

Connecting Brain Structure and Function in Schizophrenia

Since the inception of brain imaging as a research tool in psychiatry, evidence has suggested that individuals with schizophrenia may have altered brain connectivity. Volkow et al. (1) were among the first to suggest a difference in functional networks in schizophrenia patients, both at rest and during tasks. Friston and Frith (2) proposed that altered interactions between specific brain regions may be a core feature of the illness. The emergence of more sophisticated brain imaging technologies, genetic techniques, and increasingly refined research questions has since further strengthened the case for a connectivity disturbance and brings this topic to the forefront of schizophrenia research. In an editorial published in the July 2007 issue of the *Journal*, Dr. Kelvin O. Lim (3) highlighted the possible contribution of white matter abnormalities to connectivity problems in schizophrenia. In the present issue of the *Journal*, more evidence for impaired

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connectivity is examined in three imaging studies that evaluate brain structure and function in large samples of patients and comparison subjects. Although the three articles do not all focus exclusively on the topic, considering each through the lens of connectivity offers valuable insight into the pathology of schizophrenia.

An article by Lui et al. (4) relates brain structure and resting state functional connectivity to clinical symptoms in 68 antipsychotic-naïve, first-episode patients. Comparing these patients with matched comparison subjects, the authors found decreased gray matter volume in multiple brain regions, including the superior and middle temporal gyri and anterior cingulate. This is the largest study of neuroleptic-naïve patients to date to confirm the commonly reported observation of decreased superior temporal gyrus gray matter in schizophrenia (5). The most important contribution of this study, however, is that the authors move beyond reporting gray matter volume differences, which are difficult to interpret, and attempt to understand the relationship of these differences to clinical measures and to functional connectivity. The authors report that gray matter volume in these regions was negatively correlated with positive symptoms, thought disturbance, activation, and impulsive aggression.

A key question is the issue of how gray matter volume is related to behavior or clinical symptoms. Lui et al.'s examination of functional connectivity may begin to answer this question. They observed significant positive correlations between thought disturbance scores and temporo-putamen connectivity and negative correlations between Positive and Negative Syndrome Scale total, negative, and anergia scores and temporo-parietal activity. It is possible to speculate, therefore, that gray matter volume changes lead to a systems-level alteration in functional connectivity, resulting in at least some of the symptoms of schizophrenia. It is important to note, however, that the causal relationship between gray matter volume and functional connectivity is unknown. It is also possible, for example, that functional connectivity affects gray matter volume (6). Although Lui et al. found correlations between functional connectivity and clinical symptoms, they did not observe an overall difference in functional connectivity between groups. In interpreting this null finding, it is useful to consider that the study used a very conservative correction for multiple comparisons, possibly limiting sensitivity to group differences.

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Functional connectivity was also examined by Rasetti et al. (7). Their study sought to determine if amygdala dysfunction in schizophrenia is a heritable phenotype or is related to disease state. The investigators scanned 34 patients with schizophrenia, 29 siblings, and 20 healthy comparison subjects during an emotional face matching task. They report that, relative to comparison subjects, patients with schizophrenia show a deficit in amygdala reactivity to negative faces and an alteration in functional connectivity between the amygdala and the subgenual cingulate. These differences were not observed in siblings, leading the authors to conclude that amygdala responses and functional coupling are related to disease state rather than to heritable factors. A strength of this study was the use of a positive control task, the N-back task, which measures working memory. The authors observed that during this task, both patients with schizophrenia and their siblings showed altered responses. This allowed the authors to infer that some cortical functions, i.e., those involved in the working memory, are related to genetic risk for schizophrenia, while cortical responses related to amygdala function are not.

The Rasetti et al. study adds important insight about possible disease mechanisms—that limbic dysfunction is likely related to disease state rather than a heritable trait. The study highlights, however, that the exact nature of amygdala response and connectivity dysfunction in schizophrenia remains unknown. While the study found decreased amygdala reactivity to emotional faces in schizophrenia, other studies have found the opposite. In their emotional face task, Holt et al. (8) found increased, rather than decreased, amygdala response in schizophrenia. These disparate findings may reflect differences in the tasks used to elicit responses. For example, in the Rasetti et al. study, subjects performed an overt cognitive task, matching emotional faces, as opposed to the Holt et al. study, in which subjects passively viewed faces. Future studies are needed to disentangle the involvement of functional networks that include limbic structures in schizophrenia.

Also in this issue of the *Journal*, Wexler et al. (9) report cognition-related differences in white matter, an anatomical substrate for functional connectivity. The authors examined gray and white matter volumes in healthy subjects and two groups of subjects with schizophrenia: one group with near-normal cognition and a group that was neuropsychologically impaired. They found that both patient groups had less gray matter volume and greater third ventricle volume relative to healthy comparison subjects. Only the impaired patients, however, had smaller white matter volume and larger lateral ventricle volume relative to healthy comparison subjects. The authors conclude that white matter pathology plays a primary role in cognitive impairments in schizophrenia. The neuroanatomical comparison of a relatively large group of patients who differ in a small number of cognitive measures is a powerful approach that justifies this strong inference.

Wexler et al. discuss their findings in the context of a growing body of literature suggesting that schizophrenia is caused not by local lesion-like brain pathology, but rather by dysfunction of functionally and anatomically connected networks of brain regions. Much evidence suggests that white matter, which forms the physical connections of these functional networks, is compromised in schizophrenia. Structural evidence includes postmortem data showing reductions in oligodendroglial cells, ultrastructural abnormalities in myelin, and in vivo diffusion tensor imaging studies suggesting alterations in white matter tracts in schizophrenia (10). Genetic studies have implicated genes involved in oligodendrocyte and myelin-related processes, including neuregulin (NRG1), which has received much recent attention in schizophrenia research (11). Functional connectivity studies in schizophrenia also have been considered recently with increasing interest. In 2007, Garrity et al. (12) showed altered “default mode” connectivity in schizophrenia, a finding that now has been widely replicated. This finding is consistent with numerous reports of reduced synchronized activity in schizophrenia between brain regions in the default network and other areas. An elegant study by Ford

et al. (13), for example, demonstrated that a deficit in neuronal synchrony is directly related to auditory hallucinations in schizophrenia.

Although it is still unknown if neuronal changes precede or cause white matter changes or vice versa, it is becoming clear that dysfunction of integrated networks of brain regions is involved in schizophrenia. It also is likely that specific regions, such as the limbic cortex, play key roles in these networks. As such, regional or lesion-driven models of pathology can be complemented, rather than supplanted, by models of dysfunctional functional networks. Furthering our understanding of schizophrenia in these terms will require more integrated approaches to the study of brain structure, function, and connectivity.

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