Biological Psychiatry: Celebrating 50 Years

Review

Multiscale Neuroscience of Psychiatric Disorders

Martijn P. van den Heuvel, Lianne H. Scholtens, and René S. Kahn

ABSTRACT

The human brain comprises a multiscale network with multiple levels of organization. Neurons with dendritic and axonal connections form the microscale fabric of brain circuitry, and macroscale brain regions and white matter connections form the infrastructure for system-level brain communication and information integration. In this review, we discuss the emerging trend of multiscale neuroscience, the multidisciplinary field that brings together data from these different levels of nervous system organization to form a better understanding of between-scale relationships of brain structure, function, and behavior in health and disease. We provide a broad overview of this developing field and discuss recent findings of exemplary multiscale neuroscience studies that illustrate the importance of studying cross-scale interactions among the genetic, molecular, cellular, and macroscale levels of brain circuitry and connectivity and behavior. We particularly consider a central, overarching goal of these multiscale neuroscience studies of human brain connectivity: to obtain insight into how disease-related alterations at one level of organization may underlie alterations observed at other scales of brain network organization in mental disorders. We conclude by discussing the current limitations, challenges, and future directions of the field.

Keywords: Brain network, Connectivity, Cross-scale, Mental disorders, Multiscale, Psychiatry

https://doi.org/10.1016/j.biopsych.2019.05.015

The human brain comprises a hierarchical system of multiple levels of organization. At the microscale level, genetic and molecular processes shape the morphology and dynamics of neurons and their synaptic connections, among countless other crucial aspects of cell architecture and function. These neurons and their local connections are the building blocks of our nervous system; they connect into complex circuitry at the micro- and macroscales, and in turn form the anatomical infrastructure for neural communication and integration of large-scale brain systems, a prerequisite for healthy brain function and complex behavior (Figure 1). There is a long tradition of examining all of these distinct scales in detail in healthy and diseased conditions (1–10).

In recent years, there has been a growing interest in examining potential associations between these different levels of nervous system organization and addressing more deep-rooted questions of how the distinct scales of nervous system organization may be potentially related and interlinked. These multiscale studies aim to provide a better understanding of how biological processes at one scale of organization may relate to—or, more strongly, may cause or shape—processes at another level of organization of the human brain, and ultimately their relationship to brain disfunction (Figure 1) (11).

One particular field of neuroscience that greatly benefits from a multiscale view on brain structure and function is the field of network neuroscience, which maps and studies the elements and interactions of neurobiological systems from a network perspective (12). From the microscale neuron to the macroscale region level, at all scales of organization, connectivity is a central element of nervous system architecture and function. The comprehensive network of the elements and neural connections of the human brain is known as the human connectome (13) or human brain network (14), and with a growing availability of resources on both the micro- and macroscale levels of brain network connectivity, researchers have started to explore relationships among the genetic, molecular, and macroscale levels of human brain organization and behavior, and importantly, their putative multiscale interactions in disease conditions.

In this review, we discuss the upcoming field of multiscale neuroscience, with a specific focus on multiscale associations in brain connectivity in the context of mental disorders. We begin with an overview of empirical findings suggesting multiscale relationships among the genetic, molecular, cellular, and macroscale organization of healthy brain connectivity and behavior. With these interactions in mind, we then discuss multiscale findings in, among others, schizophrenia and autism, as examples of mental disorders in which studies have highlighted multiple cross-scale alterations to brain structure and function. We discuss proposed mechanisms through which micro- and macroscale properties of brain function and disfunction may be related. We conclude with a discussion on the current limitations and challenges of this field, together with the opportunities and future of multiscale neuroscience for biological psychiatry.

GENES AND MACROSCALE CONNECTIVITY

Twin-design studies (15) laid the foundation for showing a genetic basis of intersubject variation in brain structure and function, and set the stage for modern-day genome-wide association studies to provide support for a polygenic basis of intersubject variation in macroscale brain connectivity and

 ISSN: 0006-3223

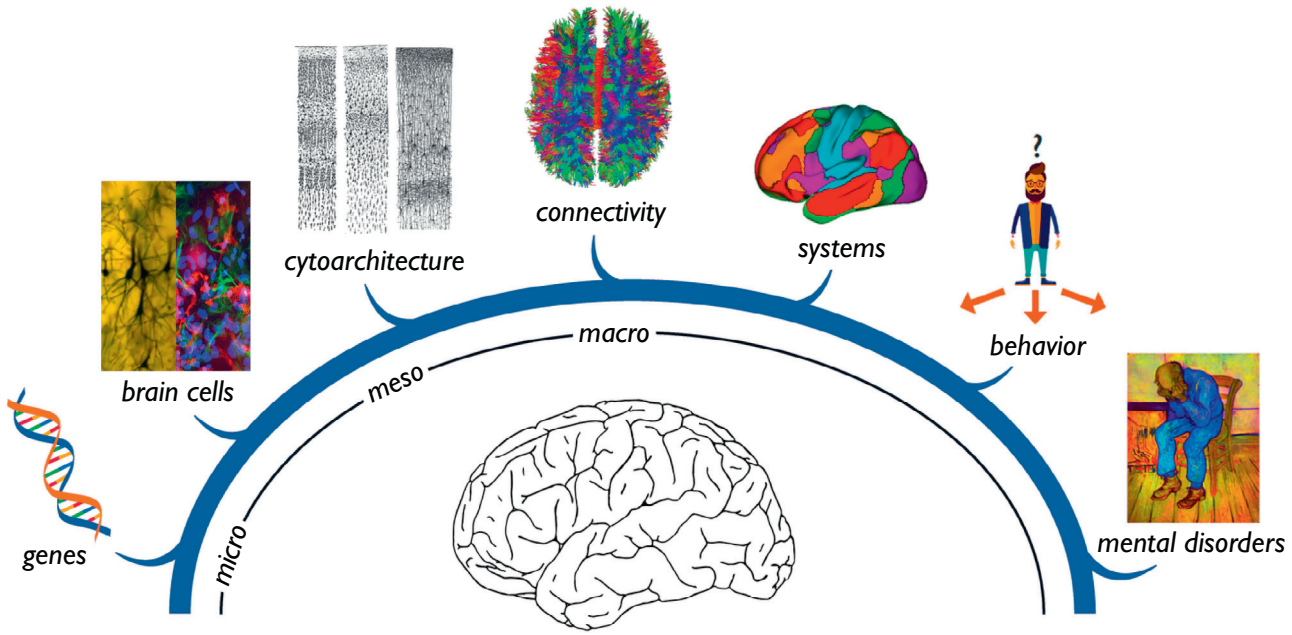

Figure 1. Multiscale organization of human brain structure, function, behavior, and disorders. Selected examples of microscale, mesoscale, and macroscale human brain organization and (dys)function, describing (from left to right) genes, brain cells (e.g., neurons in black [left], astrocytes in green, and microglia in red shown in human cultivated cells [right]), cytoarchitecture, connectivity, systems, behavior and mental disorders. Modified with permission from van den Heuvel and Yeo (11), with cytoarchitecture drawing modified with permission from Ramón y Cajal (127).

network architecture (16). Collaborative efforts of large-scale consortia (17) and global imaging genetics initiatives (18–20) have started to create a detailed image of the genetic architecture of macroscale brain structure (21) and function (22,23) and have highlighted a complex pleiotropic relationship between genetics and the macroscale organization of the human brain network and its functional systems (16,24–26).

Availability of regional gene expression data of the animal and human brain has recently further catalyzed the investigation of how microscale genetic processes may shape the properties of meso- and macroscale brain connectivity (Figure 2) (27): investigations combining gene expression data with macroscale connectome data in the animal and human brain have, for example, shown cortical regions connected by large-scale white matter tracts to display high coexpression in their genetic profile (28,29), suggesting a possible link between the spatial distribution of gene expression in the brain and corticocortical connectivity (28,30) (Figure 2). The dynamics of system-level functional connectivity have similarly been associated with the expression pattern of genes related to long-term cellular potentiation and suppression (29,31). Other examples of multiscale associations in the human brain include observations that the expression profile of genes related to synapse formation and synapse growth display large overlap with patterns of cortical metabolic activity, and that the cortical expression pattern of genes related to the organization of supragranular pyramidal cells overlap with both the global (32) and modular (33) organization of human brain resting-state functional networks, together with the organization of underlying anatomical connections (34). Distinct macroscale functional networks of the human cortex have been noted to display unique gene expression fingerprints (32), and a similar principle of distinct brain areas to show unique genetic expression profiles has been proposed for macroscale corticostriatal networks (35). As such, it is hypothesized that alterations in cortical gene expression profiles may play an important role in disconnectivity in disease. We will return to this central idea later in the context of a discussion of observations of multiscale findings in psychiatric disorders.

MICROSCALE CORTICAL STRUCTURE AND MACROSCALE CONNECTIVITY

The microscale structure and cytoarchitectonic organization of cortical regions and their microscale circuitry have also been noted as key factors in shaping brain connectivity at the macroscale. A long tradition of investigating the chemoarchitecture, cytoarchitecture, and myeloarchitecture of cortical areas (5) has demonstrated large variation in microscale neuronal cell type, size, and layer distribution across cortical areas. Multiscale studies combining information on the microscale organization of cortical areas with data on macroscale anatomical connectivity have proposed strong micro-macro associations, with the spatial overlap in cytoarchitectural organization between brain areas described as one of the major driving factors for the formation of corticocortical pathways (36). For example, animal studies in mouse (37) and cat (38) have shown brain regions with high cytoarchitectonic similarity to display stronger interregional anatomical connectivity, suggesting that the microscale neuronal organization of cortical areas may form an important factor in shaping large-scale anatomical connections of brain areas. Similar micro-macro principles have been suggested to play a

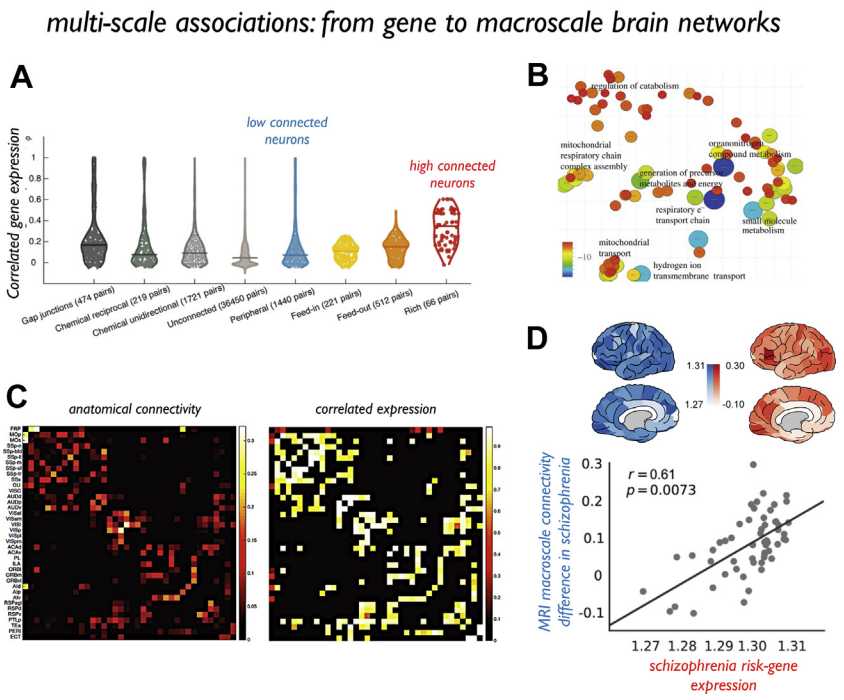

Figure 2. Examples of multiscale gene-network interactions in health and disease. **(A)** Gene profile similarity (y-axis) to increase between nodes of higher connectivity (x-axis), the highest for central connected hub nodes in the nervous system (red) of the roundworm. Modified with permission from Arnatkeviciute *et al.* (128). **(B)** Clear overlap in region-to-region macroscale connectivity (right panel, red) and transcriptomic similarity in regional gene expression profile (right panel, yellow) in the mouse brain. Modified with permission from Vertes *et al.* (33). **(C)** Enrichment analysis of gene expression profiles of genes related to long-distance connectivity and intermodular hubs in functional magnetic resonance imaging (MRI) networks in the human brain. Significantly enriched Gene Ontology terms are plotted in such a way that similar terms are represented more closely to another. Modified with permission from Richiardi *et al.* (29). **(D)** A significant association between the cortical expression profile of well-known risk genes for schizophrenia and the pattern of macroscale disconnectivity in patients as observed by means of diffusion-weighted MRI. Those regions where schizophrenia risk genes are most expressed are also those regions that show the strongest reduction in macroscale brain connectivity in disease conditions. Modified with permission from Romme *et al.* (74).

role in primate and human cortical wiring, with cytoarchitectural similarity between brain areas proposed as an important factor for the establishment of interregional anatomical pathways (37,38) (Figure 3). Centrally connected associative regions are, for example, noted to accommodate pyramidal neurons with a complex neural architecture, with larger and more spinous neurons as compared with primary regions (39); this type of neuronal architecture is well suited for a hypothesized large computational load of these regions (40).

Evidence for such a micro-macro relationship of brain connectivity further comes from studies that linked microscale properties to functional interactions between brain regions. The neurotransmitter receptor density fingerprint of cortical areas (5), determining a region's internal balance between microscale excitatory and inhibitory processes, has been suggested to influence the baseline level of resting-state functional connectivity of brain regions (41), the strength of connectivity within their corresponding functional subnetwork (42,43), and their regional functional dynamics over time (44). Multiscale findings further suggest that the granular organization of cortical regions may be associated to the type of functional connectivity of an area, with more agranular regions predominantly involved in internetwork communication and granular regions more involved in intranetwork functional connectivity (45). Likewise, myeloarchitectonic similarity has been linked to both the topological and spatial organization of macroscale functional systems (46).

GENES, NEURONS, MACROSCALE CONNECTIVITY, AND BEHAVIOR

A particular goal of multiscale studies is to examine how many of these different scales of nervous system organization finally relate to human behavior (Figure 1) and, in particular, to alterations in behavior in disease. Genetic association studies, for example, are founded on the notion of linking individual variation in genetics to variation in behavioral traits, with studies combining genetic and cognitive measurements providing insights into how microscale genetic variation relates to individual differences at the macroscale level in intelligence (47) and social behavior (48). Combined with other forms of genetic study designs, these studies provide a vital contribution in our understanding of how variation at the microscale genetic level may lead to clinical and preclinical abnormalities in human behavior [e.g., (49–51)]. Combining gene expression data with data on brain regions of specific functional systems may provide further insight into the link between genes and complex behavior, as, for example, illustrated by multiscale studies combining gene expression with data on the cortical layout of cognitive networks (32). Although less common, multiscale examinations may also involve the combination of human behavioral data with microscale neuronal data. Examples of this include multiscale studies that combine individual data on cortical cellular architecture with cognitive data, linking, for example, individual variation in human pyramidal neuronal organization and cognitive functioning (52).

MULTISCALE EFFECTS IN DISEASE

Anatomical and functional multiscale studies thus suggest that distinct organizational levels of the human brain are not independent, but rather that they share multiple architectural similarities. These findings naturally lead to the question of whether (and if so, how) changes at one level of organization relate to alterations in one or multiple other levels of brain organization. Technological advances in neuroscience have provided

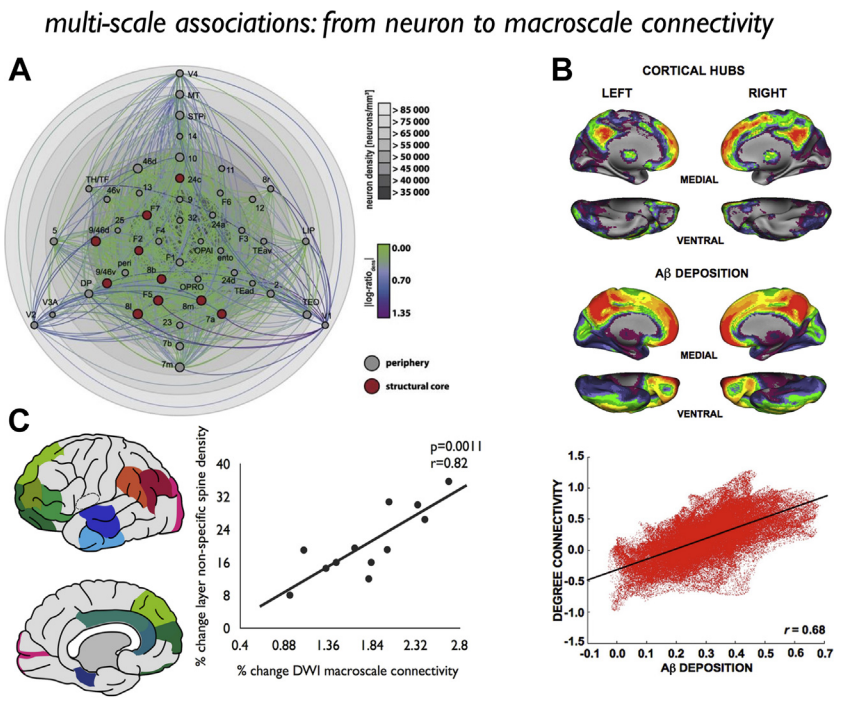

Figure 3. Examples of multiscale neuron-brain network relationships in health and disease. **(A)** Properties of macroscale connectivity in the macaque brain (higher-connected regions located in the core [red]) related to aspects of microscale neural organization (here, higher neuron density shown in grayscale). Modified with permission from Beul *et al.* (129). **(B)** The spatial overlap between macroscale functional hubs and cellular pathology (amyloid-β [Aβ] deposition) in Alzheimer's disease (upper panel) with a high correlation between brain-wide amyloid-β deposition levels across the entire cortex (lower panel). Modified with permission from Buckner *et al.* (60). **(C)** The relationship between differences at the microscale level of organization (% difference in spine density of cortical regions [y-axis], colors on the cortex indicate regions in which spine density was accumulated across literature) and macroscale disconnectivity (% change) as measured by means of diffusion-weighted magnetic resonance imaging (DWI) in schizophrenia. Modified with permission from van den Heuvel *et al.* (82).

promising progress in studying the genetic, cellular, and macroscale aspects of brain alterations in psychiatric and neurological brain disorders, but most of this empirical work so far has been focused on examining effects on one scale of brain organization at a time.

For example, twin studies and large-scale genome-wide association studies have shown a strong genetic component of schizophrenia (15,50), while studies into the molecular and cellular mechanisms of the disorder have identified synaptic reductions of pyramidal neurons in associative cortical areas as one of the key aspects of the disorder (53,54). Macroscale neuroimaging studies in turn have identified large-scale volumetric differences in cortical structure (55), anatomical dysconnectivity (56–58), and affected functional network organization (59) in patients. Such observations can be made for a wide range of brain disorders, with studies—generally focusing at a single observational scale—showing alterations at the genetic, microscale, and macroscale levels of brain organization.

A natural next step is to bring disease-related findings together and examine potential multiscale relationships in the biological background of psychiatric and neurological disorders. Buckner *et al.* (60) were some of the first to report on a voxel-to-voxel relationship between global macroscale functional brain connectivity (functional magnetic resonance imaging [MRI]) and regional levels of microscale positron emission tomography amyloid-β deposition in Alzheimer's disease and mild cognitive impairment. Most pronounced microstructural effects in the disorder were found to be located in the most densely connected areas of the brain in terms of functional interactions at the macroscale whole-brain level (60,61) (Figure 3). A proposed underlying mechanism for this multiscale observation is that highly connected association areas of the brain are biologically costlier than peripheral primary areas in terms of their rate and complexity of neuronal processing and related high metabolic demand, placing high demand on the local microscale cellular infrastructure of these areas (60,62). This micro-macro interaction may result in larger wear and tear of these regions, ultimately rendering these areas more vulnerable to disease processes.

As mentioned, schizophrenia likewise includes alterations at the genetic, cellular, molecular, and macroscale levels of brain organization. Multiscale investigations into the disorder have argued that these processes are not independent and hypothesize that these observed alterations could represent a potential continuum of effects across scales. Genetic risk for schizophrenia (63) and bipolar disorder (64,65) have, for example, been observed to be associated with individual variation in brain function, connectivity (66,67), and cognitive performance (68), as well as global brain structure (69,70). This suggests a potential relationship between a genetic risk for the disorder and alterations to macroscale brain organization, function, and behavior, although direct associations between, for example, brain volume or white matter integrity and a genetic risk for psychosis have yet to be established (71,72).

Disease-related macroscale alterations to brain structure and function may alternatively relate to the spatial distribution of where in the brain certain risk genes become mostly expressed. Multiscale studies combining gene expression data with data on changes in macroscale brain connectivity have, for example, noted substantial overlap between the pattern of where in the brain multiple genes related to a brain disorder

may be preferentially expressed and the pattern of changes in brain connectivity observed in patients. Other examples of such a genetic-macroscale connectivity relationship include studies that describe the cortical pattern of expression of schizophrenia risk genes across cortical regions to show considerable overlap with the pattern of macroscale differences in cortical thickness (73) and brain connectivity (74) (Figure 2), effects also observed for genes related to bipolar disorder (74,75), Parkinson's and Alzheimer's disease (76,77), and Huntington's disease (78). Brain regions showing white matter loss in Huntington's disease, for example, have been noted to display gene expression profiles enriched for synaptic and metabolic genes (79), suggestive of disease-related processes to simultaneously manifest at different levels of brain organization.

Such findings are consistent with the earlier discussed observation of genes enriched in supragranular layers of the cortex to be central factors in the formation of corticocortical connectivity (32), cortical layers that are argued to play a central role in the pathophysiology of schizophrenia (53,80,81). In further support of a multiscale interaction, the extent of synaptic reductions in supragranular pyramidal neurons across cortical regions has been suggested to relate to the pattern of macroscale corticocortical disconnectivity in patients (82), with regions with the largest reduction in spine density to display the largest reduction in macroscale connectivity (Figure 3).

Another illustrative example of a multiscale perspective of mental conditions comes from multimodal studies in autism. Genes associated with autism spectrum disorder, for example, have been found to be enriched in neurons involved in inhibitory neuronal processes (83), a type of neuronal circuitry argued to be disturbed at the macroscale level of brain organization (84,85). Risk genes for autism spectrum disorder (86) contribute to variation in cortical thickness and connectivity in patients (87) and are suggested to be particularly dysregulated in cortical areas of patients (87,88).

PRINCIPLES FOR MULTISCALE ASSOCIATIONS

Empirical observations of several links among the genetic, cellular, and macroscale attributes of brain organization thus suggest that the different scales of organization of the human brain are likely not independent from each other, but rather harbor several important multiscale interactions. A central theme across these studies is that the spatial location of where in the brain particular alterations (e.g., genetic, molecular, neuronal, or macroscale) occur may convey alterations to one or more other levels of brain organization.

Several underlying mechanisms of such a micro-macro relationship have been proposed (11). A first proposed mechanism is based on the notion that macroscale organizational features can result from an accumulation of microscale neuronal features, creating a continuous association between scales. Patterns of macroscale brain connectivity may result from a step-by-step accumulation of "Lego-like building block" properties of neuronal microscale circuits (89) (Figure 4A). As a result, modifications at the microcellular scale may accumulate to alterations in connectivity at the meso- and macroscale levels of nervous system organization.

Attributes of microscale cortical organization may also influence macroscale organization by applying large-scale spatial constraints on global structure and function (90). An example of such a mechanism is proposed by the tethering hypothesis (90), which suggests that molecular gradients, together with thalamocortical activity early in development, form cortical tethers that shape sensory hierarchies across the cortical sheet, posing a strong constraint on primary regions located near the anchor point, while more distant association areas are relatively untethered. This micro-macro relationship has been suggested to relate to a potential increased vulnerability of these "untethered" areas to mental disorders (90).

In many dynamical systems, however, local properties are not as easily translatable to aspects at other scales of organization, making most macroscale organizational attributes not trivially interpretable as an accumulation of features from smaller organizational scales (11). A less trivial proposed mechanism of micro-macro associations is one in which one scale places constraints on the organizational degrees of freedom of another scale of organization. Cyto- and myeloarchitectural similarity has been suggested to be an important guiding factor in the formation of interregional corticocortical connectivity (36,37). These observations have led to the suggestion that macroscale structural and functional connections may be formed according to a "similar prefers similar" wiring principle (91), in which regions sharing similarities in their organizational features (e.g., follow the same developmental trajectory, show high gene coexpression, share the same cortical type, display similar macroscale morphological properties) have a higher tendency of becoming anatomically or functionally connected and take part in the same circuitry and brain functions (Figure 4B).

The other way around may also be the case. The macroscale organization of the human brain network may play an important role in where in the brain cellular alterations may start and how they may subsequently spread to other brain areas (92). The modular organization of the human brain network, for example, has been argued to initially constrain region-to-region spreading patterns of disease pathology at the cellular level in various neurodegenerative disorders (60,92). These theories suggest that the macroscale organization of the human brain network may similarly have an effect on the microscale properties of brain function and, conversely, dysfunction.

An additional micro-macro mechanism may include the existence of similar principles governing the organization of connectivity at different levels of brain organization. Connectome studies have noted that microscale, mesoscale, and macroscale networks share many similar network attributes. Such features include a general tendency to form local circuits and specialized functional and structural modules, combined with a drive to invest in network attributes that bring topological integration like the formation of short communication paths and centrally connected hub regions (see Figures 4C and 5). These network attributes are, for example, observed across micro- and mesoscale cellular networks and circuitry [e.g., (93–95)], as well as in macroscale brain networks derived from neuroimaging and tract tracing experiments (96,97). The presence of similar network attributes at all of these distinct levels of brain organization argues for potential common

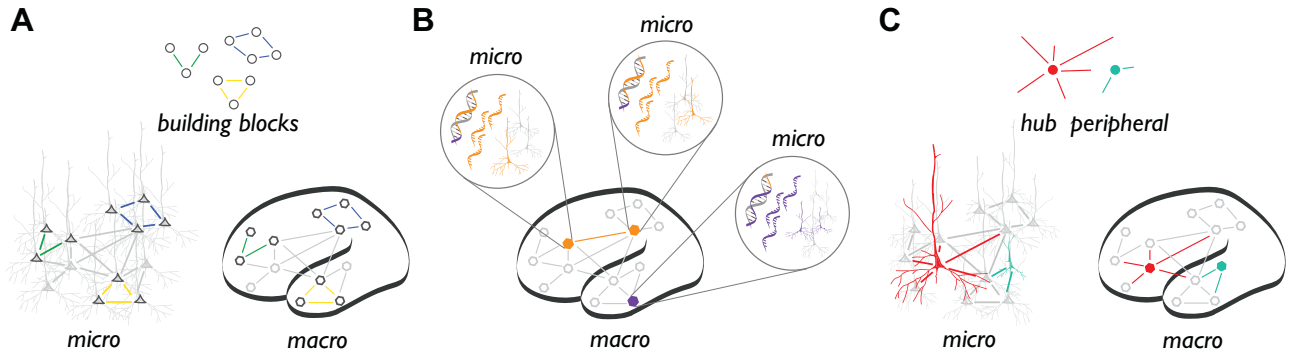

Figure 4. Examples of multiscale principles of brain organization. **(A)** A suggested principle of a step-by-step accumulation of microscale building blocks to create a continuous association between microscales (left) and macroscales (right) of brain organization (89). Examples of wiring building blocks (top) are depicted in yellow, green, and blue. **(B)** The similar-prefers-similar principle of regions with an overlapping genetic and/or cytoarchitectonic layout to have a higher probability of being connected at the macroscale level of brain organization. **(C)** The notion of networks across multiple scales of brain organization to depict similar organizational principles, showing the notion of the existence of hubs (red) across multiple scales of brain organization, ranging from the neuronal scale (left) to the macroscale level of brain organization (right).

principles of connectivity that govern both micro- and macroscale neural network connectivity, and as a result, one might argue that disease-related alterations to these common principles of connectivity may be manifested at multiple scales of brain organization at the same time (10).

It is important to mention that all such principles are likely under continuous modulation by environmental experience, behavior, and development. The frameworks discussed are necessarily abstractions of these intricate and intriguing interactions that characterize the naturalistic formation and functioning of the complex system that is the brain [for detailed reviews of this topic, see also (98,99)]. Development-related shifts, for example in gene expression, have a strong influence on both the developmental trajectory of the cytoarchitecture of cortical regions (100) and the developmental trajectory of macroscale brain structures (101). This argues for the existence of distinct differential developmental time windows for processes on both the microscale (e.g., cellular proliferation, migration, elimination [for review, see (102)]) and macroscale [e.g., myelination of large axonal pathways (103) and/or functional systems (104)] levels of brain organization, time windows that likely modulate or even introduce cross-scale relationships and similarities. Observations of alterations at multiple scales of brain organization in autism have, for example, led to the proposal of these alterations to relate back to simultaneous modifications at several anchor points in the neurodevelopmental timeline (105).

LIMITATIONS, CHALLENGES, AND FUTURE PERSPECTIVES OF MULTISCALE NEUROSCIENCE

The current state of multiscale neuroscience is that the field is still in its infancy. The field is limited by the methods and data used, many of which prompt opportunities for future developments. An important methodological aspect is that today's multiscale research involves a (pragmatic) shift away from studying the "individual" toward the examination of "brain regions and their connections." Traditional biopsychiatric research usually involves the examination of interactions between multiple layers of data by examining different sources of information collected in the same subjects, with, for example, genotypic and neuroimaging data linked together by the individual. In contrast, many of the studies reviewed in the present article are based on large-scale data collations of different data resources acquired across different individuals—for example, the cortical gene expression data from the Allen Human Brain Atlas (27), cytoarchitectonic data from historical brain atlases (106), and group-based macroscale MRI data of the Human Connectome Project (107). Cross-scale relationships are studied by bringing these different resources together in a common reference space, with cross-scale interactions examined across cortical regions, rather than across individuals. In addition, while we can call many of the examined datasets, without any hesitation, big data, the datasets are often based on relatively small sample sizes. With many of the described data resources highly complex and expensive to acquire, there are not yet many comparable replication sets available for the majority of the data resources. The lack of validation and reuse of the same datasets across a rapidly growing number of studies may limit long-term generalization and interpretability of the discussed multiscale associations. An additional resulting limitation of this paradigm shift is the inability to examine individual variation in multiscale relationships and their relationship in individual patients. The cross-sectional nature of the field leaves multiscale studies to make conclusions primarily on the basis of observed correlations and associations, without being equipped to address causal interactions between scales. In addition, the collative character of the discussed multiscale studies does not easily address differences in data quality and differences in signal properties between datasets.

An additional challenge that is so far often ignored in multiscale neuroscience research is the chronological nature of effects. The majority of the discussed multiscale studies—including both individual and collated data—are cross-sectional and thus limited in the sense that they do not provide insight into the developmental or longitudinal character of multiscale associations. Many disease-relevant mechanisms

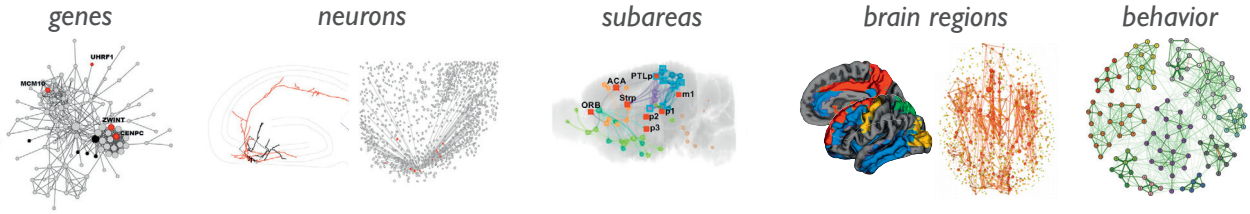

Figure 5. Several network attributes have been suggested to be present across multiple different scales of brain organization. One of such properties is the existence of densely connected hub elements within a network. Dense connectivity and hubs are observed across several levels of organization, ranging from microscale coexpression and protein-protein interaction networks to neuron-to-neuron connectivity and mesoscale and macroscale region-to-region brain networks, with dense connectivity and hubs at all these scales describing network elements that occupy a central and critical position in the network. Panels show a few empirical examples of dense elements and hubs across scales (from left to right): differentiating gene-gene expression of hub genes in autism (130) (first panel); essential protein-protein interactions in protein-protein interaction networks (131); hub neurons in the hippocampus (132) that are connected to many other neurons and argued to play an important role in critical processes of establishing neuron network organization (94) and, for example, orchestrating large-scale network dynamics (second panel); hub subareas in the mesoscale mouse connectome (third panel); and hub regions in the macroscale human connectome (left, fourth panel) and their dense level of rich club connectivity (right, fourth panel), argued to include key features of macroscale brain organization and be central for establishing efficient global communication (133), dynamics (134), and information integration (135); and dense symptom networks [conceptualizing psychiatric disorders as complex dynamic systems of mutually interacting symptoms (136); colors depict different disorders, nodes express different symptoms] (fifth panel). The shared central position of dense connectivity and hubs across all scales of brain organization has led to the hypothesis of such hubs to include general vulnerable elements of nervous system organization, making them common players in a wide range of mental disorders at multiple levels of organization. Hubs have, for example, been hypothesized to have a greater-than-average susceptibility to disease processes at the protein (137,138), microscale neuronal (139), and macroscale brain (7,10,62) levels. ACA, anterior cingulate area; m1, midbrain; ORB, orbital area; p1, pretectum; p2, thalamus; p3, prethalamus; PTLp, posterior parietal association areas; Strp, caudate nucleus. Modified with permission (left to right) from Pramparo *et al.* (130), Bonifazi *et al.* (132), Rubinov *et al.* (140), van den Heuvel and Sporns (141,142), and Boschloo *et al*. (143).

likely begin years before the disease manifests itself clinically [e.g., (108,109)] and progress over time. Examining the chronological dimension of disease effects is challenging for any field, but it is particularly so for multiscale research, in which trajectories of within-subject changes from different datasets are even less straightforwardly mapped upon each other.

Multiscale brain studies greatly benefit from a growing availability of open datasets, which allows for establishing unique combinations across different levels of brain organization. The discussed Allen Human Brain Atlas, for example, provides a unique data resource of (among other data) human gene expression levels at the whole-brain level (27), and datasets like the open Big Brain (110) otherwise allow for a unique comparison of cytoarchitectonic features to macroscale brain connectivity (111). Large-scale data frameworks such as PsychENCODE (112) that have the aim of linking molecules, genes, and regulatory elements to higher-order levels of biological complexity are of crucial importance to obtain deeper understanding of the multiscale organization of the human brain from gene to cell to behavior (113,114) in health and disease. Further combining of such data with detailed resources on transcriptional mechanisms of multiple stages of brain development, as provided by, for example, the BrainSpan database (115), provides important new avenues of examining the multiscale basis of neurodevelopment and neuropsychiatric risks (116). Cognitive neuroscience has further started several undertakings to provide ontologies of cognitive functions by meta-analysis of structural and functional MRI results and to systematically map these functions (and disease-related alterations) onto brain regions (117–119). These large-scale databases can be easily queried and combined with neuroscientific data from all levels of brain organization. New datasets describing multiscale data for the same set of individuals (and in particular in patients) would be of particular value to the field. Psychiatric brain banking by specialized brain tissue banks that focus on the collection of multiscale data of psychiatry patients represents an important step in making such investigations feasible in the near future (120).

Nonhuman animal investigations are of great importance in investigating multiscale associations of disease, in particular to provide insight into causal relationships between scales. Examples of such multiscale studies include the combination of DREADDs (designer receptors exclusively activated by designer drugs) with functional MRI in the mouse, allowing for a detailed examination of how macroscale patterns of functional connectivity networks are influenced by specific neuronal and synaptic activity at the cellular level (121). Future comparative multiscale neuroscience studies, examining commonalities and differences in multiscale principles across species [e.g., (122,123)], may provide an important translational link between animal and human neuroscience in health and disease.

While this review is focused on highlighting multiscale principles of nervous system organization, we end by mentioning that complementary insights may be gained from pinpointing where patterns of different scales of brain organization potentially diverge. Alterations at one level of organization may not always automatically translate to changes at other scales of brain organization; mechanisms of resilience may, for example, restrict these processes. Alterations at one level of brain organization may be counteracted by compensatory mechanisms at another level, providing resilience to disease effects. Empirical examples of this include macroscale MRI examinations that have suggested that attributes of macroscale connectivity may act as protective factors for the development of bipolar disorder in individuals who carry a genetic risk but have not developed the disorder (124). Further support for one level of brain organization to provide resilience to disease processes at another level may come from patient

studies showing an interaction between reserve to cognitive decline and microscale white matter lesioning. Patients who display certain organizational properties of their macroscale network—argued to be related to a larger cognitive reserve (125)—appear to be able to accrue higher levels of age-related microscale white matter lesioning without showing effects of cognitive decline (126). Such observations suggest that one level of brain organization could potentially compensate for alterations occurring at another level of organization. Future studies examining such potential multiscale principles of resilience may provide new insight into how disease effects may or may not translate across scales.

With our review, we hope to discuss some of the challenges and opportunities of the new field of multiscale neuroscience and highlight the importance of examining multiscale relationships of brain organization in mental brain disorders. Combining information on alterations in brain connectivity at the genetic, cellular, circuitry, and macroscale connectome levels sheds new light on the biological cause of mental brain disorders, placing disease-related differences in brain connectivity into a continuum of effects across multiple scales of brain organization.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by Vidi Grant No. 452-16-015 (to MPvdH) from the Netherlands Organization for Scientific Research on cross-scale neuroscience, ALW Open Grant No. ALWOP.179 (to MPvdH) on comparative connectomics from the Netherlands Ogranization for Scientific Research, and an MQ fellowship (to MPvdH). Funding agents had no influence on the content of the manuscript.

We thank Danielle Posthuma for helpful comments on topics discussed in the manuscript. We thank Vivi Heine for sharing a beautiful image of one of her stainings on astrocytes and microglia in human-cultivated cells for use in Figure 1.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Connectome Lab (MPvdH, LHS), Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam Neuroscience; and Department of Clinical Genetics (MPvdH), Amsterdam University Medical Center, Amsterdam Neuroscience, Amsterdam; and Brain Center Rudolf Magnus (RSK), Department of Psychiatry, University Medical Center Utrecht, Utrecht, the Netherlands; and the Department of Psychiatry (RSK), Icahn School of Medicine at Mount Sinai, New York, New York.

Address correspondence to Martijn P. van den Heuvel, Ph.D., Vrije Universiteit Amsterdam, Department of Complex Trait Genetics, CNCR, Boelelaan 1085, W&N B-651, 1081 HV, Amsterdam, the Netherlands; E-mail: martijn.vanden.heuvel@vu.nl.

Received Dec 28, 2018; revised May 16, 2019; accepted May 17, 2019.

REFERENCES

1. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L, *et al.* (2018): Analysis of shared heritability in common disorders of the brain. Science 360:eaap8757.
2. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, *et al.* (2011): Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol Psychiatry 16:751–762.
3. Melbourne JK, Rosen C, Feiner B, Sharma RP (2018): C4A mRNA expression in PBMCs predicts the presence and severity of delusions in schizophrenia and bipolar disorder with psychosis. Schizophr Res 77:37–45.
4. Pergola G, Di Carlo P, Jaffe AE, Papalino M, Chen Q, Hyde TM, *et al.* (2019): Prefrontal coexpression of schizophrenia risk genes is associated with treatment response in patients. Biol Psychiatry 86:45–55.
5. Amunts K, Zilles K (2015): Architectonic mapping of the human brain beyond Brodmann. Neuron 88:1086–1107.
6. Penzes P, Cahill ME, Jones KA, VanLeeuwen J-E, Woolfrey KM (2011): Dendritic spine pathology in neuropsychiatric disorders. Nat Neurosci 14:285–293.
7. Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, *et al.* (2014): The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 137:2382–2395.
8. van den Heuvel MP, Fornito A (2014): Brain networks in schizophrenia. Neuropsychol Rev 24:32–48.
9. Fornito A, Zalesky A, Breakspear M (2015): The connectomics of brain disorders. Nat Rev Neurosci 16:159–172.
10. van den Heuvel MP, Sporns O (2019): A cross-disorder connectome landscape of brain dysconnectivity. Nat Rev Neurosci 20:435–446.
11. van den Heuvel MP, Yeo BT (2017): A spotlight on bridging microscale and macroscale human brain architecture. Neuron 93:1248–1251.
12. Bassett DS, Sporns O (2017): Network neuroscience. Nat Neurosci 20:353–364.
13. Sporns O, Tononi G, Kotter R (2005): The human connectome: A structural description of the human brain. PLoS Comput Biol 1:e42.
14. van den Heuvel MP, Hulshoff Pol HE (2010): Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20:519–534.
15. Kendler KS (1993): Twin studies of psychiatric illness. Current status and future directions. Arch Gen Psychiatry 50:905–915.
16. Jahanshad N, Rajagopalan P, Hua X, Hibar DP, Nir TM, Toga AW, *et al.* (2013): Genome-wide scan of healthy human connectome discovers SPON1 gene variant influencing dementia severity. Proc Natl Acad Sci U S A 110:4768–4773.
17. Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, *et al.* (2014): The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav 8:153–182.
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, *et al.* (2015): UK biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 12:e1001779.
19. Jaddoe VW, Bakker R, van Duijn CM, van der Heijden AJ, Lindemans J, Mackenbach JP, *et al.* (2007): The Generation R Study Biobank: A resource for epidemiological studies in children and their parents. Eur J Epidemiol 22:917–923.
20. Petersen RC, Aisen PS, Beckett LA, Donohue MC, Gamst AC, Harvey DJ, *et al.* (2010): Alzheimer's Disease Neuroimaging Initiative (ADNI): Clinical characterization. Neurology 74:201–209.
21. Hibar DP, Stein JL, Renteria ME, Arias-Vasquez A, Desrivières S, Jahanshad N, *et al.* (2015): Common genetic variants influence human subcortical brain structures. Nature 520:224.
22. Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, *et al.* (2010): Genetic control over the resting brain. Proc Natl Acad Sci U S A 107:1223–1228.
23. Ge T, Holmes AJ, Buckner RL, Smoller JW, Sabuncu MR (2017): Heritability analysis with repeat measurements and its application to resting-state functional connectivity. Proc Natl Acad Sci U S A 114:5521–5526.
24. Lopez LM, Bastin ME, Maniega SM, Penke L, Davies G, Christoforou A, *et al.* (2012): A genome-wide search for genetic influences and biological pathways related to the brain's white matter integrity. Neurobiol Aging 33:1847.e1841-1847.e1814.
25. Kochunov P, Glahn D, Nichols T, Winkler A, Hong E, Holcomb H, *et al.* (2011): Genetic analysis of cortical thickness and fractional anisotropy of water diffusion in the brain. Front Neurosci 5:120.

26. Giddaluru S, Espeseth T, Salami A, Westlye LT, Lundquist A, Christoforou A, *et al.* (2016): Genetics of structural connectivity and information processing in the brain. Brain Struct Funct 221:4643–4661.
27. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, *et al.* (2012): An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 489:391–399.
28. Fulcher BD, Fornito A (2016): A transcriptional signature of hub connectivity in the mouse connectome. Proc Natl Acad Sci U S A 113:1435–1440.
29. Richiardi J, Altmann A, Milazzo AC, Chang C, Chakravarty MM, Banaschewski T, *et al.* (2015): BRAIN NETWORKS. Correlated gene expression supports synchronous activity in brain networks. Science 348:1241–1244.
30. Arnatkeviciute A, Fornito A, Fulcher BD (2018): Uncovering the transcriptional signatures of hub connectivity in neural networks [published online ahead of print Aug 8]. PsyArXiv.
31. Diez I, Sepulcre J (2018): Neurogenetic profiles delineate large-scale connectivity dynamics of the human brain. Nat Commun 9:3876.
32. Krienen FM, Yeo BTT, Ge T, Buckner RL, Sherwood CC (2016): Transcriptional profiles of supragranular-enriched genes associate with corticocortical network architecture in the human brain. Proc Natl Acad Sci U S A 113:E469–E478.
33. Vertes PE, Rittman T, Whitaker KJ, Romero-Garcia R, Vasa F, Kitzbichler MG, *et al.* (2016): Gene transcription profiles associated with inter-modular hubs and connection distance in human functional magnetic resonance imaging networks. Philos Trans R Soc Lond B Biol Sci 371:20150362.
34. Romero-Garcia R, Whitaker KJ, Váša F, Seidlitz J, Shinn M, Fonagy P, *et al.* (2018): Structural covariance networks are coupled to expression of genes enriched in supragranular layers of the human cortex. Neuroimage 171:256–267.
35. Anderson KM, Krienen FM, Choi EY, Reinen JM, Yeo BTT, Holmes AJ (2018): Gene expression links functional networks across cortex and striatum. Nat Commun 9:1428.
36. Barbas H, Rempel-Clower N (1997): Cortical structure predicts the pattern of corticocortical connections. Cereb Cortex 7:635–646.
37. Goulas A, Uylings HB, Hilgetag CC (2017): Principles of ipsilateral and contralateral cortico-cortical connectivity in the mouse. Brain Struct Funct 222:1281–1295.
38. Beul SF, Grant S, Hilgetag CC (2015): A predictive model of the cat cortical connectome based on cytoarchitecture and distance. Brain Struct Funct 220:3167–3184.
39. Scholtens LH, Schmidt R, de Reus MA, van den Heuvel MP (2014): Linking macroscale graph analytical organization to microscale neuroarchitectonics in the macaque connectome. J Neurosci 34:12192–12205.
40. Elston GN (2003): Cortex, cognition and the cell: New insights into the pyramidal neuron and prefrontal function. Cereb Cortex 13:1124–1138.
41. van den Heuvel MP, Scholtens LH, Turk E, Mantini D, Vanduffel W, Feldman Barrett L (2016): Multimodal analysis of cortical chemoarchitecture and macroscale fMRI resting-state functional connectivity. Hum Brain Mapp 37:3103–3113.
42. Stagg CJ, Bachtiar V, Amadi U, Gudberg CA, Ilie AS, Sampaio-Baptista C, *et al.* (2014): Local GABA concentration is related to network-level resting functional connectivity. eLife 3:e01465.
43. Kapogiannis D, Reiter DA, Willette AA, Mattson MP (2013): Posteromedial cortex glutamate and GABA predict intrinsic functional connectivity of the default mode network. Neuroimage 64:112–119.
44. Duarte R, Seeholzer A, Zilles K, Morrison A (2017): Synaptic patterning and the timescales of cortical dynamics. Curr Opin Neurobiol 43:156–165.
45. Wylie KP, Kronberg E, Maharajh K, Smucny J, Cornier M-A, Tregellas JR (2015): Between-network connectivity occurs in brain regions lacking layer IV input. Neuroimage 116:50–58.
46. Hunt BAE, Tewarie PK, Mougin OE, Geades N, Jones DK, Singh KD, *et al.* (2016): Relationships between cortical myeloarchitecture and electrophysiological networks. Proc Natl Acad Sci U S A 113:13510–13515.
47. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, de Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet 50:912–919.
48. Day FR, Ong KK, Perry JRB (2018): Elucidating the genetic basis of social interaction and isolation. Nat Commun 9:2457.
49. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, *et al.* (2018): Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet 50:920–927.
50. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.
51. Bralten J, van Hulzen KJ, Martens MB, Galesloot TE, Arias Vasquez A, Kiemeney LA, *et al.* (2018): Autism spectrum disorders and autistic traits share genetics and biology. Mol Psychiatry 23:1205–1212.
52. Goriounova NA, Heyer DB, Wilbers R, Verhoog MB, Giugliano M, Verbist C, *et al.* (2018): Large and fast human pyramidal neurons associate with intelligence. eLife 7:e41714.
53. Glantz LA, Lewis DA (2000): Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 57:65–73.
54. McGlashan TH, Hoffman RE (2000): Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry 57:637–648.
55. van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, *et al.* (2011): Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry 68:871–880.
56. van den Heuvel MP, Sporns O, Collin G, Scheewe T, Mandl RCW, Cahn W, *et al.* (2013): Abnormal rich club organization and functional brain dynamics in schizophrenia. JAMA Psychiatry 70:783–792.
57. Zalesky A, Fornito A, Seal ML, Cocchi L, Westin CF, Bullmore ET, *et al.* (2011): Disrupted axonal fiber connectivity in schizophrenia. Biol Psychiatry 69:80–89.
58. Whitford TJ, Grieve SM, Farrow TF, Gomes L, Brennan J, Harris AW, *et al.* (2007): Volumetric white matter abnormalities in first-episode schizophrenia: A longitudinal, tensor-based morphometry study. Am J Psychiatry 164:1082–1089.
59. Lynall M-E, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, *et al.* (2010): Functional connectivity and brain networks in schizophrenia. J Neurosci 30:9477–9487.
60. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, *et al.* (2009): Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci 29:1860–1873.
61. Prescott JW, Guidon A, Doraiswamy PM, Roy Choudhury K, Liu C, Petrella JR (2014): The Alzheimer structural connectome: Changes in cortical network topology with increased amyloid plaque burden. Radiology 273:175–184.
62. de Haan W, Mott K, van Straaten ECW, Scheltens P, Stam CJ (2012): Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. PLoS Comput Biol 8:e1002582.
63. Kauppi K, Westlye LT, Tesli M, Bettella F, Brandt CL, Mattingsdal M, *et al.* (2014): Polygenic risk for schizophrenia associated with working memory-related prefrontal brain activation in patients with schizophrenia and healthy controls. Schizophr Bull 41:736–743.
64. Dima D, de Jong S, Breen G, Frangou S (2016): The polygenic risk for bipolar disorder influences brain regional function relating to visual and default state processing of emotional information. Neuroimage Clin 12:838–844.
65. Dima D, Roberts RE, Frangou S (2016): Connectomic markers of disease expression, genetic risk and resilience in bipolar disorder. Transl Psychiatry 6:e706.
66. Wang T, Zhang X, Li A, Zhu M, Liu S, Qin W, *et al.* (2017): Polygenic risk for five psychiatric disorders and cross-disorder and disorder-specific neural connectivity in two independent populations. Neuroimage Clin 14:441–449.

67. Zhang Z, Yan T, Wang Y, Zhang Q, Zhao W, Chen X, *et al.* (2018): Polymorphism in schizophrenia risk gene MIR137 is associated with the posterior cingulate Cortex's activation and functional and structural connectivity in healthy controls. Neuroimage Clin 19:160–166.
68. Krug A, Dietsche B, Zöllner R, Yüksel D, Nöthen MM, Forstner AJ, *et al.* (2018): Polygenic risk for schizophrenia affects working memory and its neural correlates in healthy subjects. Schizophr Res 197:315–320.
69. Franke B, Stein JL, Ripke S, Anttila V, Hibar DP, van Hulzen KJE, *et al.* (2016): Genetic influences on schizophrenia and subcortical brain volumes: Large-scale proof of concept. Nat Neurosci 19:420–431.
70. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, *et al.* (2001): Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. Biol Psychiatry 49:811–823.
71. Reus LM, Shen X, Gibson J, Wigmore E, Ligthart L, Adams MJ, *et al.* (2017): Association of polygenic risk for major psychiatric illness with subcortical volumes and white matter integrity in UK Biobank. Sci Rep 7:42140.
72. Jansen PR, Muetzel RL, Polderman TJC, Jaddoe VW, Verhulst FC, van der Lugt A, *et al.* (2019): Polygenic scores for neuropsychiatric traits and white matter microstructure in the pediatric population. Biol Psychiatry Cogn Neurosci Neuroimaging 4:243–250.
73. French L, Gray C, Leonard G, Perron M, Pike GB, Richer L, *et al.* (2015): Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. JAMA Psychiatry 72:1002–1011.
74. Romme IAC, de Reus MA, Ophoff RA, Kahn RS, van den Heuvel MP (2017): Connectome disconnectivity and cortical gene expression in patients with schizophrenia. Biol Psychiatry 81:495–502.
75. McCarthy MJ, Liang S, Spadoni AD, Kelsoe JR, Simmons AN (2014): Whole brain expression of bipolar disorder associated genes: Structural and genetic analyses. PloS One 9:e100204.
76. Grothe MJ, Sepulcre J, Gonzalez-Escamilla G, Jelistratova I, Scholl M, Hansson O, *et al.* (2018): Molecular properties underlying regional vulnerability to Alzheimer's disease pathology. Brain 141:2755–2771.
77. Rittman T, Rubinov M, Vertes PE, Patel AX, Ginestet CE, Ghosh BCP, *et al.* (2016): Regional expression of the MAPT gene is associated with loss of hubs in brain networks and cognitive impairment in Parkinson disease and progressive supranuclear palsy. Neurobiol Aging 48:153–160.
78. Tabrizi SJ, Scahill RI, Durr A, Roos RA, Leavitt BR, Jones R, *et al.* (2011): Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: The 12-month longitudinal analysis. Lancet Neurol 10:31–42.
79. McColgan P, Gregory S, Seunarine KK, Razi A, Papoutsi M, Johnson E, *et al.* (2018): Brain regions showing white matter loss in Huntington's disease are enriched for synaptic and metabolic genes. Biol Psychiatry 83:456–465.
80. Kolluri N, Sun Z, Sampson AR, Lewis DA (2005): Lamina-specific reductions in dendritic spine density in the prefrontal cortex of subjects with schizophrenia. Am J Psychiatry 162:1200–1202.
81. Wagstyl K, Ronan L, Whitaker KJ, Goodyer IM, Roberts N, Crow TJ, *et al.* (2016): Multiple markers of cortical morphology reveal evidence of supragranular thinning in schizophrenia. Transl Psychiatry 6:e780.
82. van den Heuvel MP, Scholtens LH, de Reus MA, Kahn RS (2016): Associated microscale spine density and macroscale connectivity disruptions in schizophrenia. Biol Psychiatry 80:293–301.
83. Wang P, Zhao D, Lachman HM, Zheng D (2018): Enriched expression of genes associated with autism spectrum disorders in human inhibitory neurons. Transl Psychiatry 8:13.
84. Kana RK, Keller TA, Minshew NJ, Just MA (2007): Inhibitory control in high-functioning autism: Decreased activation and underconnectivity in inhibition networks. Biol Psychiatry 62:198–206.
85. Uddin LQ, Supekar K, Menon V (2013): Reconceptualizing functional brain connectivity in autism from a developmental perspective. Front Hum Neurosci 7:458.
86. Zoghbi HY, Bear MF (2012): Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. Cold Spring Harb Perspect Biol 4:a009886.
87. Romero-Garcia R, Warrier V, Bullmore ET, Baron-Cohen S, Bethlehem RAI (2019): Synaptic and transcriptionally downregulated genes are associated with cortical thickness differences in autism. Mol Psychiatry 24:1053–1064.
88. Mariani J, Coppola G, Zhang P, Abyzov A, Provini L, Tomasini L, *et al.* (2015): FOXG1-dependent dysregulation of GABA/glutamate neuron differentiation in autism spectrum disorders. Cell 162:375–390.
89. Perin R, Berger TK, Markram H (2011): A synaptic organizing principle for cortical neuronal groups. Proc Natl Acad Sci U S A 108:5419–5424.
90. Buckner RL, Krienen FM (2013): The evolution of distributed association networks in the human brain. Trends Cogn Sci 17:648–665.
91. Barbas H (2015): General cortical and special prefrontal connections: Principles from structure to function. Annu Rev Neurosci 38:269–289.
92. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD (2009): Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42–52.
93. Schroeter MS, Charlesworth P, Kitzbichler MG, Paulsen O, Bullmore ET (2015): Emergence of rich-club topology and coordinated dynamics in development of hippocampal functional networks in vitro. J Neurosci 35:5459–5470.
94. Gal E, London M, Globerson A, Ramaswamy S, Reimann MW, Muller E, *et al.* (2017): Rich cell-type-specific network topology in neocortical microcircuitry. Nat Neurosci 20:1004–1013.
95. Chiang AS, Lin CY, Chuang CC, Chang HM, Hsieh CH, Yeh CW, *et al.* (2011): Three-dimensional reconstruction of brain-wide wiring networks in Drosophila at single-cell resolution. Curr Biol 21:1–11.
96. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, *et al.* (2008): Mapping the structural core of human cerebral cortex. PLoS Biol 6:e159.
97. van den Heuvel MP, Bullmore ET, Sporns O (2016): Comparative connectomics. Trends Cogn Sci 20:345–361.
98. Cox MJ, Mills-Koonce R, Propper C, Gariepy JL (2010): Systems theory and cascades in developmental psychopathology. Dev Psychopathol 22:497–506.
99. Gariépy JL (1996): The question of continuity and change in development. In: Cairns RB, GH Elder Jr, Costello EJ, editors. Cambridge Studies in Social and Emotional Development: Developmental Science. Cambridge, United Kingdom: Cambridge University Press, 78–96.
100. Nowakowski TJ, Bhaduri A, Pollen AA, Alvarado B, Mostajo-Radji MA, Di Lullo E, *et al.* (2017): Spatiotemporal gene expression trajectories reveal developmental hierarchies of the human cortex. Science 358:1318–1323.
101. Douet V, Chang L, Cloak C, Ernst T (2014): Genetic influences on brain developmental trajectories on neuroimaging studies: From infancy to young adulthood. Brain Imaging Behav 8:234–250.
102. Stiles J, Jernigan TL (2010): The basics of brain development. Neuropsychol Rev 20:327–348.
103. Deoni SCL, Mercure E, Blasi A, Gasston D, Thomson A, Johnson M, *et al.* (2011): Mapping infant brain myelination with magnetic resonance imaging. J Neurosci 31:784–791.
104. Supekar K, Musen M, Menon V (2009): Development of large-scale functional brain networks in children. PLoS Biol 7:e1000157.
105. Zikopoulos B, Barbas H (2013): Altered neural connectivity in excitatory and inhibitory cortical circuits in autism. Front Hum Neurosci 7:609.
106. Scholtens LH, de Reus MA, de Lange SC, Schmidt R, van den Heuvel MP (2018): An MRI Von Economo - Koskinas atlas. Neuroimage 170:249–256.
107. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K (2013): The WU-Minn Human Connectome Project: An overview. Neuroimage 80:62–79.
108. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, *et al.* (2016): Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 12:292–323.

109. Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F (2001): Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry 58:158–164.
110. Amunts K, Lepage C, Borgeat L, Mohlberg H, Dickscheid T, Rousseau M-É, *et al.* (2013): BigBrain: An ultrahigh-resolution 3D human brain model. Science 340:1472–1475.
111. Wei Y, Scholtens LH, Turk E, van den Heuvel MP (2018): Multiscale examination of cytoarchitectonic similarity and human brain connectivity. Netw Neurosci 3:124–137.
112. PsychENCODE Consortium, Akbarian S, Liu C, Knowles JA, Vaccarino FM, Farnham PJ, *et al.* (2015): The PsychENCODE project. Nat Neurosci 18:1707–1712.
113. PsychENCODE Consortium (2018): Revealing the brain's molecular architecture. Science 362:1262–1263.
114. Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, *et al.* (2018): Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science 362.
115. BrainSpan Consortium: BrainSpan: Atlas of the Developing Human Brain. Available at: http://www.brainspan.org. Accessed April 1, 2019.
116. Li M, Santpere G, Imamura Kawasawa Y, Evgrafov OV, Gulden FO, Pochareddy S, *et al.* (2018): Integrative functional genomic analysis of human brain development and neuropsychiatric risks. Science 362: eaat7615.
117. Fox PT, Lancaster JL (2002): Opinion: Mapping context and content: The BrainMap model. Nat Rev Neurosci 3:319–321.
118. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD (2011): Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 8:665–670.
119. Yeo BT, Krienen FM, Eickhoff SB, Yaakub SN, Fox PT, Buckner RL, *et al.* (2015): Functional specialization and flexibility in human association cortex. Cereb Cortex 25:3654–3672.
120. Deep-Soboslay A, Benes FM, Haroutunian V, Ellis JK, Kleinman JE, Hyde TM (2011): Psychiatric brain banking: Three perspectives on current trends and future directions. Biol Psychiatry 69:104–112.
121. Giorgi A, Migliarini S, Galbusera A, Maddaloni G, Mereu M, Margiani G, *et al.* (2017): Brain-wide mapping of endogenous serotonergic transmission via chemogenetic fMRI. Cell Rep 21:910–918.
122. Scholtens LH, Feldman Barrett L, van den Heuvel MP (2018): Cross-species evidence of interplay between neural connectivity at the micro- and macroscale of connectome organization in human, mouse, and rat brain. Brain Connect 8:595–603.
123. Goulas A, Zilles K, Hilgetag CC (2018): Cortical gradients and laminar projections in mammals. Trends Neurosci 41:775–788.
124. Doucet GE, Bassett DS, Yao N, Glahn DC, Frangou S (2017): The role of intrinsic brain functional connectivity in vulnerability and resilience to bipolar disorder. Am J Psychiatry 174:1214–1222.
125. Wook Yoo S, Han CE, Shin JS, Won Seo S, Na DL, Kaiser M, *et al.* (2015): A network flow-based analysis of cognitive reserve in normal ageing and Alzheimer's disease. Sci Rep 5:10057.
126. Bozzali M, Dowling C, Serra L, Spano B, Torso M, Marra C, *et al.* (2015): The impact of cognitive reserve on brain functional connectivity in Alzheimer's disease. J Alzheimers Dis 44:243–250.
127. Ramón y Cajal S (1899): Comparative Study of the Sensory Areas of the Human Cortex. Worcester, MA: Clark University.
128. Arnatkeviciute A, Fulcher BD, Pocock R, Fornito A (2018): Hub connectivity, neuronal diversity, and gene expression in the Caenorhabditis elegans connectome. PLoS Comput Biol 14:e1005989.
129. Beul SF, Barbas H, Hilgetag CC (2017): A predictive structural model of the primate connectome. Sci Rep 7:43176.
130. Pramparo T, Lombardo MV, Campbell K, Barnes CC, Marinero S, Solso S, *et al.* (2015): Cell cycle networks link gene expression dysregulation, mutation, and brain maldevelopment in autistic toddlers. Mol Syst Biol 11:841.
131. He X, Zhang J (2006): Why do hubs tend to be essential in protein networks? PLoS Genet 2:e88.
132. Bonifazi P, Goldin M, Picardo MA, Jorquera I, Cattani A, Bianconi G, *et al.* (2009): GABAergic hub neurons orchestrate synchrony in developing hippocampal networks. Science 326:1419–1424.
133. van den Heuvel MP, Kahn RS, Goni J, Sporns O (2012): High-cost, high-capacity backbone for global brain communication. Proc Natl Acad Sci U S A 109:11372–11377.
134. Senden M, Deco G, de Reus MA, Goebel R, van den Heuvel MP (2014): Rich club organization supports a diverse set of functional network configurations. Neuroimage 96:174–182.
135. Kuroki S, Yoshida T, Tsutsui H, Iwama M, Ando R, Michikawa T, *et al.* (2018): Excitatory neuronal hubs configure multisensory integration of slow waves in association cortex. Cell Rep 22:2873–2885.
136. van Borkulo C, Boschloo L, Borsboom D, Penninx BW, Waldorp LJ, Schoevers RA (2015): Association of symptom network structure with the course of [corrected] depression. JAMA Psychiatry 72:1219–1226.
137. Calderwood MA, Venkatesan K, Xing L, Chase MR, Vazquez A, Holthaus AM, *et al.* (2007): Epstein-Barr virus and virus human protein interaction maps. Proc Natl Acad Sci U S A 104:7606–7611.
138. Vinayagam A, Gibson TE, Lee HJ, Yilmazel B, Roesel C, Hu Y, *et al.* (2016): Controllability analysis of the directed human protein interaction network identifies disease genes and drug targets. Proc Natl Acad Sci U S A 113:4976–4981.
139. Hernandez AR, Burke SN (2018): Age-related changes in 'hub' neurons. Aging 10:2551–2552.
140. Rubinov M, Ypma RJ, Watson C, Bullmore ET (2015): Wiring cost and topological participation of the mouse brain connectome. Proc Natl Acad Sci U S A 112:10032–10037.
141. van den Heuvel MP, Sporns O (2013): Network hubs in the human brain. Trends Cogn Sci 17:683–696.
142. van den Heuvel MP, Sporns O (2011): Rich-club organization of the human connectome. J Neurosci 31:15775–15786.
143. Boschloo L, van Borkulo CD, Rhemtulla M, Keyes KM, Borsboom D, Schoevers RA (2015): The network structure of symptoms of the Diagnostic and Statistical Manual of Mental Disorders. PLoS One 10(9):e0137621.