

## Searching for the Neuropathology of Schizophrenia: Neuroimaging Strategies and Findings

Seek, and ye shall find.

—Matthew 7:7

**I**t has long been known that schizophrenia is a brain disease. In the last century, psychiatrists tried to define its neuropathology through postmortem studies (1). Although histopathological characterization of schizophrenia proved to be elusive, identifiable neuropathological features were clearly and consistently associated with the illness. The findings of studies in the late nineteenth and early twentieth centuries were remarkably prescient in describing both diffuse and focal abnormalities in the size of multiple brain structures, which were subtle in magnitude and did not appreciably alter total brain size or weight.

Following this initial progress, the search for the neuropathology of schizophrenia foundered in the backwaters of medical research for more than 50 years. It was not until the advent of modern neuroimaging methods, which enabled relatively noninvasive in vivo studies of brain structure and function (2–5), that scientific discovery of the pathophysiology of schizophrenia meaningfully resumed. The results that have emerged from the several thousand studies reported since then have confirmed the early investigators' findings of abnormalities in size, shape, and functions in multiple anatomical regions in schizophrenia.

Investigators have also explored the cellular basis of this pathomorphology and its functional significance through the interrogation of neural circuits using functional imaging technologies. Although this strategy has produced some viable and compelling theories, the pathophysiology of the disease has resisted elucidation by these investigations, in the same way that it has resisted previous efforts to define its histopathology.

Two rate-limiting factors in the progress of schizophrenia research are the development of theoretical models from which to derive testable hypotheses and the availability of sophisticated methodologies. It was an inability to define the neuropathology explicitly enough that led to the conceptualization of severe mental disorders such as schizophrenia as “functional” rather than “organic.” Thus, the lack of methodological capacity (as well as the lack of theoretical accuracy) may well have led to the misrepresentation of mental illness, as it has with other medical illnesses.

As if these obstacles were not enough for schizophrenia researchers to overcome, there has also been the problem of drug effects and the potential for the introduction of treatment artifact and its misidentification as disease pathology (6).

In recent years, however, progress has accelerated following the promulgation of heuristic models such as the stress-vulnerability hypothesis, the dopamine hypothesis, the positive-negative typology, the neurodevelopmental hypothesis, and the various permutations of the glutamate hypothesis (e.g., *N*-methyl-D-aspartic acid receptor hypofunction and phencyclidine hypotheses), to name but a few (7). At the same time, the new technology and methods available to test these theories have played a critical role in hastening progress.

Three of the articles in this issue of the *Journal* exemplify the roles of theory and methodology in schizophrenia research. The study reported by Buchsbaum's group (Hazlett et al.) used positron emission tomography (PET) methods with enhanced spatial resolution and thin-slice (1.2-mm) magnetic resonance imaging (MRI) coregistration to define discrete anatomical regions of interest and substructures of the thalamus. Hazlett et al. examined patients with schizophrenia or schizotypal personality disorder and healthy volunteers by interrogating a thalamic-cortical-striatal-limbic circuit and using a serial verbal learning task that requires short-term and long-term memory. Research (imaging, postmortem, and cognitive) on the potential involvement of thalamic pathology in schizophrenia (8) provided much of the motivation and theoretical basis for this study.

Hazlett et al. report three findings on the thalamic measures: 1) a different pattern of glucose metabolism in response to cognitive activation for the patients with schizophrenia compared with the patients with schizotypal personality disorder and the healthy subjects; 2) no volume differences between any of the groups; and 3) a smaller area of activation (by a few pixels) in the anterior left thalamus in the patients with schizophrenia and in the right mediodorsal region in the patients with schizotypal personality disorder. The authors note that their findings of functional but not volumetric differences "may reflect a lack of normal frontothalamic afferent activity, which might result primarily from diminished frontal activity...or more generally from disturbed connections between frontal-striatal-thalamic regions."

Although the findings are clearly of interest, some cautionary comments are warranted. Despite the theoretical trappings of a thalamic circuit, no a priori hypothesis was explicitly tested in this technically sophisticated study. Although this might seem a rather trivial matter, it is particularly important in neuroimaging studies, where numerous dependent variables are potentially generated by the many regions (or, in this case, pixels) of interest. Given the expensive and intellectually compelling nature of this form of research, it is important to minimize the potential for criticism of post hoc findings. The use of methods providing enhanced spatial resolution with PET and MRI in an attempt to examine thalamic nuclei and other substructures is laudable but also tests the real limits of spatial resolution of these methods.

The report of Fukuzako et al. describes their results with in vivo  $^{31}\text{P}$  phosphorus magnetic resonance spectroscopy ( $^{31}\text{P}$ -MRS) in first-episode, drug-naïve patients with schizophrenia. This work follows by 8 years the initial seminal application of phosphorous spectroscopic imaging in this patient population by Pettegrew et al. (9), whose report was notable for identifying abnormalities in phospholipid concentrations in the frontal cortex, potentially implicating pathophysiological processes, both neurodevelopmental and degenerative, and resonating with the enduring phospholipid theories of schizophrenia (10). As interesting as these findings were, the field has been slow to follow them up, perhaps because of the methodological complexities of  $^{31}\text{P}$ -MRS (11). In this context, the study of Fukuzako et al. in this issue of the *Journal* is of considerable interest, particularly because the investigators targeted the temporal lobes, in contrast to previous studies, which acquired spectra from voxels placed in the frontal lobes. Like the previous studies, that of Fukuzako et al. found a decrease of phosphomonoester concentrations and an increase of phosphodiester concentrations. These results suggest that the pathological process responsible for the abnormal phospholipid levels found previously in the frontal cortex is also active in the temporal cortex, which, along with the frontal cortex, is the most strongly implicated anatomical region in the neuropathology of schizophrenia.

Fukuzako et al. point out that elevations in phosphodiesters could be produced by moieties that are more highly concentrated in white matter (e.g., glycerophosphocholine or glycerophosphoethanolamine). This interpretation is consistent with recent findings of white matter involvement in the neuropathology of schizophrenia (12). However, as the authors point out, this could also be due to other factors (e.g., decreased gray matter volume that produces larger gray-white matter ratios). To de-

termine the components of the phospholipid resonances,  $^1\text{H}$ -decoupled  $^{31}\text{P}$ -MRS must be employed. Although available and technically feasible,  $^1\text{H}$ -decoupled  $^{31}\text{P}$ -MRS has not been widely used in MRS studies of schizophrenia.

The impetus for the third article, by Corson et al., originated with a report by Jernigan et al. in 1991 (13). Although the basal ganglia was not thought to be an important structure in the neuropathology of schizophrenia (in contrast to Parkinson's disease and Huntington's disease), Jernigan et al. found larger lenticular nuclei in patients with schizophrenia than in healthy subjects and suggested that it was possibly due to deficiencies in synaptic pruning, a developmental neurobiological process that normally occurs in the second decade of life (14). Subsequent studies demonstrated that treatment-naïve patients did not exhibit this effect and suggested that the larger volumes observed in cross-sectional studies were probably due to the effects of drug treatment and, more specifically, the persistent  $\text{D}_2$  antagonism of conventional neuroleptics (15). Moreover, the atypical antipsychotic drug clozapine did not produce such effects, presumably because of its low  $\text{D}_2$  affinity. With the introduction of additional atypical drugs with low(er)  $\text{D}_2$  affinities like clozapine, the question is what their effect on the basal ganglia would be.

Corson et al. have begun to answer that question by their study. They found that patients treated with olanzapine and risperidone, as well as clozapine, exhibited smaller volumes in the caudate-putamen. It will be important to know the comparative effects of the different atypical antipsychotics on this measure of drug effect because the drugs differ in their  $\text{D}_2$  affinities as well as their effects on other neuroreceptors that modulate dopamine neurotransmission in the striatum (16). It will also be of interest to determine the clinical correlates of the volume changes that occur and see whether increases are associated with extrapyramidal symptoms, tardive dyskinesia, treatment outcome, etc. The authors make the interesting suggestion that the volume decreases seen in the patients treated with atypical antipsychotics may not be simply a reversal of the volume enlargements produced by previous exposure to neuroleptics but could also be due to the effects of the atypical drugs. This suggestion is consistent with preclinical data showing a similar volume-reducing effect of clozapine (17). If true, this observation would have important implications for our understanding of previous neuroimaging studies in schizophrenia.

In a longitudinal MRI study, Rapoport et al. (18) found progressive changes in adolescent patients with treatment-resistant prepubertal-onset schizophrenia over a 2-year period, reflected in reduction of cortical gray matter and basal ganglia volumes. These patients had received extensive pretreatment with conventional neuroleptics, and most were treated with clozapine during the study period. Thus, the reductions in caudate volume were interpreted as normalization of the basal ganglia in the context of conversion to a low-affinity  $\text{D}_2$  antagonist, and reductions in cortical volume were interpreted as due to a disease-related process. In the light of speculation of drug-induced volume reductions, such findings may need to be reexamined.

The three reports in this issue of the *Journal* illustrate how testing novel hypotheses with state-of-the-art neuroimaging methods provides a powerful research strategy by which to investigate schizophrenia. How long this mysterious illness can continue to resist elucidation of its neuropathological basis will depend in large part on how rigorously and creatively we make use of these methodologies.

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