論文の内容の要旨

論文題目

Theoretical and experimental researches on large-scale human brain networks: from efficiency of brain network topology to neural networks for memory consolidation and impaired neural networks in high-functioning autism.

（大域ネットワークとしてのヒト大脳の理論的実験的研究：大脳ネットワーク構造の効率性から、記憶定着に関する神経ネットワーク及び、高機能自閉症に見られる神経ネットワーク障害まで）

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Over the past decade, explosive increase of computational power in scientific fields has accelerated the expansion of network science, which is originally derived from a graph theory. A line of studies across a wide range of scientific disciplines have demonstrated that complex networks are observed not only in the social sciences, but also in the organization of single cells and structures of entire ecosystems. In macroscopic neuroscience that investigates the human whole brain by using, for example, positron emission tomography and functional magnetic resonance imaging (fMRI), an increasing number of literatures have proposed that human cognitive functions can be described from the perspective of large-scale brain networks.

However, the current network-based perspective in macroscopic neuroscience has several weak points: First, the conventional method to quantify functional connectivity among brain regions cannot estimate network structures with considering global effects from an entire network. Therefore, it remains unclear about, for example, why the brain network has a specific and characteristic topology in a whole-brain level. Second, the conventional analysis can quantify functional connectivity network during rest but cannot estimate connectivity specific to active cognitive status. Finally, it has not yet been demonstrated that functional connectivity networks can be altered by administration of any drug.

In the present thesis, I aimed at addressing these issues by (i) presenting alternatives to estimate network structures on a whole-brain level that will give novel interpretation on several characteristics of the human brain, (ii) revealing brain networks during specific cognitive status such as encoding and retrieval of remote memory, and (iii)

demonstrating that brain networks specific to social communication can be altered by intranasal administration of oxytocin, a pro-social neuropeptide.

For the purpose (i), I first sated on why the anatomical connections in the human brain constitute relatively sparse networks. Theoretically, sparse network structures are not considered to be good for synchronization among multiple neuronal oscillators which are most likely to be synchronized when the oscillators are fully connected with each other. The actual neural network in the brain is, however, not such a fully connected network but a sparsely connected complex network. Why does the brain dare to choose such network topology that does not seem to good at synchronization? In the first section of this thesis, I address this issue by demonstrating that synchronization among neuronal activity can be enhanced if the process of making networks sparse obeys specific procedures. This finding gives us some insight on the specifically programmed developmental process in the neural network in the brain.

For the purpose (i), I second stated on why the human brain networks show a rich-club topology: Recent studies have found the existence of a specific network architecture called "rich-club topology" in anatomical and functional structures of human brains. The architecture is characterized by a densely connected hub module and peripheral nodes tagging the hub module. Although the prior studies imply the relevance between the network topology and several brain functions, it remains unclear for what such characteristic network architecture is universally underlying the human brain. In this section, by computational analyses using a rewiring-based optimization method, I demonstrate that the rich-club topology is one of the best network structures to minimize cost for synchronization among neuronal activity. Moreover, I also provide analytical interpretation on why the rich-club topology reduces the synchronization cost. These results can be one of the first quantitative explanation on observation of the characteristic network architecture in the human brain.

For the purpose (i), I finally estimated the complexity of the human brain networks by applying a new method to quantifying functional connectivity among brain regions: Even during resting, the human brain shows spontaneous activity. A line of previous studies have demonstrated that such spontaneous brain activity during rest constitute several brain networks called resting-state human brain networks (RSNs) and shown the significant relevance of the RSNs to fundamental cognitive functions such as memory maintenance and self reference. Although the RSNs are known to consist of complex interactions among brain regions, the level of complexity of the RSNs has not been quantified, which has consequently avoided comprehensive descriptions of the brain activity as an integrative system. In this section, I address this issue by demonstrating that a pairwise maximum entropy model

(MEM), which only takes into account region-specific activity rates and pairwise interactions, can be robustly and accurately fitted to resting-state human brain activities obtained by functional magnetic resonance imaging. The result indicates that large-scale brain networks during rest can be represented by a relatively simple model.

For the preparation of the purpose (ii), I first stated the memory information coded in the hippocampus: The hippocampus is known to be an essential brain structure for memory encoding. Previous studies using non-human animals have shown that the processes underlying the memory encoding are coded in neuronal activity in the hippocampus. However, in researches employing human subjects, it has been difficult to directly prove the relationship. Indeed, prior human researches using non-invasive neuroimaging technique such as fMRI have only reported the correlation between the hippocampal activity and the performance of memory encoding but not demonstrated the fact that the memory encoding performance is coded in the activity of the hippocampus. In this section, to clarify the fact in the human brain, I apply a multi-voxel pattern analysis (MVPA) to fMRI signals in the hippocampus while human subjects are learning multiple verbal stimuli. Only using the hippocampal activity during memory encoding, the MVPA can accurately predict whether each of the subjects can remember each of the verbal stimuli one by one. This result provides direct evidence that even in the human brain the memory encoding performance is coded in the hippocampal activity.

Based on this result, I then depicted hierarchal neural networks in the temporal lobe for processing of recent and remote memory: As represented by the hippocampal activity during memory learning, the temporal lobe has a crucial role in memory processing. The posterior temporal area is thought to store memory information for a long time period. The anterior temporal pole is suggested to be related to retrieval of remote memory. However, it is unclear how these important areas in the temporal lobe interact with each other during encoding and retrieval of memory information. Indeed, electrophysiological approaches that are powerful at investigation of local events are not good at examination of large-scale network activity in the brain. In this section, I elucidate the functional network in the temporal lobe underlying the memory processing by applying newly-developed multi-variate pattern analyses to functional connectivity among the temporal brain regions. Consequently, I found that (1) learning unfamiliar and novel information recruits functional interaction from category-specific perception areas (e.g., fusiform face area and parahippocampal place area) to the hippocampus, (2) consolidation of the learned memory occurs in the interaction from the hippocampus to category-specific memory storage areas in the posterior temporal lobe, and (3) retrieval of the consolidated memory is retrieved through the interaction from the

category-specific memory storage areas to category-general anterior temporal region. These findings reconcile a series of prior knowledge on functions of the temporal brain areas related to memory learning and retrieval, and depict a comprehensive large-scale memory processing network in the human temporal lobe.

For the purpose (iii), I first showed neural networks in healthy control human participants during resolving incongruent social communication contents: In this fMRI study, I investigated the functional networks for resolution of social conflicts by measuring human brain activity during resolving incongruity between verbal and nonverbal emotional contents. I found that the posterior dorso-medial prefrontal cortex (dmPFC) and right ventral posterior inferior gyrus (pIFG) were hub regions in networks underlying nonverbal- and verbal-content-biased resolutions, respectively. Moreover, I revealed that these resolution-type-specific networks were bridged by the anterior dmPFC, which was recruited for the conflict resolutions earlier than the two hub regions. These findings suggest that, in social conflict resolutions, the anterior dmPFC selectively recruits one of the resolution-type-specific networks through its interaction with resolution-type-specific hub regions.

For the purpose (iii), I second stated about behavioral and neuronal impairments in individuals with autism spectrum disorders (ASD): Individuals with autism spectrum disorders (ASD) tend to make inadequate social judgments, particularly when the nonverbal and verbal emotional expressions of other people are incongruent. By using fMRI, I compared brain activity during resolving social conflicts in 15 non-medicated adult males with high-functioning ASD to that of 17 age-, parental-background-, socioeconomic-, and intelligence-quotient-matched typically-developed (TD) male participants. I found that diminished activity in the anterior cingulate cortex and dmPFC underlies the impaired abilities of individuals with ASD to use nonverbal content when making judgments regarding other people based on incongruent social information.

For the purpose (iii), I finally demonstrated that oxytocin can mitigate behavioral and neural impairment in social communications: In this double-blind placebo-controlled trial recruiting 40 high-functioning ASD males, I used the same psychological task as in the above-mentioned case-control study and examined whether intranasal administration of oxytocin mitigates the behavioral and neural impairments observed in the case-control study. Consequently, I found that oxytocin mitigates ASD communication deficits through recovery of the medial prefrontal activity.