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Spotlight

A Spotlight on Bridging Microscale and Macroscale Human Brain Architecture

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We place a spotlight on the emerging trend of jointly studying the micro- and macroscale organization of nervous systems. We discuss the pioneering studies of Ding et al. (2016) and Glasser et al. (2016) in the context of growing efforts to combine and integrate multiple features of brain organization into a multi-modal and multi-scale examination of the human brain.

The human brain is a complex system of neural elements working at different levels of organization concurrently. At the cellular microscale level, neurons and their dendritic and axonal projections form the basic elements of brain architecture, and histological studies have shown a rich variety of myelo-, chemo-, and cytoarchitecture across the cortex. For example, studies have shown large differences in the complexity of pyramidal neurons between brain regions, with pyramidal neurons in primary and association regions showing strong differences in dendritic tree length, number of dendritic branches, and/or spine density, suggesting that neuronal features are directly linked to a region's communication and information processing efficiency.

At the macroscale level at which we consider brain regions and large-scale communication pathways, studies have noted a similar richness in organizational features. Neuroimaging studies in humans and invasive studies in animals have shown a large variety of both anatomical and functional aspects of cortical regions, including complex morphological shapes, diverse functional specialization, and a complex network organization of macroscale connectivity.

While there is ample evidence that both microscale and macroscale features are key factors of nervous system organization (Figure 1), our knowledge about how these different scales of organization interact is remarkably sparse. Two recent studies have made an important new step in bridging the micro- and macroscale features of nervous system organization.

In a recent Human Connectome Project (HCP) study, Glasser and colleagues (Glasser et al., 2016) integrated a diverse range of magnetic resonance imaging (MRI) data that correlate with macroscale (e.g., spontaneous brain activity and functional connectivity derived from fMRI) and microscale (e.g., relative myelination measured by means of combining T1 and T2 imaging) cellular features. Their goal was to estimate a multi-modal atlas of human cortical areas (Figure 2), defined as regions posited to represent fundamental computational units with uniform microscale and macroscale features. Spatial gradients for each imaging modality were computed, highlighting cortical locations where imaging features were changing abruptly, thus suggesting the presence of areal boundaries. Fitted gradients from different modalities were manually reconciled, resulting in a multi-modal parcellation of 160 cortical regions, 83 of which appeared to correspond to previously known cortical areas and 77 potentially newly defined cortical regions. A subset of macroscale regions was compared to histologically derived cortical areas, illustrating the power of combining MRI and cellular examinations. Notably, many of the newly discovered regions were situated in the association cortex, which is the portion of the human cerebral cortex critical for higher cognitive functions. While the boundaries of primary cortical areas are relatively well established, the interpretation and use of multi-modal gradients to define areas within association cortex is not trivial. Further multi-modal and multi-scale examination of these newly defined cortical regions is thus very welcome, e.g., using histology to further validate MRI-based cortical regions, combined with experiments to search for distinct functional roles of selected regions. An additional important feature of the Glasser et al. (2016) study is their use of state-of-the-art technology that potentially allows the atlas to be adapted to new datasets. A machine learning algorithm was trained to define and recognize multi-modal "fingerprints" for each cortical region, allowing automated delineation of the cortical regions in other HCP subjects, and potentially subjects from other studies.

The recent study of Ding and colleagues from the Allen Institute for Brain Science (Ding et al., 2016) provides another unique resource of multi-modal and multi-scale neuroscience data. As mentioned by the Ding et al. (2016), detailed parcellation of the human cortex is crucial for understanding functional organization of the human brain, but scientific progress in this respect is hindered by the lack of detailed reference datasets that provide information at both scales of organization. In their study, Ding et al. (2016) provided a unique, highly detailed multi-modal digital atlas of the human brain, incorporating and combining information from both macroscale magnetic resonance imaging and microscale cellular stainings. Using a meticulous workflow, Ding et al. (2016) collected

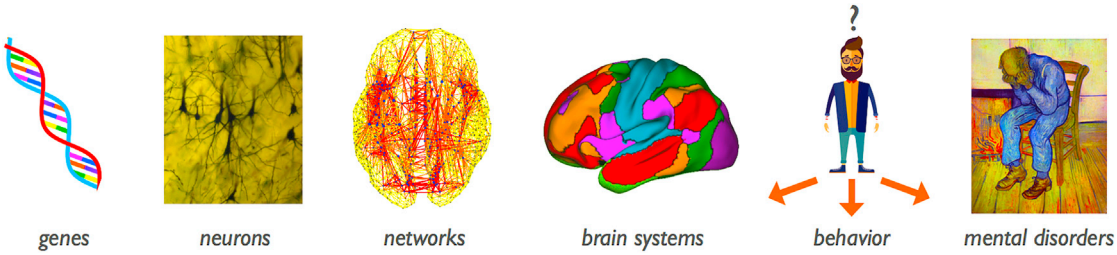

Figure 1. Neuroscience from the Microscale to the Macroscale Level of Human Brain Anatomy and Function

neuroimaging data (e.g., T1 and diffusion MRI) of a post-mortem female brain, followed by serial sectioning and microscale cellular Nissl and immunohistochemistry stainings of the same material. Identifying various macro-anatomical gyri and sulci in the histological slices, a comprehensive annotation of 862 structures was made, including a large number of distinct white matter tracts as well as several newly defined areas based on their cyto- and chemoarchitectonic profiles (Figure 2). Interestingly, these neocortical delineations were performed for gyri, sulci, and several Brodmann areas to fuse macro-anatomical and micro-cytoarchitecural parcellations of cortical areas together. Furthermore, Ding et al. (2016) made great effort to translate many of these annotations into the MRI dataset. As described by the authors, directly transposing histological anatomical delineations into a single 3D space is challenging due to incomplete and often nonuniform transformations between the two maps. To overcome this, Ding et al. (2016) matched individual Nissl plates to corresponding planes in the high-resolution anatomical MRI scans, which enabled identification of cytoarchitectonic delineated structures in macroscale 3D space. Such efforts of merging multiple data types together allow more and more macro- and microscale features of the same tissue to become available, allowing for fine feature identification of the MRI data as well as future examination of microscale features of large-scale anatomical and functional systems.

In the spirit of a strong and ongoing ambition of the neuroimaging community to put histological maps into MRI standardized space (e.g., Fischl et al., 2008), the Ding et al. (2016) and Glasser et al. (2016) studies highlight a rapidly growing interest of the neuroscience community to specifically combine and examine the multi-modal and multi-scale aspects of the human and animal brain (Figure 1). The aim of these studies is not only to "validate" MRI, but also because of an intrinsic, long-lasting motivation to bridge micro- and macro-anatomical and functional features of nervous systems. In the last 5 years, at least a dozen studies have aimed to bring together genetic, cellular, chemical, and macroscale tract-tracing and neuroimaging data to bridge different scales of cortical architecture. For example, cross-referencing the Allen Institute's transcriptional gene atlas with examinations of macroscale fMRI functional connectivity, Krienen and colleagues (Krienen et al., 2016) showed that genes enriched in the supragranular layers of the human cerebral cortex display distinct expression patterns across large-scale functional resting-state networks, and Richiardi and colleagues demonstrated that cortical patterns of gene-gene co-expression support synchronous activity in brain networks (Richiardi et al., 2015). Furthermore, several studies have combined gene expression and microscale cytoarchitectonics with macroscale tract-tracing data in animal brains and have found multiple relationships between macroscale connectivity and microscale gene expression (Fulcher and Fornito, 2016), cortical cytoarchitectonic type (Hilgetag et al., 2016), and chemoarchitecture (Turk et al., 2016). Continuing along this path, multi-scale studies of our group have shown evidence of an association between cortical organization of microscale supra-granular pyramidal complexity and human macroscale connectome organization (van den Heuvel et al., 2016b).

Further evidence for a micro-macro relationship of brain organization comes from studies that combine micro- and macroscale changes in disease conditions. Already several years ago, Buckner and colleagues pioneered a multimodal and cross-scale examination, linking the level of cellular amyloid deposition in Alzheimer patients with large-scale functional connectomics, reporting on a strong preference of cellular changes in the most densely connected functional regions of the brain (Buckner et al., 2009). Inspired by Buckner's and Krienen's approach, several recent studies have started to examine the cortical pattern of gene expression in the context of disease-related changes in macroscale brain properties. For example, Romme et al. (2017) combined cortical expression of genes related to schizophrenia and bipolar disorder with macroscale diffusion MRI. They showed that the spatial pattern of risk-gene expression is associated with the extent of macroscale cortico-cortical disconnectivity in patients, changes in turn also associated with the level of loss of microscale spine density of supragranular neurons in temporal and frontal areas of the brain, one of the hallmark features of schizophrenia (van den Heuvel et al., 2016b).

What could be an explanation for a relationship between micro- and macroscale neuronal and whole-brain organizational properties? One could argue that micro-macro relationships are trivial because neurons form the LEGO building blocks of nervous systems, and therefore macroscale features are simply the consequence of averaging the microscale building blocks on a bigger scale. In many dynamic systems, however, local organizational features are not trivially linked or easily translatable to macroscale organization, with different sets of principles governing organizational features at different scales. For example, in the field

of economics, micro- and macroscale processes are often described and studied independently, referred to as micro- and macro-economics. Similarly, we make clear distinctions when studying micro-, meso-, and macro social interactions. One potential type of interaction between the micro- and macroscale in brain systems might be that one scale places constraints on the organizational degrees of freedom of the other. For example, regions with a similar type of cytoarchitecture (Hilgetag et al., 2016) and/or gene-expression pattern (Krienen et al., 2016) may be more likely to connect to each other, introducing a "like-connect-to-like" constraint on the formation of macroscale connectivity. One suggested mechanism (but very likely not exhaustive) of such an interaction is the sequential ordering of brain region maturation during development and evolution of new cortical areas due to natural selection, resulting in conditions where microscale features ended up constraining macroscale features during developmental and evolutionary processes (Buckner and Krienen, 2013).

The converse might also be true. The macro-anatomical organization of the brain might shape spatial-temporal patterns of microscale processes, with perhaps the clearest examples in brain disorders. There have been significant studies on an "infectious" model of disease progression in several neurodegenerative disorders, including Alzheimer's disease (Zhou et al., 2012) and ALS (Schmidt et al., 2016), where the spatial-temporal pattern of regional dysfunction is found to follow the organization of macroscale functional and structural networks. Following a "prion-spread" pathology as in Creutzfeldt-Jacob's disease, combined neurological and computational neuroscience studies have argued that for a subset of neurodegenerative disorders, disease effects may begin with the misfolding of important neuronal proteins in a single or confined disease "epicenter" (Zhou et al., 2012) and with other brain regions becoming "infected" by means of axonal and synaptic propagation. The human brain exhibits several attributes of an efficient network organization, such as a cost-effective small-world modular organization, where there is a strong concentration of connectivity within confined modular subsystems that co-exists with the existence of short global communication routes across the entire brain (Hagmann et al., 2008). As a consequence of this network organization of connectivity, disease effects remain initially confined to the anatomical and functional network of the disease epicenter (Zhou et al., 2012) with later disease effects spreading to topologically more remote regions following the more global architecture of connectivity. A further consequence of this type of sequential disease propagation is that highly connected cortical hub regions with a large number of efferent and afferent tracts may become central elements in spread of disease effects across the entire brain, making them generally vulnerable regions and commonly reported players in the later stages of disease in a wide variety of brain disorders (Crossley et al., 2014).

An alternative, perhaps somewhat more exotic, micro-macro relationship might involve the existence of universal principles governing the organization at both the micro- and macroscale levels. Studies have noted similar organizational principles of connectivity at the microscale cellular as well as at the macroscale level. A general tendency toward sparse neural connectivity with connectivity concentrated within strongly connected segregated subsystems, combined with strong investment in network attributes that favor topological integration, are features consistently observed in a wide variety of species and experimental conditions. Datasets supporting these features range from complete microscale neural systems of simple species (Varshney et al., 2011), to reconstructions of cellular connectivity of small mammalian brain tissue samples (Helmstaedter et al., 2013), to mesoscale reconstructions of rodent brain connectome (Oh et al., 2014) and whole-brain connectivity at the large-scale level in humans (Hagmann et al., 2008). The observation of overlapping organizational principles across all these different datasets suggest universal principles shaping neural connectivity at different levels of nervous system organization (van den Heuvel et al., 2016a), resulting in potential interaction and interplay across scales.

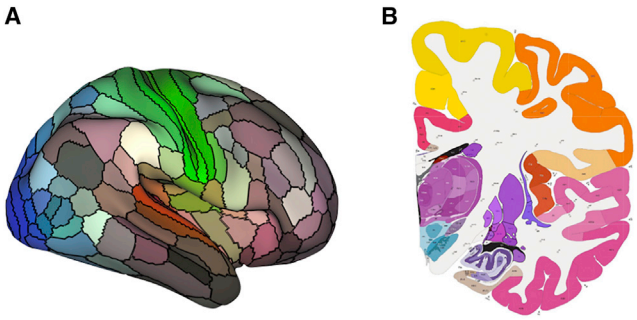

Figure 2. Multimodal and Multiscale Atlases of the Human Brain
(A) Right lateral view of Glasser's MRI-based multimodal parcellation (Glasser et al., 2016).
(B) Coronal slice of Ding's histogically defined modified Brodmann areas (Ding et al., 2016).

The Glasser et al. (2016) and Ding et al. (2016) studies herald new ways to study micro-macro interactions in the human and non-human brain. Besides their novel multimodal view, at least one additional aspect is worth emphasizing. Fully in line with the open character of the Human Connectome Project and the Allen Institute for Brain Science, both studies have made their data and methodology freely and publicly available. Glasser et al. (2016) have incorporated their atlas into the digital Brain Analysis Library of Spatial maps and Atlases framework (https://balsa.wustl.edu/), allowing old maps (e.g., Yeo et al., 2011) and new data to be compared with the high-resolution and multimodal atlas of the Human Connectome Project. Similarly, Ding et al. (2016) have integrated their multi-scale atlas with other atlases of the Allen Institute for Brain Science (for example, their human gene expression atlas: http://brain-map.org), forming a rich, freely available data resource for the neuroscience community. As such, these datasets form an invaluable resource for needed validation of in vivo brain imaging and derived metrics of cortical morphometry, connectivity, and activation. But perhaps of even more importance, the

unconstrained accessibility of these datasets facilitates future out-of-the-box combinations and cross-examinations with other types of publicly available data. All sorts of combinations are possible, ranging from old resources of cytoarchitectonic data to state-of-the-art methods to map and combine micro and macro features of brain organization. Setting a very welcome trend for open science, this "open kitchen" philosophy will have a long-lasting impact on neuroscience, supporting creative ideas on the examination of multimodal and multi-scale features of the human brain for many years to come.

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