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Multimodal Connectomics in Psychiatry: Bridging Scales From Micro to Macro

Lianne H. Scholtens and Martijn P. van den Heuvel

ABSTRACT

The human brain is a highly complex system, with a large variety of microscale cellular morphologies and macroscale global properties. Working at multiple scales, it forms an efficient system for processing and integration of multimodal information. Studies have repeatedly demonstrated strong associations between modalities of both microscales and macroscales of brain organization. These consistent observations point toward potential common organization principles where regions with a microscale architecture supportive of a larger computational load have more and stronger connections in the brain network on the macroscale. Conversely, disruptions observed on one organizational scale could modulate the other. First neuropsychiatric micro-macro comparisons in, among other conditions, Alzheimer's disease and schizophrenia, have, for example, shown overlapping alterations across both scales. We give an overview of recent findings on associations between microscale and macroscale organization observed in the healthy brain, followed by a summary of microscale and macroscale findings reported in the context of brain disorders. We conclude with suggestions for future multiscale connectome comparisons linking multiple scales and modalities of organization and suggest how such comparisons could contribute to a more complete fundamental understanding of brain organization and associated disease-related alterations.

Keywords: Connectivity, Connectomics, Multimodal, Multiscale, Neuroimaging, Psychiatry

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Neuroanatomists investigating the brain across different species and across scales of observation have reported on substantial regional variability in brain organization (Figure 1). For example, on the microscale, large variation in cortical microscale cyto-, myelo-, and chemoarchitecture has been observed [see (1) for review]. On the macroscale of corticocortical connectivity, regions have widely differentiating connectivity profiles, with some regions connecting to regions broadly distributed across the cortex, while others have mostly local connections (2). Variability in both scales of organization has been observed to coincide with differentiated functional roles of cortical regions within the healthy brain as well as with disease-related biomarkers (3,4). Microscale cortical structure has been described to be predictive of region-to-region cortical connectivity (5), posing an interesting avenue of research in the context of neuroimaging-derived macroscale organization. Much remains to be learned, especially on the topic of how the relationship between microscale and macroscale organization influences brain function in disease.

In this review, we aim to first provide the reader with a broad overview of regional variation on the microscale (i.e., cortical morphology) and macroscale (i.e., structural and functional connectivity) of brain organization, followed by a summary of studies linking both scales of observation in the literature. Next, we give an overview of studies linking microscale and macroscale brain information in neuropsychiatric disorders. Finally, we propose topics for future multiscale connectomics

studies, which could further the fundamental understanding of brain organization and disease mechanisms.

MICROSCALE PATTERNS OF CORTICAL ORGANIZATION

Microscale cortical variation has been described in a multitude of modalities (see Figure 1A–D for examples) and has been proposed to reflect differences in the role of a particular region in brain function. In an effort to elucidate brain structure and (localization of) brain function, pioneering neuroanatomists have extensively demonstrated a large heterogeneity of cortical structure on the microscale of brain organization. At the turn of the 20th century, microscale variation was observed in neuronal cell type, size, and layer distribution by neuroanatomy pioneers such as Hammarberg (6), Campbell (7), Brodmann (8), and von Economo and Koskinas (9), as well as in cortical myelinated fiber distribution by, among others, Smith (10), Flechsig (11), and Vogt and Vogt (12). These observations led to increasingly detailed subdivisions of the cortical mantle into up to 150 to 200 (1) cytoarchitecturally and/or myeloarchitecturally distinct regions, which often—but not yet always—could be associated with the observation of similarly diverse regional functional profiles. Following these findings, modern-day studies employing chemoarchitectural quantifications of neurotransmitter receptor densities have shown great variability in the presence, density, and layer distribution of both inhibitory and excitatory

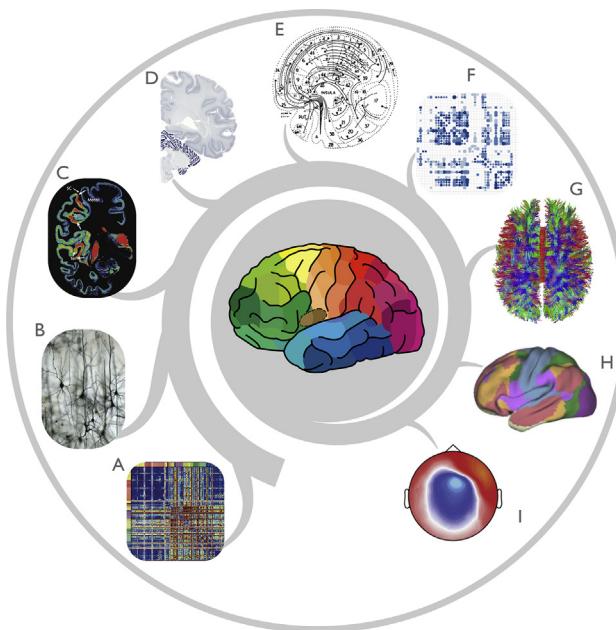


Figure 1. Brain organization has been studied on a wide range of scales, each providing a unique and complementary perspective on brain structure and function. Selected examples of microscale (**A–D**) and macroscale (**E–I**) measurement modalities of brain structure and function include (**A**) gene expression (20); (**B**) pyramidal cell morphology; (**C**) neurotransmitter receptor fingerprint (chemoarchitecture) (111); (**D**) Nissl staining-based cortical laminar architecture (114); (**E**) macaque strychnine-based effective functional connectivity (115); (**F**) macaque tract-tracing structural connectome (48); (**G**) diffusion-weighted imaging; (**H**) resting-state functional magnetic resonance imaging networks (67); (**I**) magnetoencephalography (116).

neurotransmitter receptors, describing a microscale regional variation that has enabled even more fine-grained delineation of cortical regions (13).

In addition to parcellating the cortex into distinct subregions, cortex-wide patterns of microscale characteristics have been associated with general functional profiles of cortical regions. Cortical type (ranging from granular to agranular, broadly defined based on the definition of cortical layers or sublayers, distribution of neuronal cell types, and neuronal cell size) has been related to the general function of a cortical area, with, for instance, primary sensory areas having a very clearly defined granular layer structure, whereas higher order association areas are mostly agranular and have a much less clearly defined cortical layer IV (8,9,14,15). Additionally, studies investigating layer III pyramidal cell complexity across regions in both macaque and human cortex have reported clear differences in both cell size and spine density between cortical regions, with areas involved in higher order processing having larger and more spinous pyramidal neurons (16,17), aspects of neuronal organization suggested to be related to increased processing and integration capacity of neurons (18,19).

Gene expression analysis (transcriptomics), reflecting localized modulation of gene function, is another measure showing great regional variability at the microscale of cortical organization (20). Recent studies exploring the brain-wide transcriptome of the developing mouse (21), primate (22), and human (23) brain, as well as in the adult mouse (24),

macaque (25) and human (20) brain, have reported differentiated expression profiles across cortical brain regions, where regions with more similar expression profiles are located in spatial proximity of each other (20,24,25).

MACROSCALE PATTERNS OF CORTICAL ORGANIZATION

At the macroscale organizational level of brain connectivity, the field of connectomics aims to study the comprehensive set of connections between all brain regions (Figure 1E–I) (2). Macroscale connectivity patterns vary across regions and have been associated with functional organization and efficiency of information processing in the brain.

In the mammalian brain, anatomical connections are mostly studied using invasive tract tracing to label monosynaptic pathways or noninvasive neuroimaging methods, such as diffusion-weighted magnetic resonance imaging (MRI). In addition to mapping anatomical connections, functional connectivity is defined as the statistical dependency between remote physiological events in the brain (26) and is often examined by means of resting-state functional MRI, electroencephalography, or magnetoencephalography. Findings across macroscale connectome modalities in the human brain have consistently shown a strong genetic component in brain connectivity (27–29) and regional connectivity patterns related to differentiated functional profiles of regions (30,31).

Based on its topology, the brain network can be divided into modules of highly interconnected regions, with relatively sparse connections between modules (32). Following this characteristic, most cortical regions are primarily linked to other regions within their own functional module (32,33). In contrast, a select subset of regions—also described as hubs—has widely distributed lines of communication across the cortical mantle (34,35). These highly and widely connected hub regions have been hypothesized to play an important role in information integration in the brain, linking functional modules. By integrating different types and sources of information across the cortex, hub regions could provide a scaffold for the brain in performing important higher order processes, such as cognition, and have been shown to overlap with all resting-state functional networks (36–38). Simulated selective lesioning studies show removal of rich club hub nodes from the brain network to have a much larger effect on the brain's integrative capacity than removal of other nonhub nodes (36,39,40). Extending on the observations and simulations in the healthy connectome, rich club hubs have been shown to be affected across a range of brain disorders (4) and to play an important role in, for example, Alzheimer's disease (41) and schizophrenia (42).

INTEGRATING MICROSCALE AND MACROSCALE INFORMATION IN HEALTH

Having observed large variability in cortical architecture on both the microscale and macroscale of brain organization, how are the two scales of organization related to each other? The seminal article by Barbas and Rempel-Clower (5) was the first to formally propose that the two scales are related and that in fact cortical structure predicts corticocortical connectivity, a model that since has been confirmed multiple times [e.g., (43–49)]. Recent studies combining information on microscale

cortical characteristics with macroscale connectivity data have further confirmed microscale and macroscale associations to be present across a wide range of modalities on both scales. These observations have been made in brains of multiple different mammalian species, including the rodent, cat, macaque, and human brain [for review see (50)]. Here, we first describe general cortex-wide microscale and macroscale associations in the structural and functional connectome, followed by an overview of characteristics specific to highly connected hub regions.

STRUCTURAL CONNECTOME

Extending the observations of cortical structural heterogeneity made on the microscale, studies employing tract tracing to study connections of specific regions in the macaque monkey [e.g., (51,52)] and cat brain [as collated and analyzed by (53)] have shown that the majority of cortical regions are predominantly connected to regions with a similar cytoarchitecture, hypothesizing that a large portion of cortical connections occur between regions with similar functional profiles (5,14). Most notably, layer III pyramidal cell complexity, neuron density, cortical type, and gene expression have been shown to be associated with regional macroscale connectivity patterns (50,54–56). Furthermore, neuronal complexity of cortical layer III pyramidal cells—the neuron type and layer hypothesized to constitute the majority of corticocortical connectivity—was associated with the extent of regional connectivity. Correlating the degree of corticocortical connectivity of macroscale regions to layer III pyramidal cell complexity in the tract tracing-based macaque connectome [CoCoMac database (57)] revealed that regions with more corticocortical connections tend to have larger, more branched, and more spinous layer III pyramidal cells (48), indicative of a larger computational capacity in these regions on both the microscale and the macroscale. Investigating the relationship between microscale characteristics and macroscale connectivity in a different dataset of macroscale tract tracing-based connectivity (58), cortical neuron density was observed to be the strongest predictive factor for regional macroscale connectivity (59), with regions with a lower neuron density having more macroscale connectivity.

In the human brain, cortical regions characterized by larger layer III neuron size tend to have a higher macroscale connectivity strength compared with regions with small neurons in cortical layer III (49). A comparison using collated information on morphometry of Golgi-stained layer III pyramidal cells has further shown that regions in which layer III pyramidal cells have longer basal dendrites, more spines, and higher spine density have a larger number of corticocortical connections than regions with smaller, less complex layer III pyramidal cells (Figure 2D) (60).

The cytoarchitectonic structural type of cortical regions also plays an important role in the formation of long-range connectivity. This relationship was described in the nonhuman primate (61) and formalized in a model describing how cortical structure predicts corticocortical connectivity patterns (5). A recent study combining regional cytoarchitectural cortical type and tract tracing-based corticocortical connectivity in the cat connectome confirmed that the majority of regions connect

with other regions of the same cortical type (54) and that more agranular multimodal association regions tend to have a larger number of macroscale corticocortical connections than regions of other cortical types (54). Furthermore, architectonic similarity across cortical areas was found to be strongly related to a region's laminar projection pattern as well as to its number of corticocortical connections. This indeed suggests microscale cortical architecture to be a predictor for macroscale connectivity patterns (59). These findings were further supported by observations in rodents, reporting a similar association between cytoarchitectural similarity and corticocortical connectivity (62). Extending these observations, studies in the human brain have shown similar findings, with cytoarchitecturally similar regions showing strong correspondence specifically in supragranular neuron density to be preferentially connected to each other (Figure 2A) (55).

Additional observations extending the described relationship between cytoarchitectonic organization of cortical areas and their connectivity may come from studies combining information from genetics and imaging. A first study combining information on cortical gene expression with the macroscale structural connectome in the rodent brain showed that regions with similar gene expression profiles tend to have similar projection patterns and that connected regions have more similar gene expression (63). Linking gene expression and structural connectivity in the mouse brain showed a strong association between molecular organization and macroscale connectivity, with the amount of connectivity driven by genes regulating neuronal, synaptic, and axonal structures (64).

Taken together, these observations are indicative of a cortical organization in which the majority of connections in the network occur locally between regions of similar macroscale makeup. Furthermore, regions with microscale morphology supportive of larger computational capacity tend to have more macroscale corticocortical connections, facilitating high integration of information across modalities.

FUNCTIONAL CONNECTOME

Multimodal studies investigating the relationship between microscale chemoarchitecture and functional connectivity measures have shown regions with a larger proportion of excitatory versus inhibitory neurotransmitter receptor levels to have stronger functional connections (65,66). Linking a region's microscale cytoarchitectural profile with its macroscale connectivity to different resting-state functional networks [such as described in (67)] showed cortical regions with high between-network connectivity to have a cytoarchitectural makeup characterized by an absent or disrupted layer IV (68). This suggests an absence of layer IV to be a potential organizational characteristic for internetwork communication hubs (68), in line with observations in microscale and macroscale associations in the structural connectome of the cat (54). Likewise, similarity in cortical microstructural myeloarchitecture has been related to shared membership of functional connectivity networks (modules) in magnetoencephalography (69) as well as in resting-state functional MRI (70). Additionally, analysis of the postsynaptic proteome in 12 Brodmann areas of the human cortex revealed each region to have a proteomic signature reflecting regional functional differences when linked

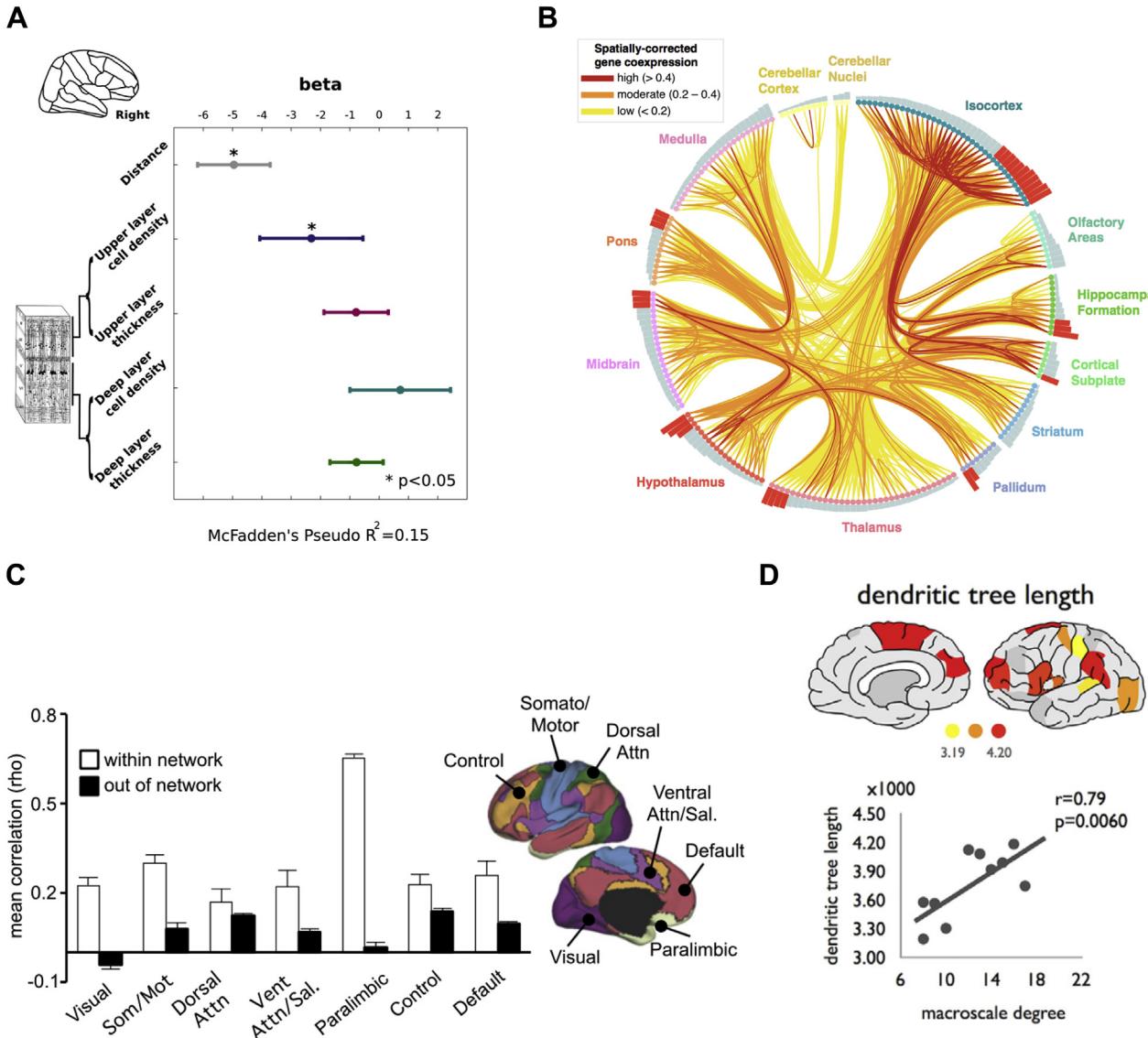


Figure 2. Examples of associations between microscale and macroscale organization in the healthy brain. **(A)** Investigating the relationship between the presence and absence of macroscale connections and microscale structural traits resulted in a good fit for physical distance between regions and similarity in supragranular neuron density (figure shows results for the right hemisphere) (55). **(B)** Combining regional gene expression data with connectivity in the mouse brain revealed a link between molecular function and neuronal connectivity, showing highly correlated gene expression of hub regions specifically in genes involved in synthesis and metabolism of adenosine triphosphate (the primary energetic currency of neuronal communication) (64). **(C)** Linking regional gene expression profiles with information on resting-state functional network membership showed regions that are part of the same functional network to have highly correlated gene expression patterns (72). **(D)** Combining microscale data on Golgi-based layer III pyramidal cell morphology with macroscale data on diffusion-weighted magnetic resonance imaging-based corticocortical connectivity showed larger microscale pyramidal cell complexity to be associated with more macroscale structural connections (60). Attn, attention; Mot, motor; Sal, salience; Som, somato; Vent, ventral.

to functional MRI and positron emission tomography as well as genetic and behavioral data (71).

Furthermore, studies combining functional connectomics with information on gene expression showed cortical expression of genes enriched in human supragranular cortical layers to be more similar within than between functional networks (Figure 2C) (72), and correlated expression of genes enriched for ion channels to be associated with membership of resting-state functional networks (73). These findings are again—as

predicted (5)—indicative of regions with similar microscale organization having an increased likelihood of being interconnected.

MICROSCALE AND MACROSCALE IN HIGHLY CONNECTED HUB REGIONS

Adding to these general cortex-wide trends, comparisons between highly connected hub regions and less well

connected peripheral regions have shown hub regions to be associated with differential microscale regional profiles. Combining tract tracing connectivity and regional gene expression profiles in the rat brain showed hub regions to have increased expression of genes involved in cellular energy metabolism (Figure 2B) (64), in contrast to connectivity in general, which was associated with genes regulating neuronal, synaptic, and axonal structures (64). In the human functional connectome, hub regions were characterized by an increased expression of genes related to mitochondrial glucose metabolism (74). Additionally, hub regions in the macaque as well as in the human connectome have larger layer III pyramidal cells, with a higher spine density than peripheral regions (48,60), characteristics hypothesized to be related to a neuron's larger integrative and computational capacity (18,19). Comparing cortical type between regions showed hub regions in the cat brain to on average be of a more agranular structural type than nonhubs (54). In accordance with the functional requirements of the integrative role of agranular hub regions in the connectome, agranular and dysgranular areas of the macaque brain showed higher expression of markers favoring synaptic plasticity than eulaminar areas (75).

Interestingly, these findings are supported by computer simulations. In line with the findings based on histological microscale measures in the mammalian cortex, a recent *in silico* study implementing graph theoretical analyses within a set of simulated rat somatosensory cortical columns showed neurons with the largest dendritic trees to be highly connected incoming hubs within the microscale cortical column (76), whereas neurons with large axons were observed to be the largest outgoing hubs in the simulated cortical column (76). Taken together, combining microscale and macroscale information on brain organization has been shown to provide novel insights into the function of the brain as a whole.

Microscale and Macroscale Integration in Brain Disorders

Can the observed relationship between microscale and macroscale of brain organization be extended to disease-related alterations in the brain? Alterations in relation to neuropsychiatric disorders have been reported by studies on both the microscale and macroscale of cortex organization. Such across-scale approaches to understanding brain function in disease could provide promising new mechanistic insights. In the following paragraphs, we give an overview and discuss recent microscale and macroscale findings reported in Alzheimer's disease and schizophrenia.

Alzheimer's Disease. Alzheimer's disease is neuroanatomically characterized by amyloid- β (A β) plaque depositions and tau tangles as well as regional loss of dendritic spines, together with progressive loss of cortical gray and white matter (77). Neuropathological analysis of brains with Alzheimer's disease showed a relationship between cortical structure and the direction of tangle pathology spread across the brain (78) and led to a hypothesis of an ordered selective regional vulnerability of particular brain areas (79).

On the macroscale, neuroimaging studies investigating brain structure have consistently reported on loss of cortical

volume in line with observations on the microscale (80,81). Connectome studies in Alzheimer's disease have reported highly connected hub regions to consistently be affected, both in resting-state functional connectivity (41) and in the diffusion-weighted MRI-derived structural connectome (82). These observations suggest hub regions to be more vulnerable or to at least play a contributing role in the disease processes of the disorder. Indeed, Buckner *et al.* (41) showed a clear voxel-to-voxel association between positron emission tomography A β deposition estimates and degree of resting-state functional connectivity in Alzheimer's disease (Figure 3A), demonstrating that—also on the microscale—more highly connected regions tend to be preferentially affected in Alzheimer's disease. These findings have since been replicated in the structural connectome of patients with Alzheimer's disease (83).

There are multiple hypotheses to explain why highly connected hub regions are most affected in Alzheimer's disease. Their central position in the brain network could mean that any disease-related alterations starting in the periphery could accumulate in the hubs (4). In addition to the contribution of topology, hub connections have been suggested to be biologically expensive. Hub connections span longer distances (34), and the higher blood flow and metabolic rate observed in hub regions (84,85) has been hypothesized to reflect an increased demand posed on the cellular infrastructure within hub regions. This increased demand on hub regions and their connections has been hypothesized to lead to increased wear and tear and ultimately to an increased accumulation of A β depositions in hub regions in Alzheimer's disease (41). Indeed, agranular and dysgranular cortical regions of the macaque prefrontal cortex—overlapping with known hub locations—show increased expression of markers favoring synaptic plasticity, paired with a marker of activated astrocytes—suggesting elevated cellular stress (75). Interestingly, APOE expression—one of the most well-described Alzheimer's disease risk genes—is elevated in association cortex (86). Additionally, *in vivo* regional synaptic activity is associated with increased vulnerability to A β deposition (87–89). A simulation study combining both scales of information reported degradation of highly connected hub regions in Alzheimer's disease to be dependent on the spike density within a region (90). Together, these findings illustrate how functional characteristics at the microscale and macroscale interact and how alterations on one scale can modulate the other.

Schizophrenia. Multiple observations of a potential interaction between disease effects on the microscale and macroscale of brain organization have been reported in schizophrenia. Schizophrenia is a heterogeneous disorder characterized by hallucinations, delusions, loss of initiative, and cognitive dysfunction and has long been hypothesized to be a disorder of brain dysconnectivity [e.g., (91,92)]. MRI studies have revealed consistent widespread dysconnectivity patterns in patients with schizophrenia [e.g., (92–95)]. Additionally, connectomics studies in both resting-state functional connectivity and diffusion-weighted connectomes have reported abnormalities in network organization (96–99) and specifically in connection strength (42,100,101) between hubs in the connectome.

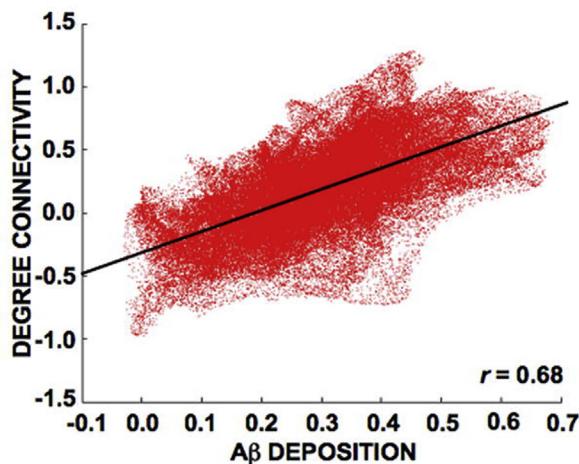
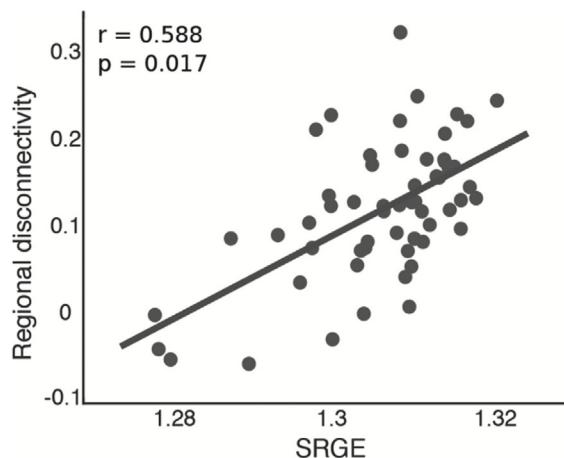
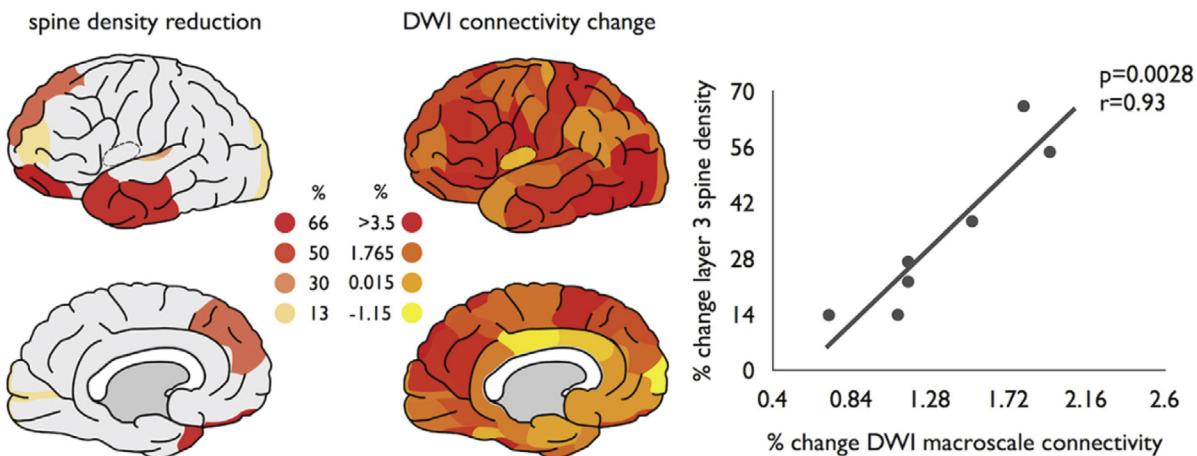
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Figure 3. Examples of associations between microscale and macroscale organization in brain disorders. **(A)** Buckner et al. (41) combined positron emission tomography-based data on amyloid- β ($A\beta$) deposition (x axis) to be associated with larger functional connectivity (y axis). **(B)** Combining Allan Human Brain Atlas data on gene expression in the healthy human brain with data on regionwise corticocortical disconnectivity in patients with schizophrenia showed regions with higher schizophrenia risk gene expression (SRGE) (x axis) to have larger regional disconnectivity (y axis) in patients with schizophrenia (110). **(C)** Linking collated literature data on regional changes in microscale layer III pyramidal cell spine density in patients with schizophrenia to information on macroscale dysconnectivity in schizophrenia showed a positive association between % change in macroscale connectivity (x axis) and % change in layer III spine density (y axis) (60). DWI, diffusion-weighted imaging.

On the microscale, studies have reported on reductions in spine density in cortical association areas [e.g., (102,103)], and Lewis's group has suggested a specific role of layer III pyramidal cells in schizophrenia (104,105). Furthermore, observations have been made of abnormal cell migration [more neurons found remaining in subcortical white matter, indicating potential problems in neuronal migration (106)], altered distribution and density of cortical interneurons [e.g., (107,108)], and a potential increased neuroinflammatory response in schizophrenia (109). While mostly examined separately, these reported effects on the microscale and macroscale are potentially related to each other.

Linking both scales of information in schizophrenia, a potential association between microscale spine density reductions on layer III pyramidal cells and macroscale disruptions of rich club connectivity has been observed (Figure 3C) (60). Furthermore, combining regional gene expression profiles of the healthy brain has shown regions with higher schizophrenia risk gene expression to display more severely affected macroscale connectivity (Figure 3B) (110). This shows that also in schizophrenia, microscale and macroscale observations of disease-related disruptions go hand in hand, indicating that they interact or may even be part of the same process.

SUMMARY AND FUTURE PERSPECTIVES

Strong microscale and macroscale associations have been observed in connectomes of many species and across a wide range of modalities. Microscale regional characteristics are consistently associated with, or even predictive of, macroscale connectivity patterns. Similar multiscale connectomics patterns have been reported in both the structural and the functional connectome, with most brain regions primarily connecting to other regions with similar microscale characteristics. Conversely, a relatively small subset of highly connected multimodal hub regions is characterized on the microscale by an agranular cortical type, larger neuron complexity, and gene expression profiles supportive of increased cellular signaling and metabolism.

Considering the wide variety of measures reported to be associated with macroscale connectivity, some notable overlap between characteristics can be observed. Broadly, two types of microscale and macroscale associations can be observed. The first concerns a general observation [as described in (5)] that regions that share a connection (be it structural or functional) tend to have larger microscale architectural similarity than unconnected regions [see, for instance, (43,47,55,59,70,72)]. The second observation is that cortical regions that have a larger number of connections to the rest of the brain tend to have a microscale architecture distinct from regions with fewer connections. More highly connected (hub) regions tend to be of a more agranular structural type (54,68) and to have a more complex neuronal morphology (48,60) having a neuronal architecture that is suited for highly integrative and computational processing.

Multiscale connectomics studies of (early) brain development could provide novel insights as to when and how microscale and macroscale associations observed in the adult brain arise. Exploring potential temporal dynamics of plasticity and aging in the interplay between microscale and macroscale brain organization would be of great interest and may provide an important starting point for computational models of complex brain function. Furthermore, studies into mechanisms of brain disorders employing multiscale connectomics could extend microscale and macroscale comparisons to other brain disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder, amyotrophic lateral sclerosis, or Huntington's disease.

An important consideration with regard to cross-scale integration of data in the brain is that microscale organization and macroscale organization are not mutually independent. Although some cortical structural variation is too small to be resolved using MRI, it can influence the MRI signal at the voxel level. Another point to note is the limitation posed by the integration of data acquired from disparate samples, sometimes many years apart. Microscale measures of cortical structure are typically invasive, and—certainly in the case of the human brain—such analyses are performed postmortem in a very limited number of samples. Considering the importance of interindividual variability in regional cortical structure [e.g., as described in (111–113)], the possibility should be kept in mind that owing to the typical low number of samples included, resulting data are potentially not representative of the population as a whole.

Advancing from comparisons employing information collated across different sources and individuals for multiscale connectomics studies, ideally future endeavors would aim to directly compare high-resolution brain-wide multiscale data within individual subjects. A nonexhaustive list of measures of interest could include classical measures such as neuron density, neuron morphometry, myelination, and synapse density such as collated previously across the literature. These could be complemented by expanding existing datasets with whole-brain quantification of other microscale measures, such as glial and specific interneuron density, inflammatory markers, or brain-wide layer-specific gene expression profiles together with high-resolution neuroimaging protocols. Such a broad large-scale data acquisition is a monumental task, and the feasibility of such an endeavor would arguably be for a large part dependent on innovations in automated tissue processing and quantification as well as big data type analyses. Nevertheless, direct multiscale observations in multiple subjects or even across control and patient groups could provide a great leap in our understanding of the interplay of multiple scales of brain organization in health as well as in brain disease.

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ARTICLE INFORMATION

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REFERENCES

- Amunts K, Zilles K (2015): Architectonic mapping of the human brain beyond Brodmann. *Neuron* 88:1086–1107.
- Sporns O (2011): Networks of the Brain. Cambridge, MA: MIT Press.
- Penzes P, Cahill ME, Jones KA, VanLeeuwen J-E, Woolfrey KM (2011): Dendritic spine pathology in neuropsychiatric disorders. *Nat Neurosci* 14:285–293.
- 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.
- Barbas H, Rempel-Clower N (1997): Cortical structure predicts the pattern of corticocortical connections. *Cereb Cortex* 7:635–646.
- Hammarberg C (1895): Studien über Klinik und Pathologie der Idiotie, Nebst Untersuchungen Über die Normale Anatomie der Hirnrinde. Upsala: Druck der Edv. Berling.

7. Campbell AW (1905): Histological Studies on the Localisation of Cerebral Function. Cambridge: Cambridge University Press.
8. Brodmann K (1909): Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: Barth.
9. von Economo CF, Koskinas GN (1925): Die Cytoarchitektonik der Hirnrinde des Erwachsenen Menschen. Vienna: J. Springer.
10. Smith GE (1907): A new topographical survey of the human cerebral cortex, being an account of the distribution of the anatomically distinct cortical areas and their relationship to the cerebral sulci. *J Anat Physiol* 41:237.
11. Flechsig PE (1920): Anatomie des Menschlichen Gehirns und Rückenmarks auf Myelogenetischer Grundlage. Leipzig: G. Thieme.
12. Vogt C, Vogt O (1919): Allgemeine ergebnisse unserer hirnforschung. *J Psychol Neurol* 25:279–462.
13. Amunts K, Lenzken M, Friederici AD, Schleicher A, Morosan P, Palomero-Gallagher N, et al. (2010): Broca's region: Novel organizational principles and multiple receptor mapping. *PLoS Biol* 8:e1000489.
14. Barbas H (2015): General cortical and special prefrontal connections: Principles from structure to function. *Annu Rev Neurosci* 38:269–289.
15. Mesulam M-M (1998): From sensation to cognition. *Brain* 121:1013–1052.
16. Elston GN (2003): Cortex, cognition and the cell: New insights into the pyramidal neuron and prefrontal function. *Cereb Cortex* 13:1124–1138.
17. Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, et al. (2001): Regional dendritic and spine variation in human cerebral cortex: A quantitative Golgi study. *Cereb Cortex* 11:558–571.
18. Koch C (1997): Computation and the single neuron. *Nature* 385:207–210.
19. McCulloch WS, Pitts W (1943): A logical calculus of the ideas immanent in nervous activity. *Bull Math Biophys* 5:115–133.
20. Hawrylycz MJ, Lein ES, Giuliozzi-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.
21. Thompson CL, Ng L, Menon V, Martinez S, Lee C-K, Glattfelder K, et al. (2014): A high-resolution spatiotemporal atlas of gene expression of the developing mouse brain. *Neuron* 83:309–323.
22. Bakken TE, Miller JA, Ding SL, Sunkin SM, Smith KA, Ng L, et al. (2016): A comprehensive transcriptional map of primate brain development. *Nature* 535:367–375.
23. Miller JA, Ding S-L, Sunkin SM, Smith KA, Ng L, Szafer A, et al. (2014): Transcriptional landscape of the prenatal human brain. *Nature* 508:199–206.
24. Lein ES, Hawrylycz MJ, Ao N, Ayres M, Bensinger A, Bernard A, et al. (2007): Genome-wide atlas of gene expression in the adult mouse brain. *Nature* 445:168–176.
25. Bernard A, Lubbers LS, Tanis KQ, Luo R, Podtelezhnikov AA, Finney EM, et al. (2012): Transcriptional architecture of the primate neocortex. *Neuron* 73:1083–1099.
26. Friston KJ (1994): Functional and effective connectivity in neuroimaging: A synthesis. *Hum Brain Mapp* 2:56–78.
27. Fornito A, Zalesky A, Bassett DS, Meunier D, Ellison-Wright I, Yücel M, et al. (2011): Genetic influences on cost-efficient organization of human cortical functional networks. *J Neurosci* 31:3261–3270.
28. Glahn DC, Winkler A, Kochunov P, Almasy L, Duggirala R, Carless M, et al. (2010): Genetic control over the resting brain. *Proc Natl Acad Sci U S A* 107:1223–1228.
29. van den Heuvel MP, van Soelen ILC, Stam CJ, Kahn RS, Boomsma DI, Hulshoff Pol HE (2013): Genetic control of functional brain network efficiency in children. *Eur Neuropsychopharmacol* 23:19–23.
30. Bullmore E, Sporns O (2009): Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10:186–198.
31. Tomasi D, Volkow ND (2011): Association between functional connectivity hubs and brain networks. *Cereb Cortex* 21:2003–2013.
32. Newman ME, Girvan M (2004): Finding and evaluating community structure in networks. *Phys Rev E Stat Nonlin Soft Matter Phys* 69(Pt 2): 026113.
33. Meunier D, Lambiotte R, Bullmore E (2010): Modular and hierarchically modular organization of brain networks. *Front Neurosci* 4:200.
34. van den Heuvel MP, Kahn RS, Goñi J, Sporns O (2012): High-cost, high-capacity backbone for global brain communication. *Proc Natl Acad Sci U S A* 109:11372–11377.
35. Harriger L, van den Heuvel MP, Sporns O (2012): Rich club organization of macaque cerebral cortex and its role in network communication. *PloS One* 7:e46497.
36. Zamora-López G, Zhou C, Kurths J (2010): Cortical hubs form a module for multisensory integration on top of the hierarchy of cortical networks. *Front Neuroinform* 4:1.
37. Zamora-López G, Zhou C, Kurths J (2011): Exploring brain function from anatomical connectivity. *Front Neurosci* 5:83.
38. van den Heuvel MP, Sporns O (2013): An anatomical substrate for integration among functional networks in human cortex. *J Neurosci* 33:14489–14500.
39. Schmidt R, LaFleur KJ, de Reus MA, van den Berg LH, van den Heuvel MP (2015): Kuramoto model simulation of neural hubs and dynamic synchrony in the human cerebral connectome. *BMC Neurosci* 16:54.
40. de Reus MA, van den Heuvel MP (2014): Simulated rich club lesioning in brain networks: A scaffold for communication and integration? *Front Hum Neurosci* 8:647.
41. 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.
42. 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.
43. Barbas H, Ghashghaei H, Dombrowski S, Rempel-Clower N (1999): Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *J Comp Neurol* 410:343–367.
44. Hilgetag CC, Grant S (2010): Cytoarchitectural differences are a key determinant of laminar projection origins in the visual cortex. *Neuroimage* 51:1006–1017.
45. Grant S, Hilgetag CC (2005): Graded classes of cortical connections: Quantitative analyses of laminar projections to motion areas of cat extrastriate cortex. *Eur J Neurosci* 22:681–696.
46. Medalla M, Barbas H (2006): Diversity of laminar connections linking periarculate and lateral intraparietal areas depends on cortical structure. *Eur J Neurosci* 23:161–179.
47. Hilgetag CC, Medalla M, Beul SF, Barbas H (2016): The primate connectome in context: Principles of connections of the cortical visual system. *Neuroimage* 134:685–702.
48. 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.
49. van den Heuvel MP, Scholtens LH, Feldman Barrett L, Hilgetag CC, de Reus MA (2015): Bridging cytoarchitectonics and connectomics in human cerebral cortex. *J Neurosci* 35:13943–13948.
50. van den Heuvel MP, Bullmore ET, Sporns O (2016): Comparative connectomics. *Trends Cogn Sci* 20:345–361.
51. Seltzer B, Pandya DN (1978): Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. *Brain Res* 149:1–24.
52. Rockland K, Pandya D (1979): Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res* 179:3–20.
53. Scannell JW, Blakemore C, Young MP (1995): Analysis of connectivity in the cat cerebral cortex. *J Neurosci* 15:1463–1483.

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54. 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.
55. Goulas A, Werner R, Beul SF, Saering D, van den Heuvel M, Triarhou LC, et al. (2016): Cytoarchitectonic similarity is a wiring principle of the human connectome [published online ahead of print Aug 6]. *bioRxiv*.
56. Beul SF, Hilgetag CC (2017): Neuron density is a fundamental determinant of structural connectivity in the primate cerebral cortex [published online ahead of print Mar 15]. *bioRxiv*.
57. Stephan KE, Kamper L, Bozkurt A, Burns GA, Young MP, Kötter R (2001): Advanced database methodology for the Collation of Connectivity data on the Macaque brain (CoCoMac). *Philos Trans R Soc Lond B Biol Sci* 356:1159–1186.
58. Markov NT, Ercsey-Ravasz MM, Ribeiro Gomes AR, Lamy C, Magrou L, Vezoli J, et al. (2014): A weighted and directed interareal connectivity matrix for macaque cerebral cortex. *Cereb Cortex* 24:17–36.
59. Beul SF, Barbas H, Hilgetag CC (2017): A predictive structural model of the primate connectome. *Sci Rep* 7:43176.
60. 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.
61. Barbas H (1986): Pattern in the laminar origin of corticocortical connections. *J Comp Neurol* 252:415–422.
62. Goulas A, Uylings HB, Hilgetag CC (2017): Principles of ipsilateral and contralateral cortico-cortical connectivity in the mouse. *Brain Struct Funct* 222:1281–1295.
63. French L, Pavlidis P (2011): Relationships between gene expression and brain wiring in the adult rodent brain. *PLoS Comput Biol* 7:e1001049.
64. 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.
65. Turk E, Scholtens LH, van den Heuvel MP (2016): Cortical chemo-architecture shapes macroscale effective functional connectivity patterns in macaque cerebral cortex. *Hum Brain Mapp* 37:1856–1865.
66. van den Heuvel MP, Scholtens LH, Turk E, Mantini D, Vanduffel W, Feldman Barrett L (2016): Multimodal analysis of cortical chemo-architecture and macroscale fMRI resting-state functional connectivity. *Hum Brain Mapp* 37:3103–3113.
67. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. (2011): The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol* 106:1125–1165.
68. 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.
69. 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.
70. Huntenburg JM, Bazin PL, Goulas A, Tardif CL, Villringer A, Margulies DS (2017): A systematic relationship between functional connectivity and intracortical myelin in the human cerebral cortex. *Cereb Cortex* 27:981–997.
71. Roy M, Sorokina O, Skene N, Simonnet C, Mazzo F, Zwart R, et al. (2018): Proteomic analysis of postsynaptic proteins in regions of the human neocortex. *Nat Neurosci* 21:130.
72. 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.
73. 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.
74. Vértes PE, Rittman T, Whitaker KJ, Romero-Garcia R, Váša 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(1705).
75. García-Cabezas MÁ, Joyce MKP, John YJ, Zikopoulos B, Barbas H (2017): Mirror trends of plasticity and stability indicators in primate prefrontal cortex. *Eur J Neurosci* 46:2392–2405.
76. 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.
77. Tackenberg C, Ghori A, Brandt R (2009): Thin, stubby or mushroom: Spine pathology in Alzheimer's disease. *Curr Alzheimer Res* 6:261–268.
78. Arnold SE, Hyman BT, Flory J, Damasio AR, Van Hoesen GW (1991): The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex* 1:103–116.
79. Braak H, Braak E (1996): Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. *Acta Neuropathologica* 92:197–201.
80. McDonald CR, McEvoy LK, Gharpetian L, Fennema-Notestine C, Hagler DJ, Holland D, et al. (2009): Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. *Neurology* 73:457–465.
81. Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, et al. (2003): Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci* 23:994–1005.
82. Lo C-Y, Wang P-N, Chou K-H, Wang J, He Y, Lin C-P (2010): Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. *J Neurosci* 30:16876–16885.
83. 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.
84. Vaishnavi SN, Vlassenko AG, Rundle MM, Snyder AZ, Mintun MA, Raichle ME (2010): Regional aerobic glycolysis in the human brain. *Proc Natl Acad Sci* 107:17757–17762.
85. Bullmore E, Sporns O (2012): The economy of brain network organization. *Nat Rev Neurosci* 13:336–349.
86. Burt JB, Demirtaş M, Eckner WJ, Navejar NM, Ji JL, Martin WJ, et al. (2018): Hierarchy of transcriptomic specialization across human cortex captured by myelin map topography [published online ahead of print Aug 6]. *Nat Neurosci*.
87. Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, et al. (2011): Neuronal activity regulates the regional vulnerability to amyloid-[beta] deposition. *Nat Neurosci* 14:750–756.
88. Walker LC, Jucker M (2011): Amyloid by default. *Nat Neurosci* 14:669–670.
89. Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, et al. (2005): Synaptic activity regulates interstitial fluid amyloid- β levels in vivo. *Neuron* 48:913–922.
90. 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.
91. Friston KJ (1998): The disconnection hypothesis. *Schizophr Res* 30:115–125.
92. Stephan KE, Friston KJ, Frith CD (2009): Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull* 35:509–527.
93. Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK (2005): Diffusion tensor imaging in schizophrenia. *Biol Psychiatry* 58:921–929.
94. Ellison-Wright I, Glahn DC, Laird AR, Thelen SM, Bullmore E (2008): The anatomy of first-episode and chronic schizophrenia: An anatomical likelihood estimation meta-analysis. *Am J Psychiatry* 165:1015–1023.

95. Kubicki M, Park H, Westin C-F, Nestor PG, Mulkern RV, Maier SE, et al. (2005): DTI and MTR abnormalities in schizophrenia: Analysis of white matter integrity. *Neuroimage* 26:1109–1118.
96. He Y, Chen Z, Evans A (2008): Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *J Neurosci* 28:4756–4766.
97. Fornito A, Zalesky A, Pantelis C, Bullmore ET (2012): Schizophrenia, neuroimaging and connectomics. *Neuroimage* 62:2296–2314.
98. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008): Hierarchical organization of human cortical networks in health and schizophrenia. *J Neurosci* 28:9239–9248.
99. Lynall ME, 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.
100. Skudlarski P, Jagannathan K, Anderson K, Stevens MC, Calhoun VD, Skudlarska BA, et al. (2010): Brain connectivity is not only lower but different in schizophrenia: a combined anatomical and functional approach. *Biol Psychiatry* 68:61–69.
101. Griffa A, Baumann PS, Ferrari C, Do KQ, Conus P, Thiran JP, et al. (2015): Characterizing the connectome in schizophrenia with diffusion spectrum imaging. *Hum Brain Mapp* 36:354–366.
102. Glantz LA, Lewis DA (2000): Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry* 57:65–73.
103. Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, et al. (1998): Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry* 65:446–453.
104. 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.
105. Pierri JN, Volk CL, Auh S, Sampson A, Lewis DA (2001): Decreased somal size of deep layer 3 pyramidal neurons in the prefrontal cortex of subjects with schizophrenia. *Arch Gen Psychiatry* 58:466–473.
106. Connor CM, Crawford BC, Akbarian S (2011): White matter neuron alterations in schizophrenia and related disorders. *Int J Dev Neurosci* 29:325–334.
107. Akbarian S, Bunney WE, Potkin SG, Wigal SB, Hagman JO, Sandman CA, et al. (1993): Altered distribution of nicotinamide-adenine dinucleotide phosphate—diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. *Arch Gen Psychiatry* 50:169–177.
108. Ikeda K, Ikeda K, Iritani S, Ueno H, Niizato K (2004): Distribution of neuropeptide Y interneurons in the dorsal prefrontal cortex of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 28:379–383.
109. Trépanier MO, Hoperton KE, Mizrahi R, Mechawar N, Bazinet RP (2016): Postmortem evidence of cerebral inflammation in schizophrenia: A systematic review. *Mol Psychiatry* 21:1009–1026.
110. Romme IA, 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.
111. Zilles K, Amunts K (2010): Centenary of Brodmann's map—conception and fate. *Nat Rev Neurosci* 11:139–145.
112. Amunts K, Schleicher A, Zilles K (2007): Cytoarchitecture of the cerebral cortex—more than localization. *Neuroimage* 37:1061–1065 [discussion: 1066–1068].
113. Zilles K, Palomero-Gallagher N, Grefkes C, Scheperjans F, Boy C, Amunts K, et al. (2002): Architectonics of the human cerebral cortex and transmitter receptor fingerprints: Reconciling functional neuroanatomy and neurochemistry. *Eur Neuropsychopharmacol* 12:587–599.
114. Ding SL, Royall JJ, Sunkin SM, Ng L, Facer BA, Lesnar P, et al. (2016): Comprehensive cellular-resolution atlas of the adult human brain. *J Comp Neurol* 524:3127–3481.
115. McCulloch W (1944): The functional organization of the cerebral cortex. *Physiol Rev* 24:390–407.
116. Baillet S (2017): Magnetoencephalography for brain electrophysiology and imaging. *Nat Neurosci* 20:327–339.