Neurocognition and White Matter Imaging: Can the Relationship Be Reliably Quantified?

Schizophrenia is a heterogeneous disorder that is marked by considerable variation in both its expression and pathophysiology. Central to the illness, however, are widespread cognitive deficits in reasoning, perceiving, remembering, and concentration, all of which are often, but not always, evident by a diminution of scores across neuropsychological tests of intelligence, attention, and memory (for instance, see references 1 and 2). These neuropsychological impairments have long been presumed to reflect underlying neuropathology. However, only relatively recently, with the advent of high-resolution brain imaging studies, has the nature of the relationship between disease-related changes in brain anatomy and cognitive function begun to unfold.

An article in the current issue addresses an important issue related to the neuropsychology of schizophrenia. In this imaging study, Pérez-Iglesias and colleagues (3) examined the relationship between fractional anisotropy (a measure of white matter coherence, organization, and myelination derived from diffusion tensor imaging [4]) and neurocognitive deficits in a group of patients in their first psychotic episode. The authors used maps of brain white matter integrity and four neuropsychological tests (Continuous Performance Test, Grooved Pegboard Test, Rey Auditory Verbal Learning Test, and Trail Making Test Part B) that tap into four cognitive domains known to be impaired in schizophrenia: executive function, verbal memory, attention, and motor dexterity. An analytic approach called voxel-based morphometry (5) was used, and attempts were made to find corresponding anatomical features across all subjects and to analyze group differences in white matter integrity at each picture element (voxel). Four independent analyses were performed, in which patients' anatomical data were divided according to whether the patients did or did not have a particular cognitive deficit and the data for the two groups were compared.

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The results revealed clusters (groups of voxels) of reduced white matter integrity corresponding to cognitive impairments on two of the four tests administered. That is, impairment on the Trail Making Test Part B was associated with reduced fractional anisotropy in the right and left anterior thalamic radiation and inferior fronto-occipital fasciculus, forceps minor, and left superior and inferior longitudinal fasciculi. Additionally, patients with impaired performance on the Grooved Pegboard Test showed reduced fractional anisotropy in the forceps minor, inferior fronto-occipital fasciculus, anterior thalamic radiation, and corticospinal and corticopontine tracts. Impairments on the Rey Auditory Verbal Learning Test and Continuous Performance Test were not associated with significant differences in fractional anisotropy.

The results of this investigation provide new and interesting insights into the links between cognitive symptoms and white matter abnormalities in schizophrenia. The notion of a direct relationship between neuropsychological performance and white matter integrity measured with diffusion tensor imaging is interesting, but it is also somewhat controversial. More specifically, for every study that shows such a relationship, there is at least one that does not (for a review, see reference 6). This problem gets more complicated because most of the studies of schizophrenia that used diffusion tensor imaging were based on relatively small samples of chronically ill subjects, thereby

introducing possible confounds of extended medication use, institutionalization, age, and other factors that are often present in patients with chronic schizophrenia. Thus, studies like this one—performed on a relatively large (N=49) group of mostly unmedicated (or medicated for a very short time), young subjects—are important and needed.

Findings from this study suggest that moderate to severe deficits in executive and motor functions might be linked to structural deficits in white matter tracts that connect frontal and temporal as well as frontal and subcortical brain regions, at very early stages of the illness. These results also indicate that attention and verbal memory deficits, even though present in schizophrenia, might not be related to abnormalities in white matter integrity, at least not in the early stages of this illness. An interpretation suggested by the authors, that the "attention deficits during the first episode of psychosis might be attributable (at least in part) to transient factors like acute symptoms or medication, and therefore subject to variation over time, and less likely to be related to structural abnormalities," is interesting but needs to be further tested in studies with longitudinal designs, especially in regard to the fact that the relationship between white matter integrity and attentional deficits in chronic schizophrenia is among the most frequently reported in the literature (7–10).

As the authors note, it is important to list and discuss some limitations of this research, as well as those of other, similar studies. Despite over 14 years of research, diffusion tensor imaging is still in its infancy when it comes to clinical applications. In general, two of the major limitations of clinical research with this technology, which have hampered progress in the field, are 1) variability in acquisition and analytic techniques and 2) lack of validation of the methodology, including derived white matter measures. While the former is probably responsible for most of the inconsistencies in the literature on diffusion tensor imaging studies of schizophrenia, the latter is even more significant. More specifically, despite over 80 studies that have been published to date that used diffusion tensor imaging in schizophrenia research, it is still not known whether when we report group differences in fractional anisotropy, or any other popular or less popular diffusion index, what we report are abnormalities in myelination, axonal integrity, variability in tract orientation and organization, all of these, or none of these. It is still also not known how different parameters of image acquisition, processing, and analysis impact results and whether results indicate real white matter abnormalities or are merely indicative of biases introduced by specific image analysis approaches (in the case of voxel-based morphometry, used in this study, errors in automatic normalization, segmentation, and registration). It is further not known how age, medication, eating and drinking habits, etc., influence the diffusion tensor imaging signal.

Diffusion tensor imaging is nonetheless the most powerful tool to date with which to visualize and quantify abnormalities in human brain white matter connections in vivo. The degree to which it can be reliably used to indicate neuropsychological disturbances in schizophrenia, however, remains to be determined. Clearly, more research is needed in order to understand biological sources of anomalies in the diffusion tensor imaging signal, as well as clinical and cognitive correlates of such anomalies.

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