Multiscale neuroscience of the healthy and diseased brain

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In this chapter, I will first summarize the main findings presented in this thesis, followed by a general discussion with a comprehensive literature review. The discussion is categorized into two parts: 1) multiscale wiring principles of the human brain connectome, and 2) multiscale neuropathology of schizophrenia. Furthermore, methodological considerations of the present thesis and future directions in the field of multiscale neuroscience will be deliberated.

Summary

Integrating the genetic, histological, and brain imaging data have provided a rich body of evidence for the relationship across multiscale brain organization [1, 2]. Studies on non-human mammalian species have shown that the similarity of the microscale cortical cytoarchitecture is associated with the formation of macroscale cortico-cortical connectivity [3–5]. **Chapter 2** investigates whether such a micro-macro association is evolutionarily conserved in the human brain, by combining the state-of-the-art ultra-high-resolution BigBrain dataset and the macroscale human brain connectome. BigBrain data, which delineate the microscale cytoarchitecture, such as cell density and cell size [6], were used in this study to capture the laminar cytoarchitectonic profile of human cortical regions. In parallel, the macroscale human connectome was reconstructed using diffusion weighted imaging (DWI) data of healthy individuals from the Human Connectome Project (HCP) [7]. Bridging the two ends of scales showed that the cytoarchitectonic profiles were more similar between interconnected cortical regions as compared to non-connected regions. The level of the cytoarchitectonic profile similarity was positively correlated with the connectivity strength, suggesting that cortical regions with more similar cytoarchitecture tend to be stronger connected by white matter connections. These results thus confirm one of the important wiring principles of the connectome – the microscale cortical cytoarchitectonic similarity shapes the macroscale brain connectome organization – to be evolutionarily conserved in the human brain.

The relationship of microscale cytoarchitecture and macroscale connectivity reflects the commonality across species, now the question arises as to how the human connectome is differentiated from other non-human primates to support human's complex cognitive abilities. Thus, in **Chapter 3**, I demonstrate the wiring principles of higher-order cognitive networks from the perspective of evolutionary genetics. In the human brain, there are functional networks, such as the frontoparietal network

(FPN), salience network (SN), and default-mode network (DMN), supporting higher-order brain functions that differentiate human from other intelligent evolutionary relatives [8]. I thus hypothesized that brain regions of these higher-order cognitive networks are largely expanded in human evolution and this expansion is influenced by the underlying genetic differences between humans and other non-human primates. To test this hypothesis, cortical ribbon of humans and chimpanzees was first reconstructed using magnetic resonance imaging (MRI) data, and surface area of homologous cortical regions was compared between humans and chimpanzees. This comparison showed the highest cortical expansion in regions of higher-order cognitive networks, such as the FPN and DMN, in the human brain. Next, the pattern of brain expansion was linked to the gene expression pattern of the human-accelerated genes (HAR genes) in the human brain. Brain regions with more expansion in human evolution were found to demonstrate higher expression levels of HAR genes, with regions of the DMN showing the highest level of HAR gene expression. Comparative gene expression analysis further showed that HAR genes were differentially more expressed in higher-order cognitive networks in humans compared to chimpanzees and macaques. These findings together suggest that the upregulated expression of HAR genes may have played a role in the large expansion of cognitive functional networks during human brain evolution. Furthermore, **Chapter 3** identified a set of genes with specifically over-expression in the DMN and noted this gene set to be significantly overrepresented in HAR genes, and to be involved in synapse and dendrite formation. HAR genes and DMN-related genes show significant associations with individual variations in high-order cognitive functions, namely intelligence and sociability, and with risks of mental conditions, such as schizophrenia and autism. These findings highlight the potential role of HAR genes in shaping the higher-order cognitive functional networks in the human brain, and ultimately influencing cognitions and behaviors, and resulting in mental disorders of humans.

Examining the transcription-neuroimaging association provides insights for functional annotation of genes of interests and for exploration of genes associated with specific phenotypes of cognitive abilities or brain disorders. In **Chapter 4**, I present an integrative online platform, GAMBA (short for Gene Annotation using Macroscale Brain-imaging Association), which can be used to easily scrutinize the potential gene-transcription-neuroimaging associations. Given a set of genes of interest, GAMBA displays the cortical expression profile of these genes derived from the Allen Human Brain Atlas (AHBA) dataset [9] and its associations to spatial patterns of a wide range of neuroimaging phenotypes, including the topological layout of resting-

state brain functional networks, brain structural connectivity, cognitive components, cortical metabolic properties, functional and structural alterations across a range of brain disorders, et cetera. As an example of the application of GAMBA, I presented the cortical transcriptional profile of genes involved in microscale neuronal connectivity and its association with the organization of macroscale connectome. Moreover, I presented two examples in the context of brain disorders. One example showed APOE expression pattern to be associated with the pattern of brain structural/functional alterations in Alzheimer's disease, and the other showed the association between expression of autism spectrum disorder (ASD) risk genes and brain functional alterations in Asperger's syndrome. Together, GAMBA provides a user-friendly, open-source platform for functional annotation of genes with respect to macroscale neuroimaging-derived phenotypes of the healthy and diseased brain.

Schizophrenia is a mental disorder that is characterized by brain disconnectivity, in particular disconnectivity among highly connected rich-club regions [10]. However, confounded by factors such as prior therapeutic exposure and the potential influence of chronicity, it remained unclear to what extent the rich-club disconnectivity reflects the pathophysiology inherent to the nature of schizophrenia. **Chapter 5** thus aimed to examine the connectome abnormalities in first-episode, medication-naïve schizophrenia patients whose medical therapy is absent. To do so, DWI data and resting-state fMRI data from two independent samples were collected, including a principal dataset of 42 medication-naïve, previously untreated patients and 48 healthy controls, and a replication dataset of 39 first-episode patients (10 untreated patients) and 66 healthy controls. The connectome was reconstructed and the rich club organization was analyzed and compared between patients and controls. I showed that the rich club organization was significantly disrupted in medication-naïve schizophrenia patients as compared to healthy controls, with decreased rich-club connection strength in patients. The coupling between structural connectivity and functional connectivity among rich club regions was also decreased in medication-naïve schizophrenia patients. Using the replication dataset revealed similar results. These findings suggest that the disruption of rich club organization and functional dynamics may reflect an early feature of schizophrenia pathophysiology, which is independent of therapeutic exposure.

Observations of the association between microscale cytoarchitecture and macroscale connectome in the human brain lead to the assumption that macroscale brain disconnectivity in schizophrenia could be related to microscale neuropathology [1]. **Chapter 6** offers novel evidence for this cross-scale association by using in vivo

magnetization transfer imaging (MTI), which describes an indirect measurement of brain microstructure, such as myelination [11]. MTI data and DWI data from 78 schizophrenia patients and 93 healthy controls were collected to compute the magnetization transfer ratio (MTR) and to reconstruct the brain connectome, respectively. Significant MTR reductions were observed in prefrontal cortical regions, including bilateral rostral middle frontal areas, and right pars orbitalis and frontal pole, in schizophrenia patients as compared to controls. This finding confirms the prefrontal disruption of brain microstructure [12, 13]. Moreover, the cortical pattern of MTR reduction was observed to be associated with the pattern of macroscale dysconnectivity in schizophrenia, implicating regions with more myelination reduction to have more connectivity disruptions at the macroscale. This study thus provides empirical evidence for the prefrontal neuropathology in schizophrenia and further suggests the microscale deficits be associated with macroscale connectome abnormalities in schizophrenia.

General discussion

Multiscale wiring principles of the human brain connectome

The major goal of this thesis is to provide new insights into the wiring principles of the human brain connectome, namely, the rules governing the formation of macroscale structural and functional brain connectivity. Emerging evidence across a wide range of species has identified two evolutionarily conserved topological principles of the connectome: the community structure and the hub/rich-club organization [14]. The community structure at the macroscale describes that spatially or functionally close brain regions are preferentially connected to each other to form distinct communities that are functionally specialized in certain cognitive domains [15–17]. These distributed communities are connected by hub/rich-club brain regions via long-range and costly connections to enable efficient neural information integration within the whole brain [18, 19]. Therefore, the hub/rich-club organization displays a trade-off between minimizing the cost of neural resources and maximizing the efficiency of information communication [20, 21]. This thesis discusses and extends these two topological motifs in the context of the microscale brain structure to gain a deeper understanding of the biological wiring principles of the human brain connectome.

Results in **Chapter 2** support the notion that the microscale cytoarchitecture of cortical regions plays a role in shaping the macroscale brain connectivity. Neu-