progress. See original paper for figures.*

*Source: ChinaXiv –Machine translation. Verify with original.*