·Project Spotlight·

Grand Research Plan for Neural Circuits of Emotion and Memory - Current status of neural circuit studies in China

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During recent years, major advances have been made in neuroscience, i.e., asynchronous release, three-dimensional structural data sets, saliency maps, magnesium in brain research, and new functional roles of long non-coding RNAs. Especially, the development of optogenetic technology provides access to important information about relevant neural circuits by allowing the activation of specific neurons in awake mammals and directly observing the resulting behavior. The Grand Research Plan for Neural Circuits of Emotion and Memory was launched by the National Natural Science Foundation of China. It takes emotion and memory as its main objects, making the best use of cutting-edge technologies from medical science, life science and information science. In this paper, we outline the current status of neural circuit studies in China and the technologies and methodologies being applied, as well as studies related to the impairments of emotion and memory. In this phase, we are making efforts to repair the current deficiencies by making adjustments, mainly involving four aspects of core scientific issues to investigate these circuits at multiple levels. Five research directions have been taken to solve important scientific problems while the Grand Research Plan is implemented. Future research into this area will be multimodal, incorporating a range of methods and sciences into each project. Addressing these issues will ensure a bright future, major discoveries, and a higher level of treatment for all affected by debilitating brain illnesses.

Keywords: neural circuits; emotion and memory; funding; Grand Research Plan

Introduction

Emotion and memory form the core of cognitive functions, and memory is the basis for cognition. Neural circuits are the biological basis of emotions and memories, and impairments of emotion and memory are associated with abnormal anatomy and dysfunction in neural circuits. Analysis of how emotions and memories are related to abnormal structures and dysfunctions of neural circuits in neurological and psychiatric diseases will provide a scientific basis and new ideas for the next generation of technical methods for diagnosis and treatment. Under such circumstances, the Grand Research Plan for Neural Circuits of Emotion and Memory was launched by the National Natural Science Foundation of China (NSFC) in July, 2011, and a total of 200 million RMB was allocated for the next eight years. This Grand Research Plan takes emotion and memory as its main objects, making the best use of cutting-edge technologies from medical science, the life sciences and information science. A systemic point of view, looking at connectional groups and functional groups for example, in parallel with a clinical perspective, will be used to gain a deeper understanding of the basic structures and functions of the neural circuitry involved in emotion and memory. Understanding the integrative mechanisms of the neural circuits and the pathological processes that lead to neurological and psychiatric diseases on the molecular level is fundamental to improving diagnosis and patient rehabilitation.

Adjustments to Be Made on Background of Previous Projects

Some deficiencies still exist for the projects launched in 2011. For example: the application of truly new technologies and methods to neuronal circuit research is rare; genetic studies of the neural circuits in emotion and memory are few; hardly any studies are carried out with non-human primate models; and simultaneous multi-level and milti-modal projects on emotion and memory are lacking. Moreover, among a variety of applications concerning emotion and memory and neural circuits in neurological and psychiatric diseases, some lack innovation. Cooperation between clinicians and basic researchers and interdisciplinary collaboration need to be strengthened.

In this project, we are making efforts to remedy the deficiencies by making some adjustments, mainly in four aspects of the core scientific issues to investigate these circuits at multiple levels, and to assess the impact of genes and the environment as follows: (1) the structural and functional basis of the circuitry for emotion and memory and their relationships, (2) the interactions between the circuits for emotion and memory and their mechanisms, (3) the circuitry underlying emotion- and memory-related neurological and psychiatric diseases, and (4) the mechanisms by which the circuits for emotion and memory are regulated by genetic and environmental factors.

Focused Research Directions in the 2013 Plan

The Grand Research Plan was implemented around the above important scientific problems by taking the following five research directions: (1) the structural and functional basis of the circuits for emotion and memory and their relationships, (2) interactions between the circuits for emotion and memory and their mechanisms, (3) the mechanisms underlying the regulation of the circuits for emotion and memory by genetic and environmental factors, (4) the circuit mechanisms underlying emotion- and memory-related neurological and psychiatric diseases, and (5) the development of new methods and new technologies for studying the circuits underlying emotion and memory.

Current Status of Neural Circuit Studies in China

Neural circuits are the biological basis of emotions and memories, and impairments of emotion and memory are associated with abnormal anatomy and dysfunction in neural circuits. Analysis of emotions and memories related to abnormal structures and dysfunctions of neural circuits in neurological and psychiatric diseases will provide a scientific basis and new ideas for the next generation of technical methods of diagnosis and treatment. In recent years, the rapid development of newly-emerging technologies in molecular biology, physics, chemistry, and computer science provides new opportunities for in-depth study of the neural circuits driving emotion and memory.

Neural Circuit Research in Emotion and Memory

During recent years, asynchronous release of neurotransmitters has been reported to act as functional nodes in the modulation of network reverberation, allowing us to directly evaluate fundamental principles and uncover basic mechanisms relevant to complex behavior in an experimentally accessible setting[1]. A three-dimensional structural data set of a Golgi-stained whole brain at the neurite level has been obtained to explore connectional groups and functional groups in the basic structure and function of neural circuitry[2]. The dominant view that a saliency map is generated in the parietal cortex has been challenged because a bottom-up saliency map is created in V1[1]. Likely, an increase in brain magnesium enhances both short-term synaptic facilitation and long-term potentiation and improves learning and memory functions[3-5]. Moreover, long non-coding RNAs play important roles in cellular processes, neuronal development, and even in cognitive and behavioral processes; new functional roles of these RNAs have provided insights into the pathogenesis of movement disorders. As for the visual system, different types of motion information are differentially processed in parallel and segregated compartments within primate early visual cortices, before these motion features are fully combined in high-tier visual areas[6,7]. More plasticity and wider generalization in the amblyopic visual system has been found, thus providing a strong empirical and theoretical basis for perceptual learning as a potential treatment for amblyopia. Furthermore, the GABAergic anterior paired lateral neurons function by inhibitory regulation to facilitate olfactory reversal learning by suppressing initial memory in *Drosophila*[8,9]. In addition, a computational modeling approach has been adopted to investigate how the dopamine systems in different brain areas work together to drive a fly to make a decision[10].

Neural Circuit Research Related to Impairment of Emotion and Memory

Recently, research into the neuronal circuit mechanisms of diseases associated with emotion and memory impairment has shown excellent advances. Take Alzheimer's disease (AD) for example: the topological properties of brain functional networks are disrupted in patients with AD (the apolipoprotein E genotype modulates brain network properties, especially in patients with AD), mainly in the temporal lobe and certain subcortical regions that are closely associated with the neuropathological changes in AD[11,12]. Graph theory has been used to study the aberrant brain structures in AD and suggested that the organization of the cortical network is least optimal in AD. Evidence for interregional correlations within local areas and disrupted long-distance interregional correlations in groups with mild cognitive impairment and AD is increasing[13]. As for other aspects, benfotiamine appears to improve cognitive function and reduce amyloid deposition *via* thiamine-independent mechanisms, which are likely to include the suppression of glycogen synthase kinase-3 activity[14]. Neuregulin 1–ErbB4 signaling contributes to human epilepsy, suggesting that ErbB4 may be a new target for anticonvulsant drugs[15]. All the breakthroughs noted above suggest that research on the neural circuit mechanisms underlying diseases with emotion and memory impairment has made outstanding progress in the past few years.

Technologies and Methodologies of Neural Circuit Research

By developing a system-level neuronal network, a two-pathway circuit has been proposed for the transmission mechanism and coordination between learning and memory. Also, a series of mathematical tools has been developed to describe the information processing of continuous attractor networks both in a random environment and under stimulus conditions. A computational modeling approach has been adopted to investigate how different brain areas and the dopamine system work together to drive a fly to make a decision. Whole-brain network analysis has proved to be the most effective approach in studying the pathological mechanism of AD. Multiple recording electrode arrays, voltage-sensitive dye imaging and whole-cell recording *in vivo* have been developed for sequential learning studies in the primary visual cortex of the adult rodent. Three-dimensional imaging can be used at the submicron level to visualize fine structures.

A microscopic optical sectioning tomography system has been invented and developed. Notably, the development of optogenetic technology provides access to important information on relevant neural circuits by activating specific neurons in the awake mammal and directly demonstrating the resulting behavior[16]. Thus, optogenetics is an important method for research on neural circuit structures and functional characteristics. This method is also of vital significance for in-depth understanding of brain function, neurobiological mechanisms and intervention therapies for neurological/psychiatric disorders[17]. Several novel optogenetic tools have been designed and used to causally investigate the cellular excitation/inhibition balance hypothesis in freely-moving mammals, and to explore the associated circuit physiology[18,19]. The field of optogenetics has been successfully used to understand the mechanisms of neuropsychiatric diseases through the precise spatial and temporal control of specific groups of neurons in a neural circuit. However, it remains a great challenge to integrate optogenetic modulation with electrophysiological and behavioral read-out methods as a means to explore the causal, temporally precise, and behaviorally relevant interactions among neurons in the specific circuits of freely behaving animals. In conclusion, all the technologies and methods noted above have effectively promoted advancement in understanding neural circuits.

Future

The aim of this research is mainly to search for the key circuit nodes associated with emotion and memory at multiple levels and thereby reveal the relationships between phenotypes and abnormal neural circuits, describe the circuits driving pathological processes in mental disorders, develop an in-depth understanding of the mechanisms of neurological and psychiatric diseases, find new means of prevention, diagnosis and treatment, and provide a scientific basis for improving people's psychological health. Future research into this area should be be multimodal, incorporating a range of methods and sciences into each project. It is only by looking at the whole picture and how each aspect interacts with other aspects can we take the diagnosis and treatment of psychiatric disorders to a new level. With the right allocation of funding, and effective collaboration and exchange of data, there is no reason why China cannot lead the world in the advancement of neuronal psychology. Although great progress has been made in cognitive neuroscience in recent years, there are still some areas in which sufficient research is lacking. Addressing these lacunae will ensure a bright future, the making of great discoveries and a higher level of treatment for all affected by these debilitating illnesses.

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