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CLINICAL CORRELATES OF MRI WHITE MATTER ABNORMALITIES IN SCHIZOPHRENIA

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A b s t r a c t: Schizophrenia is a severe psychiatric illness that can be accompanied by positive symptoms, negative symptoms, and cognitive dysfunctions in most cognitive domains. Neuroimaging studies have focused on understanding the relationship between schizophrenia and brain abnormalities. Most of these have focused on the well-documented gray matter abnormalities. However, emphasis has recently been placed on white matter abnormalities associated with the disorder. A number of studies have found reduced white matter volumes in schizophrenia and abnormalities in genes associated with white matter. The clinical significance of these abnormalities is just beginning to be understood. The advent of diffusion tensor imaging (DTI) has been particularly important in this regard, as it allows us to draw inferences regarding the organization of white matter in the brain. In this article, I will review recent work showing clinical correlates of neuroimaging-based white matter abnormalities in schizophrenia.

Key words: schizophrenia, positive symptoms, negative symptoms, cognitive dysfunction, diffusion tensor imaging, white matter.

Introduction

Schizophrenia is a severe psychiatric illness that can be accompanied by positive symptoms (e.g., hallucinations, delusions), negative symptoms (alogia, social withdrawal, affective flattening), and cognitive dysfunctions in most cognitive domains. The worldwide prevalence of the disease is approximately 1%, and schizophrenia is associated with prolonged and/or recurrent psychiatric

hospitalizations. As such, it represents a significant public health problem that needs to be better understood.

Magnetic resonance imaging (MRI) provides an important noninvasive window into the brain abnormalities associated with schizophrenia. Such studies have found reductions in a number of regional cortical volumes including the dorsolateral prefrontal cortex, anterior cingulate cortex, auditory cortex, hippocampus [1–4], and thalamus [5–7] in patients with schizophrenia compared to healthy controls. Moreover, reduced cortical thickness has been found in a number of regions in schizophrenia, even at first episode [8, 9], suggesting a reduction in neuropil in the disorder (see [10], for a review).

Whereas these findings have primarily focused on gray matter abnormalities, white matter volumetric abnormalities also have been found [11]. These abnormalities are consistent with the idea that schizophrenia is a disorder of brain connectivity [12], a notion also supported by findings of dysregulation in white matter-related genes in schizophrenia [13].

A richer picture of white matter abnormalities has emerged with the advent of diffusion tensor imaging (DTI). Diffusion tensor imaging is an MRI modality that examines the self-diffusion of water [14]. In the absence of structural boundaries, white matter diffuses in all directions equally (isotropic diffusion). However, boundaries such as axonal membranes and myelin sheaths impart directionality to the diffusion (anisotropic diffusion). DTI can provide, among other things, a measure of the directionality of diffusion known as fractional anisotropy (FA; [15]). FA ranges from 0 to 1, with 0 indicating completely random diffusion and 1 indicating completely directional diffusion, as would be exhibited by a water molecule traveling along an infinitesimally narrow path. FA is higher in white matter than gray matter, although the main determinant of anisotropic diffusion appears to be axonal integrity, with myelin playing a modulatory role [16, 17]. For this reason, FA is seen as an index not of myelin integrity, but of white matter integrity in general. Another measure derived from DTI is the trace, which is a measure of overall bulk diffusion. It tends to be highest in white matter regions with lower FA.

A number of other neuroimaging modalities have been used to examine white matter in schizophrenia. These include magnetization transfer imaging [18, 19] and T2 relaxography [20, 21]. Although these methods are useful and informative in schizophrenia [22–24], the number of studies is relatively small compared to those using DTI.

This article will focus on DTI abnormalities in schizophrenia and their clinical relevance. I will review the relationship of DTI abnormalities to clinical symptoms, sensory abnormalities, and cognitive deficits seen in the disorder and will then turn to a discussion of evidence of functional abnormalities and their relevance to understanding schizophrenia as a disorder of brain connecti-

vity. However, before discussing the findings in schizophrenia in more detail, I will review some of the methodological concerns associated with such studies.

Methodological Concerns

These papers have primarily region-of-interest (ROI) or whole brain (voxelwise) approaches. In the former approach, ROIs are placed or drawn on the images (typically not on the FA maps because that might induce a measurement bias) for each subject, and the mean or median FA is extracted for that region. This has the advantage of limiting the number of statistical tests performed, but has the disadvantage of depending on *a priori* hypotheses, which may not always be available.

The voxelwise approach has the opposite issues. It is not dependent on *a priori* hypotheses, but the large number of comparisons necessitates statistical correction. The use of Gaussian random fields correction [25], as is done in fMRI studies, is somewhat problematic; this method depends on spatial smoothing of the data, and it is unclear how much smoothing should be applied [26]. It also depends on intersubject registration of images to a standard space, which is inherently imperfect. Recent work has been done to quantitatively compare intersubject registration algorithms. In general, nonlinear registrations perform better than linear ones [27]. Moreover, at least in fMRI studies, better registration algorithms yield more substantial activation patterns [28]. Thus, at least some of the variable findings in the literature might be due to registration methods.

A method that has also been used to examine FA changes across the brain is Tract Based Spatial Statistics (TBSS; [29]). This method attempts to create a skeletonized map based on the centers of tracts and then projects on to them, for each subject, the maximum FA value lateral to that tract. TBSS is not as dependent on intersubject registration methods, but the cost is that a considerable amount of data is discarded. Moreover, the assumption that the maximal FA value in the neighborhood of the voxel under consideration is the best to be used may be problematic.

The other main method that has been used in DTI studies of schizophrenia is the definition of tract-based ROIs. DTI tractography [30–32] is based on the idea that the principal direction of the tensors within coherent white matter tracts will follow a regular pattern with a relatively small angular deviation from voxel to voxel. Multiple approaches have been used, including deterministic tracking, based on an application of FA and angular deviation thresholds [33], and probabilistic approaches [34, 35], which examines the probability distributions of the directionality of diffusion at a given voxel (such approaches require more than the minimum of six diffusion weighted directions). Elegant

tractography has been performed on DTI and has been used to define ROIs on a subject-wise basis [36–39], including in schizophrenia [39]. The main limitations of this method is that the source data underlying tractography is of relatively low resolution (often at the resolution of the desired tracts), and that the anatomical validation of such tracts is in its early stages [40]. Moreover, tracts may be influenced by issues such as signal to noise ratio, which is low in DTI, and may be variable across populations. Finally, although the reproducibility of tractography has been shown in various studies [41], the best way to "seed" the tracts to be derived is yet to be determined.

DTI findings in schizophrenia

FA. Numerous studies have found that FA is lower in patients with schizophrenia (e.g., [42, 43], although the precise localization varies across studies [44–46]. It is likely that some of the differences pertain to scanning measures and that others may pertain to sampling characteristics, such as numbers of subjects, subtypes of schizophrenia, and severity of illness.

A recent activation likelihood estimation (ALE) meta-analysis of these studies has implicated the left frontal deep white matter and the left temporal deep white matter as the most consistent loci of FA deficits [47]. The former locus is associated with fibers of the cingulum, left anterior thalamic radiation, left cortiobulbar tract, left inferior fronto-occipital fasciculus, and the genu of the corpus callosum. The latter locus is associated with tracts such as the fornix/stria terminalis, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, and the splenium of the corpus callosum. These FA abnormalities are present even in first episode patients [48–50] and in childhood-onset schizophrenia [51–55], as well as in individuals at high genetic risk for schizophrenia [56, 57] and those at ultra high risk (UHR) for schizophrenia [58]. This suggests that the abnormalities cannot be simply attributed to antipsychotic medication and that they have a genetic component. These conclusions are supported by Kanaan *et al*.'s findings that FA deficits in schizophrenia were uncorrelated with illness duration and did not differ between age-matched chronically and briefly medicated patients [59]. Carpenter *et al*. [60], however, found a decline in FA with illness duration in the genu and splenium of the corpus callosum.

Trace. Trace has been shown to be increased in multiple regions in schizophrenic populations [61, 62]. Some have proposed that trace might be used as a surrogate marker for volumetric deficits seen in schizophrenia [61], and indeed trace has been found to be correlated with CSF volume in patients with schizophrenia [63]. These abnormalities appear to be present both in those at genetic high risk for the disorder [64], although there is some evidence that successful antipsychotic treatment may have some normalizing effects on trace [65].

Clinical Correlates of DTI in Schizophrenia

Symptomatology. From the beginning of DTI studies in schizophrenia, there has been an interest in understanding the functional significance of these deficits. For example, in an ROI analysis, Hoptman *et al*. [66] showed that lower FA in inferior frontal white matter correlated with higher levels of self-reported impulsivity in men with schizophrenia. In addition, higher trace in these regions correlated with higher levels of self-reported aggression. Hoptman *et al*. replicated and extended these findings in a voxelwise analysis [67]. These findings are interesting in light of fMRI studies showing that reduced activation of the inferior frontal gyri is associated with poor response inhibition [68–70]. Moreover, impulsive aggression is most commonly thought to involve abnormalities in frontal and medial temporal structures [71], which are connected by fibers that traverse inferior frontal regions.

FA reductions in inferior frontal regions also have been correlated with the degree of negative symptoms in schizophrenia using both ROI [72] and voxelwise [73] approaches. These finding suggest that patients with schizophrenia might have abnormal connectivity in pathways involved in motivated behavior. In an ROI analysis, Shin *et al*. [62] found that increased ADC in the insular region was correlated with higher trace.

The deficit syndrome of schizophrenia [74], which is characterized by enduring negative symptoms that are primary to the clinical presentation, is thought to represent a neurobiologically distinct subgroup (e.g., [75]). In a recent study, patients with deficit schizophrenia [76] demonstrated reduced FA in the right superior longitudinal fasciculus (SLF), which interconnects prefrontal and parietal areas, as well as in middle frontal regions.

With regard to positive symptoms, a number of studies have shown that patients with schizophrenia who have auditory hallucinations appear to have *increased* FA in left superior gyral white matter [73, 77] and arcuate fasciculus [78]. In particular, FA was correlated positively with greater severity of hallucinations and delusions. Seok *et al*. [79] found reduced FA in the SLF of patients who did and did not show auditory hallucinations, but that the severity of hallucinations in the former group was correlated with anterior SLF FA. In a tractographic approach, Shergill *et al*. [39] obtained similar findings, such that the propensity toward auditory hallucinations was associated with higher FA in the SLF and anterior cingulum. Interestingly, increased trace in the anterior corpus callosum has also been associated with higher levels of positive symptoms [80]. Higher FA can occur in pathological conditions if, for instance, crossing fibers are selectively lost. Alternatively, cortical areas might be hyperconnected, leading to dysregulation in the neural circuitry.

However, in another voxelwise study [81], positive symptoms were negatively correlated with FA in the uncinate fasciculus (UF), sagittal stratum, and SLF. Similarly, using a tractographic approach, Ashtari *et al*. [53] found lower FA in the inferior longitudinal fasciculus (ILF) in adolescents with schizophrenia who had experienced *visual* hallucinations. Finally, Fujiwara *et al*. [82] found reduced FA in the posterior cingulum was correlated with higher levels of positive symptoms. It is clear that the nature of the white matter pathology underlying positive symptoms remains to be determined. It is likely that converging neuropathological investigations will prove fruitful in this regard.

In the passivity syndrome, patients feel that their experiences are controlled externally. In a recent study, Sim *et al*. [83] showed that patients with this syndrome show increased FA in frontal cortex, cingulate, and basal ganglia, along with reduced FA in the thalamus compared to patients without this syndrome. Again, the reason for higher FA in these patients is somewhat unclear, but could relate to loss of crossing fibers. Within patients with passivity, lower frontal FA was associated with poorer attentional and executive function, and was associated with earlier age of onset and more prominent positive symptom scores.

Lower FA appears to predict outcome in patients with schizophrenia [84]. For example, in a voxelwise analysis, Mitelman *et al*. [85] found that FA in multiple regions was associated with poor outcome. These regions included the corpus callosum, fronto-occipital fasciculus, left optic radiation, and fronto-temporal white matter.

White matter abnormalities in individuals at UHR for schizophrenia also appear to predict social and role functioning. Thus, in a 15-month longitudinal TBSS study, UHR subjects showed reduced FA in the superior longitudinal fasciculus (SLF). They also failed to show the increase in FA in the medial temporal lobe and inferior longitudinal fasciculus (ILF) that healthy controls showed. Moreover, lower FA at baseline predicted deterioration in social and role functioning in the UHR individuals as measured using the Global Functioning: Social scale [86] and Global Functioning: Role scale [87]. In this same study, UHR subjects showed significant negative correlations between global psychopathology scores and FA in the left SLF and anterior thalamic radiations. They also found negative correlations between negative symptoms and right ILF and MTL regions.

Sensory functions. Patients with schizophrenia show well-established deficits in relatively low-level visual [88–90] and auditory [91–93] sensory functions. These deficits appear to upwardly generalize to other cognitive deficits seen in schizophrenia. That is, deficits in sensory processing appear to account for a significant amount of the variance in higher level cognitive deficits such as prosodic problems [94], reading difficulties [95], and perceptual closure [96].

These deficits support a widespread cortical inefficiency and are taken as supporting the NMDA receptor model of schizophrenia [97].

White matter abnormalities are associated with sensory deficits in schizophrenia. For example, using an ROI approach, Butler *et al*. [89] found that the amplitude of steady state visual evoked potentials is correlated with FA in the optic radiations. Moreover, Leitman *et al*. [98] found that performance on a voice emotion identification task was correlated with FA in primary and secondary auditory pathways, as well as in orbitofrontal white matter, the corpus callosum, and the peri-amygdala white matter. Impaired performance on a distorted tunes task was associated with lower FA in auditory and amygdalar pathways, but not in prefrontal regions. These studies support the involvement of white matter abnormalities in these sensory dysfunctions.

Cognitive functions. FA abnormalities have also been associated with cognitive dysfunctions in domains known to be abnormal in schizophrenia. For example, in an ROI-based study, Kubicki *et al*. [99] found that reduced FA in the left cingulum bundle was associated with poor performance on the Wisconsin Card Sorting Test (WCST), a test of working memory and executive function in patients with schizophrenia. Nestor *et al*. [100] found that poorer verbal memory correlated with reduced FA in the left UF, whereas deficits on the WCST were associated with reduced FA in the left cingulum bundle in patients compared to controls. In addition, in a TBSS study, Karlsgodt *et al*. [101] found reduced FA in the SLF in patients with recent-onset schizophrenia. In both patients and controls, FA in the left SLF was correlated with better verbal working memory performance.

In voxelwise analyses, Lim et al. found correlations between higher FA in anterior cingulate and other regions and performance on tasks of attention and executive function, whereas higher FA in left parahippocampal and fusiform white matter and fornix, among other regions, was correlated with better performance on verbal learning tasks. Manoach *et al*. [102] found consistent findings with respect to attentional function, such that saccadic latency was related to FA in anterior cingulate white matter. In addition, Nestor *et al*. [103] found that performance on the Attention Network Test (ANT; [104]) was correlated with FA in the anterior cingulum.

With regard to declarative memory, correlations between performance and medial temporal lobe FA were found by Rametti *et al*. [105]. Whereas Rametti *et al*. used a voxelwise approach, others have obtained similar results in the fornix using ROI [106] and tractographic [107, 108] approaches. Szeszko *et al*. [73] found that verbal learning and memory was associated with FA in the bilateral UF in their recent-onset study.

In an interesting recent study, Nestor *et al*. [109] examined the relationship between executive and declarative memory function and FA in the cingulum and UF. Using hierarchical linear regression, they found that reduced FA in the cingulum predicted impaired executive function but not declarative memory, whereas FA reductions in the UF predicted deficits in declarative memory but not executive function. Cingulum FA was also related to other cognitive domains.

Relevance of Brain Structural Connectivity Abnormalities to Neural Circuitry

The literature to date suggests that white matter abnormalities are present in schizophrenia and that they correlate with psychiatric symptoms and sensory and cognitive deficits seen in the disorder. These findings support the idea that schizophrenia is a disorder of brain connectivity. The next steps for the field will likely involve a deeper understanding of how brain structural connectivity abnormalities are related to functional circuit abnormalities in schizophrenia. A particularly interesting area in this regard is a consideration of functional connectivity [110], which refers to the temporal correlation of brain activity in disparate regions. A related concept is effective connectivity [110], which examines the influence of one brain region on another, and thereby has relevance to causal connections. Both concepts have been the subject of a great deal of attention in schizophrenia research [111–114].

Functional and effective connectivity can be demonstrated even under resting conditions, as first demonstrated by Biswal *et al.* [115], thereby avoiding performance related aspects of brain activation. Functional and effective connectivity studies provide important information as to how disparate brain regions may interact. Activity in a number of brain regions appears to be correlated at rest and has been defined as networks. For instance, the precuneus, medial prefrontal cortex, and lateral parietal regions have been repeatedly identified in resting state studies. These regions together have been defined as a default mode network (DMN) [116]. Activity in these regions is suppressed during a task and their activity may be negatively correlated in time (anticorrelated) with another set of regions termed the task-related network (TRN) [117], which includes the anterior cingulate as well as different lateral prefrontal regions than are activated in the DMN. Abnormalities in the architecture of the default mode network have been found in schizophrenia both at rest [118, 119] and in the context of task performance [120], suggesting that this network is dysfunctional in the disorder. Moreover, these abnormalities are correlated with psychiatric symptoms [118–120].

A number of other functional networks have also been identified at rest, including visual areas, auditory areas, and attention areas [121]. Moreover,

anatomical regions that are abnormal in schizophrenia have been shown to be differentiable into multiple functional networks. These include the cingulate [122], striatum [123], and amygdala [124]. Aberrant functional connectivity between the amygdala and ventral prefrontal regions has been found in schizophrenia, and this abnormality correlates with self-reported aggression [125].

Combined fMRI/DTI studies are beginning to be performed [70, 126–130], although studies in schizophrenia are rare [131]. Such studies would provide information on the correspondence between white matter integrity and online brain activity, but provide a methodological challenge in terms of how to combine data of differing types. It is extremely likely, however, that these combined studies will provide critical insights into the nature of schizophrenia as a disorder of brain connectivity.

Conclusions

The last 15 years have brought about a virtual explosion of studies on brain connectivity in schizophrenia. These studies have shown that white matter organization is disrupted in schizophrenia, and that these disruptions have important implications for psychiatric symptomatology and sensory and cognitive deficits seen in the disorder. Recent studies showing that variations in white matter integrity are associated with genetic variants (e.g., in neuregulin [132–134]) that have been implicated in schizophrenia [135] offer an exciting and important avenue to better understand the mechanism of these abnormalities, as do converging neuropathological studies of white matter [136–138].

In parallel, studies have shown abnormalities in functional circuitry in the disorder. These studies show that the functional and effective connectivity between brain regions are disrupted in schizophrenia. These abnormalities also appear to have relevance to both psychiatric and cognitive abnormalities in the disorder. The integration of these studies with examinations of structural integrity offers a tremendous opportunity to better interrogate brain circuitry. The next 15 years will likely bring a deeper understanding of how disrupted brain circuits on a structural level play out on the functional level, thereby providing important keys to understanding the nature of schizophrenia.

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Резиме

КЛИНИЧКИ КОРЕЛАТИ ОД МАГНЕТНА РЕЗОНАНСА НА БЕЛАТА МАТЕРИЈА ВО ШИЗОФРЕНИЈАТА

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Шизофренијата е сериозно психијатриско заболување што може да биде проследено со позитивни и негативни симптоми, и когнитивна дисфункција во повеќе когнитивни домени. Студиите со невроснимање се фокусираат на односот помеѓу шизофренијата и мозочните абнормалности. Повеќето од овие студии се

однесуваат на добро документираните абнормалности во сивата маса. Сепак во поново време се обрнува внимание на абнормалностите во белата мозочна маса кои се поврзани со нарушувањето. Повеќе студии имаат откриено намален волумен на белата маса кај шизофренијата, како и абнормалности кај гените поврзани со белата маса. Клиничкото значење на овие абнормалности штотуку започнуваме да го разбираме. Техниката на снимање на дифузниот тензор (ДТИ) е посебно значајна во овој контекст, бидејќи овозможува да се извлечат заклучоци за организираноста на белата маса во мозокот. Во овој труд ќе направам преглед на скорешните истражувања засновани на невроснимање кои покажуваат клинички корелати на абнормалности на белата маса во шизофренијата.

Клучни зборови: шизофренија, позитивни симптоми, негативни симптоми, когнитивна дисфункција, снимање на дифузниот тензор, бела маса.

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