Journal Club

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Emerging Evidence of Connectomic Abnormalities in Schizophrenia

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Review of van den Heuvel et al.

Schizophrenia is an etiologically and clinically heterogeneous psychiatric disorder, characterized by psychotic symptoms, motivational disturbances, and cognitive disorganization. Pioneers of neuropathology such as Meynert and Wernicke proposed in the late 19th century that schizophrenia is associated with abnormalities in anatomical connectivity between specialized brain regions. Over the last 30 years, neuroimaging studies have provided general evidence for the existence of such anatomical dysconnectivity. For instance, functional neuroimaging studies in schizophrenia show abnormal integration between multiple cortical and subcortical regions (Friston and Frith, 1995; Gur and Gur, 2010), implying the presence of underlying anatomical connection abnormalities. Structural neuroimaging studies show deep white-matter abnormalities in frontal and temporal regions and gray-matter reductions in frontal, temporal, limbic, and thalamic regions (Ellison-Wright and Bullmore, 2009, 2010). However, the precise location of affected anatomical connections in schizophrenia and the relationship between these connectivity abnormalities and emergent functional deficits remain unknown.

Recent advances in diffusion magnetic resonance imaging (MRI) technology and white-matter fiber reconstruction algorithms make it increasingly possible to assemble high-resolution large-scale anatomical connectivity maps of the human brain. Such "connectomic" maps allow researchers to characterize the organization of anatomical brain networks and to identify the anatomical correlates of functional abnormalities in brain disorders (Sporns et al., 2005). One of the first diffusion MRI connectomic studies of schizophrenia was recently described by van den Heuvel et al. (2010). The authors characterized large-scale anatomical brain networks extracted from diffusion imaging data acquired from 40 healthy people and 40 people with schizophrenia. The location, direction, and length of white matter fiber tracts in these networks were inferred from diffusion of water molecules in brain tissue, using a white-matter fiber reconstruction algorithm. The connectivity strength of white matter tracts was inferred from the level of tract myelination, which was estimated using magnetization transfer imaging, a technique that quantifies the amount of macromolecules (including myelin) in the tracts. The tracts were combined with a parcellation of the brain into 108 regions of interest to construct whole-brain anatomical networks. The regional and global properties of these networks were then characterized as described below and compared between healthy and schizophrenia groups.

van den Heuvel et al. (2010) characterized the properties of anatomical brain networks with statistical measures of network topology. The authors used four complementary network measures to assess the structural organization and infer the potential functional role of individual brain regions. First, the measure of regional connectivity, based on the total number of connections associated with each region, was used to assess the strength of direct regional communication. Second, the measure of clustering, based on the density of connections surrounding each region, was used to assess the regional capacity for functional specialization. Third, the measure of path length, based on the average length of shortest network paths between the region and all other regions, was used to assess the regional capacity for functional integration. Fourth, the measure of betweenness centrality, based on the proportion of regional participation in shortest network paths, was used to assess regional importance, by inferring the capacity for participation in distributed information processing.

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The van den Heuvel et al. (2010) study reports increases in path length and reductions in betweenness centrality in several frontal and temporal regions in schizophrenia. The authors interpret these findings by concluding that the affected regions are likely to be associated with reduced structural capacity to integrate information. These findings agree with previous reports of focal white-matter abnormalities in schizophrenia, and extend these reports by directly demonstrating anatomical dysconnectivity and by attempting to infer the functional deficits associated with this dysconnectivity.

The authors' central conclusion of reduced capacity for information integration of frontal and temporal brain regions rests on important but unacknowledged assumptions associated with the above-described functional interpretations of anatomical network measures. For instance, given the dependence of path length and betweenness centrality on interregional shortest path lengths, there is an assumption that shortest path lengths accurately and reliably reflect interregional information flow. Such an assumption is plausible, but may also be overly simplistic in ignoring other aspects of interregional connectivity, such as the number of interregional shortest paths and the differential speed and capacity of individual tracts. More generally, the current lack of empirical evidence for functional correlates of most network measures precludes neurobiologically grounded conclusions of functional network abnormalities and makes empirical validation of these interpretations a high priority. Such validation could, for instance, involve direct comparisons of structural and functional brain connectivity in the same individuals (Hagmann et al., 2010; Van Dijk et al., 2010) or the study of relationships between structural and functional connectivity in biologically realistic large-scale computational models of the brain (Deco et al., 2011).

The relationship between structural network organization and emergent functional effects may also allow researchers to infer the influence of local anatomical abnormalities on global functional organization. Recent evidence suggests that such local abnormalities may be associated with distributed functional changes as far removed as the contralateral hemisphere (Crofts et al., 2011). van den Heuvel et al. (2010) explored this relationship by averaging individual network measures over all regions and found no significant differences in network-wide averages between the schizophrenia and control groups. The absence of these differences may suggest that averages of structural measures over all regions are insufficiently sensitive to infer the functional abnormalities characteristic of schizophrenia. One way to improve this sensitivity in future studies is to include information about observed gray-matter changes in the constructed brain networks.

An important problem in network studies of brain connectivity is the accurate distinction between simple differences of network connectivity strength (total amount of wiring) and more subtle differences of network topology (organization of wiring). van den Heuvel et al. (2010) took care to disambiguate these differences with three tests. First, the authors normalized all connection weights by the maximum weight of each network to control for gross changes in connectivity when comparing network topologies. Second, the authors examined the effect of discarding all weights by comparing the topology of binary networks. This characterization successfully recovered most of the originally reported frontal and temporal regional abnormalities. Third, the authors attempted to directly replicate observed disturbances in schizophrenia by randomly replacing connection weights in control-group networks with connection weights derived from schizophrenia-group networks. These replacements did not result in statistically significant alterations of network measures. Together, these tests suggest that detected between-group differences reflect differences in network organization, rather than simpler changes in network connectivity strength.

The van den Heuvel et al. (2010) study is one of the first diffusion MRI connectomic analyses of schizophrenia. The only other comparable study was published almost simultaneously by Zalesky et al. (2011). Unlike van den Heuvel et al. (2010), Zalesky et al. (2011) report global reductions in white-matter connectivity, rather than more subtle regional changes in connectivity. While these reported differences may arise from the relatively small sample size in both studies and the heterogeneity of neuropathology in schizophrenia, it is also worth mentioning an important methodological difference between the two studies. Specifically, the two studies define connection weights in principally different ways: van den Heuvel et al. (2010) define connection weights by the level of tract myelination, while Zalesky et al. (2011) define connection weights by the number of interregional streamlines. The number of streamlines is the number of computed trajectories associated with each detected white-matter tract and is thought to reflect the size and capacity for information transmission of the tract. The number of streamlines is the most commonly used measure of connection weight in diffusion MRI connectomic studies, although this measure assumes a homogeneous probability of tract reconstruction throughout the brain. On the other hand, the level of tract myelination is a potentially less abstract measure of connectivity strength, although the relationship between myelination and strength of interregional connectivity is unlikely to be direct. It is also notable that van den Heuvel et al. (2010) considered an additional control measure of tract integrity, the fractional anisotropy. Interestingly, the between-group effect was substantially reduced in networks with fractional-anisotropy generated weights, implying that the choice of weighting scheme has important effects on the results and must hence be carefully motivated.

In summary, the study by van den Heuvel et al. (2010) marks a qualitative shift for structural imaging analyses of schizophrenia. Unlike previous studies of focal gray- or white-matter structure, the study directly analyzes the large-scale anatomical organization of brain networks in patients with schizophrenia and attempts to infer the relationship between observed anatomical abnormalities and associated functional deficits. van den Heuvel et al. (2010) found strong evidence of network disorganization involving frontal and temporal cortical regions, but the functional effects of these anatomical disturbances will remain speculative until we have sufficient empirical validation for the functional correlates of anatomical network organization.

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