A Review of Diffusion Tensor Imaging in Schizophrenia

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Abstract

Functional and structural neural pathway disconnection may play a prominent role in the pathophysiology of schizophrenia. Diffusion tensor imaging (DTI) is a noninvasive magnetic resonance imaging technique ideally suited to investigate neuroanatomical connectivity in schizophrenia. DTI provides information about the integrity and physiology of white matter fiber tracts. This review describes basic DTI methods and studies of schizophrenia. The aims are to provide a basic understanding of the DTI imaging technique, describe general DTI study findings in schizophrenia and genetically vulnerable populations, and the pathological mechanisms that may account for white matter disturbances in schizophrenia.

Key Words: Schizophrenia, Diffusion Tensor Imaging, Brain, Connectivity, White Matter

Introduction

Schizophrenia is a debilitating mental disorder that afflicts approximately 1–2% of the general population and is a major public health cost worldwide. Characteristic features of the disease include positive symptoms (hallucinations, paranoia, delusions), negative symptoms (avolition, anhedonia, affective flattening), and cognitive impairments (attention, learning, memory deficits). At present, the causal factors of schizophrenia are not known. Neuroimaging and postmortem studies (1, 3) implicate widespread brain abnormalities, especially in frontal and temporal regions. One prominent theory posits that functional and anatomical brain disconnection plays a prominent role in the pathophysiology of schizophrenia (4, 5).

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Diffusion tensor imaging (DTI) is a noninvasive magnetic resonance imaging technique ideally suited to investigate neuroanatomical connectivity in schizophrenia. DTI provides information about the integrity and physiology of white matter fiber tracts. Fiber tracts consist of myelin-coated axonal projections, which are responsible for rapid information processing between cortical-cortical and cortical-subcortical gray matter. Compromised integrity of white matter could result in disrupted communication between brain regions. Such asynchronous information processing could account for the clinical manifestations of schizophrenia.

This review describes basic DTI methods and studies of schizophrenia. The aims are to provide a basic understanding of the DTI imaging technique and what is currently known about: 1) white matter abnormalities in schizophrenia and

genetically vulnerable populations; 2) how white matter abnormalities relate to clinical manifestations of schizophrenia and antipsychotic drug treatment; and, 3) the underlying pathophysiological mechanisms that could account for these white matter disturbances in schizophrenia.

Basic Principles

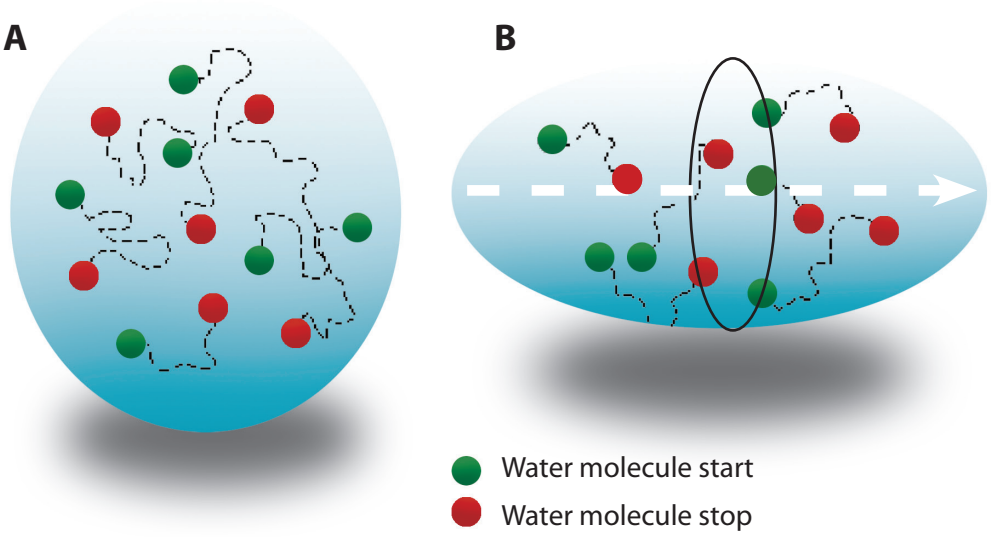
DTI measures random (Brownian) motion or diffusion of water molecules; these measures provide information about the integrity and biology of white matter tissue (6). DTI is acquired on a conventional magnetic resonance scanner but applies magnetic gradients in at least six noncollinear directions to yield information about the magnitude and direction of water diffusion within the brain. Different patterns of water movement occur in different brain tissues due to the presence of physical boundaries such as cell membranes, cell structures, and myelin. For instance, water diffusion in cerebrospinal fluid (CSF) is unobstructed in all directions, and this pattern is known as "isotropy." Isotropy is well represented as a sphere. In white matter, diffusion is greater in directions parallel to fiber tracts and hindered in directions perpendicular to fiber tracts. This pattern is known as "anisotropy." Anisotropy is well represented as an ellipsoid with the greatest mean diffusion along the longest axis. By measuring water diffusion along at least six different spatial directions, a mathematical model (i.e., the diffusion tensor) is generated to characterize the diffusion ellipsoid for each voxel in an image. Information regarding the magnitude and orientation of diffusion can be determined. See Figure 1 for an illustration of isotropic and anisotropic diffusion.

DTI Indices

Several indices of water diffusion such as mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity, and axial diffusivity can be measured with DTI (7-10). Both FA and MD are commonly reported in the literature. The MD reflects the total magnitude of water diffusion. White matter damage is associated with an increase in MD. The FA reflects directionally averaged water diffusion. FA ranges from 0 to 1, where 0=isotropic diffusion and 1=fully anisotropic diffusion. FA decreases with white matter damage. Many factors like myelin integrity, axonal density, and the configuration of axonal packing are thought to affect FA. FA is greatest in white matter, whereas MD is greatest in CSF. Axial($\lambda_{||}$) and radial($\lambda_{\perp}$) are directional diffusivity indices that may provide better insight into the pathophysiological mechanisms underlying white matter alterations but are less often reported in the literature. $\lambda_{||}$ is diffusivity along the main direction (i.e., fiber tract), and less diffusivity may reflect axonal injury. $\lambda_{\perp}$ is diffusion along directions parallel to the main direction and greater diffusivity may reflect demyelination or dysmyelination. For instance, in mice with a genetic mutation that causes dysmyelination but no axonal injury or inflammation $\lambda_{\perp}$ was increased compared to control mice and correlated with histopathological measures of dysmyelination (11).

Image maps created from DTI indices per voxel can be generated and used for analyses (12). See Figure 2 for illustration of FA and MD image maps. In addition, color map images can be generated. For these images a color represents the direction of diffusivity and the signal intensity/brightness represents the degree of anisotropy. Color maps are very

Figure 1 Isotropic and Anisotropic Diffusion



(A) **Isotropy:** water diffusion is random and unobstructed in all directions. (B) **Anisotropy**: water diffusion is greater in one main direction (i.e., white arrow) and hindered in directions perpendicular to the main direction.

useful for some analysis procedures like fiber tractography. See Figure 2 for an illustration of a color-coded orientation image.

DTI Analysis Methods

Voxel-based analysis (VBA) determines the numerical distribution of group measures at each voxel by mathematically mapping each brain to a common anatomical template (13, 14). This spatial normalization procedure makes it possible to compute group statistics at each voxel. In contrast, the region-of-interest (ROI) based method is useful for testing a hypothesis about a specific brain region or pathway. Traditional ROI analysis entails tracing a brain region to obtain an average value for a chosen DTI index. Drawbacks to this type of ROI analysis include time investment and the need to establish reliable and valid methods. In recent years, semiautomated ROI methods have been developed that reduce the time investment. A simpler ROI analysis approach consists of placing an ROI in the shape of a sphere or cube in the area of interest to extract a mean DTI index. The whole brain region is not assessed. This method is commonly used as a follow-up to whole brain VBA.

Fiber tractography is a recently developed method used to delineate specific white matter tracts. Information on diffusion measures, volume, and length of a specific tract can be obtained. The fiber tracking method uses the ROI tracing method and fiber tracking algorithms to generate a 3D tract reconstruction (7, 9, 15). See Figure 2 for illustration of fiber tractography.

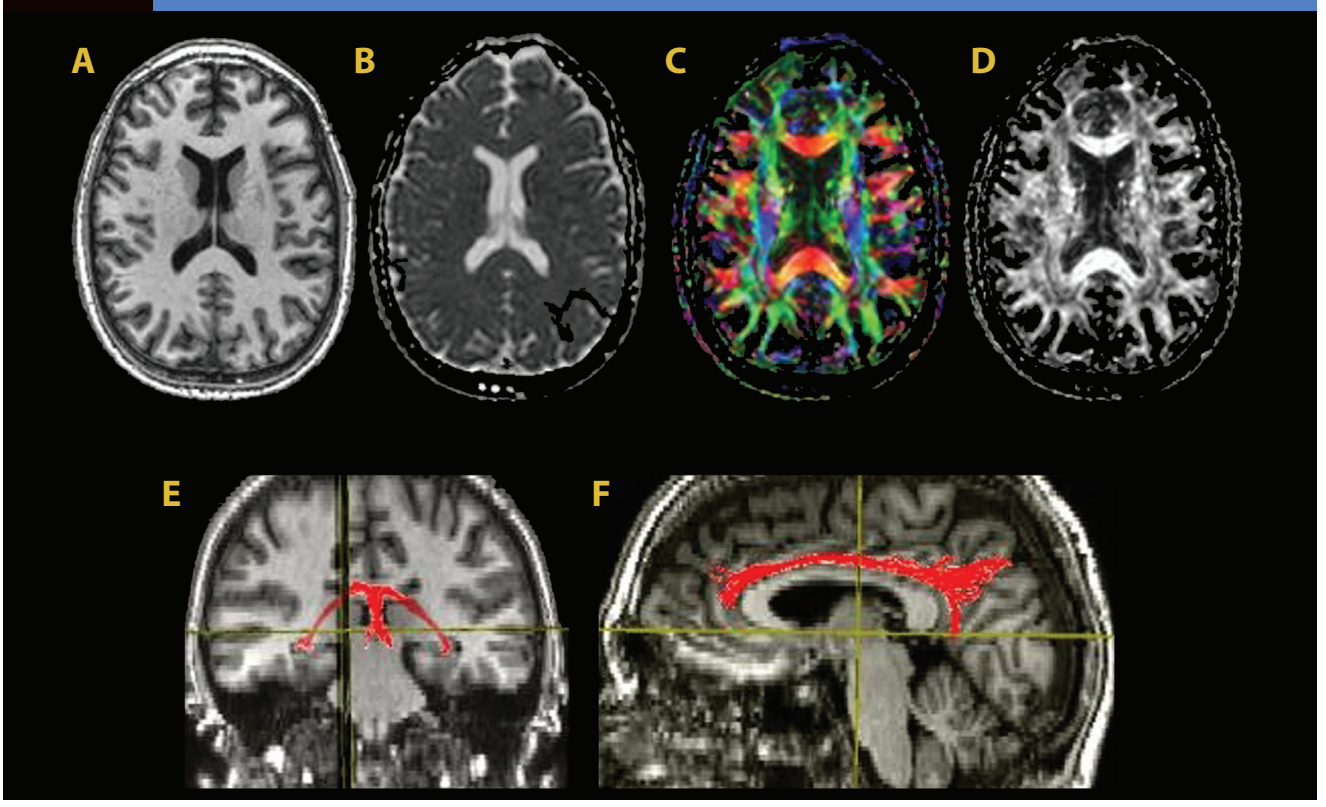
Overview of Major White Matter Fiber Tracts

Major white matter fibers commonly investigated with DTI constitute association, projection, brainstem, and commissural fibers. Association fibers connect cortical regions and include the superior longitudinal fasciculus, inferior longitudinal fasciculus, superior occipital fasciculus, inferior fronto-occiptal fasciculus, uncinate fasciculus, cingulum, fornix, and the stria terminalis. Projection fibers connect cortical and subcortical regions such as cortico-thalamic and cortico-striatal connections. Brainstem fibers connect parts of the cortex, brainstem and cerebellum, whereas commissural fibers such as the corpus callosum connect the two hemispheres. See Table 1 for a listing of major white matter tracts commonly assessed with DTI.

Methods

Research studies from 1998–2008 were included if they met the following criteria: 1) were in peer-reviewed journals; 2) included patients that met criteria for schizophrenia,

Figure 2 Image Maps



(A) T1-weighted anatomical image; (B) Mean Diffusivity (MD) map; (C) Color-coded orientation map (red: left-right, blue: Superior-Inferior, green: Anterior-Posterior); (D) Fractional Anisotropy (FA) map; and, fiber tractography of the (E) fornix and (F) cingulum.

Table 1 Major White Matter Tracts Investigated with Diffusion Tensor Imaging

Fiber Tract Classification System	Regions Connected
Brainstem Fibers:	
Superior cerebellar peduncle	Cerebellum (dentate nucleus), midbrain, and thalamus
Middle cerebellar peduncle	Pons, and cerebellum
Inferior cerebellar peduncle	Medulla, pons, and cerebellar cortex
Medial lemniscus	Medulla, pons, midbrain, thalamus
Projection Fibers:	
Thalamic radiations*	Cortex and thalamus
Corticofugal*: - Corticopontine/Corticoreticular/ Corticobulbar - Corticospinal	 Cortex, midbrain, pons, and medulla Cortex, midbrain, pons, medulla, spinal cord
Association Fibers:	
Superior longitudinal fasciculus	Frontal, parietal, occipital, and temporal lobes
Inferior longitudinal fasciculus	Frontal, temporal, and occipital lobes
Superior fronto-occipital fasciculus	Frontal, parietal, and occipital lobes
Inferior fronto-occipital fasciculus	Frontal and occipital lobes
Uncinate fasciculus	Frontal and temporal lobes
Cingulum	Frontal, parietal, occipital, and entorhinal area
Fornix	Hippocampus, mammilary bodies, and septal area
Stria terminalis	Amygdala, septal area, hypothalamus and thalamus
Commissural Fibers:	
Corpus Callosum	Right and left cerebral hemispheres

*Enters the internal capsule and corona radiata

schizophreniform, or schizoaffective disorder established with either the *Diagnostic and Statistical Manual of Mental Disorders (DSM) III, III-R*, or *IV edition* (American Psychiatric Association 1980, 1987, 1994) or the *International Statistical Classification of Diseases and Related Health Problems, 9th* or *10th edition* (WHO 1977, 1992) or included subjects meeting "high risk" for schizophrenia; 3) included a psychiatrically normal comparison group; 4) assessed white matter tissue exclusively; 5) written in the English language; and, 6) were in print.

Literature searches were performed using the search key words "schizophrenia," "diffusion tensor imaging," and "DTI."

Review of DTI Studies of Schizophrenia

See Table 2 for a summary of studies that met inclusion criteria. The studies are discussed within the following framework: 1) disease course that includes chronic (greater than five years), first-episode and early schizophrenia (less than five years), and high risk; 2) relationship to psychiatric and cognitive symptoms; 3) drug-treatment effects; and, 4) integration with other neuroimaging techniques.

Disease Course

Chronic Schizophrenia

The majority of evidence from DTI research of chronic, and antipsychotic-medicated, schizophrenia suggests widespread white matter alterations but with pronounced effects observed in frontal and temporal lobe circuitry. Those studies that do not specify illness duration are noted.

Several studies have investigated frontal-temporal and frontal-thalamic connectivity in chronic schizophrenia. One fiber tractography study found reduced FA in the uncinate fasciculus, the tract connecting the medial prefrontal cortex and the anterior temporal lobe, and the anterior thalamic radiation, the tract connecting the anterior thalamus with the prefrontal cortex in schizophrenia (16). Other studies of chronic schizophrenia also found reduced FA in the uncinate fasciculus (17-19) (but see 20, 21), in white matter near the anterior thalamus radiation (19, 22, 23), and in the anterior limb of the internal capsule (22, 24, 25) (but see 26). The anterior limb of the internal capsule contains fibers running from the frontal lobe to the thalamus and within the basal ganglia. Another study investigated the portion of the superior occipitofrontal fasciculus that connects the prefrontal

area to the thalamus, in antipsychotic-medicated, mixed illness duration schizophrenia (27). They reported reduced FA and elevated MD in patients compared to control subjects. Similarly, reduced FA in the thalamic-orbitofrontal tract was found in chronic, medicated subjects with schizophrenia (28). Overall, these consistent findings support compromised prefrontal-thalamic connectivity in chronic schizophrenia.

Association fibers connecting frontal and other cortical regions have also been investigated in chronic schizophrenia. A fiber tractography study of participants with chronic schizophrenia revealed reduced FA in the cingulum bundle, which connects frontal, parietal, occipital, and entorhinal regions, and the inferior fronto-occipital fasciculus, which connects frontal and occipital regions (21). Other studies, using varying methodologies, consistently found reduced FA in the cingulum (17, 22-26, 29-32) (but see 19, 33), and inferior frontal-occipital fasciculus (19, 22, 23). One study showed reduced FA was associated with longer illness duration (34). Many studies that examined the superior longitudinal fasciculus, a major bundle mainly connecting frontal, parietal, and temporal cortical regions, also reported reduced anisotropy in chronic schizophrenic subjects (19, 22-24, 31, 33, 35-37). These results provide strong support for compromised connectivity in association fibers that connect the frontal and other cortical regions in chronic schizophrenia.

The integrity of the corpus callosum (CC), the major fiber tract that connects the cerebral hemispheres, has been studied extensively in chronic schizophrenia with DTI. Kubicki (38) used fiber tractography to investigate the integrity of CC sections that correspond to frontal, parietal, and occipital-temporal interconnections. As predicted, reduced FA was found only in the section of the CC that interconnects the frontal lobes. This is consistent with studies that found FA reductions in the forceps minor (39), the frontal callosal fibers, and frontal white matter ROIs (40, 41) (but see 26) in chronic schizophrenia. Several other studies have found reduced FA in the CC genu (17, 22, 24, 37), body (17, 25, 30, 42) and splenium (17, 22, 42-44) (but see 19, 45). Another fiber tractography study of the CC in a large sample of subjects with a wide range of illness durations revealed a significant positive relationship between FA and duration of illness (46). It is plausible that reduced FA in the CC in chronic schizophrenia reflects white matter disruptions that occur with illness progression.

Disruption in the cortical-thalamic-cerebellar-cortical circuit is hypothesized to be involved in the pathophysiology of schizophrenia (4, 47). Magnotta et al. (4, 47) investigated the integrity of fiber tracts that connect the thalamus with the cerebellum in chronic schizophrenia using tractography methods. Results revealed reduced FA in fibers from the superior cerebellar peduncle to the red nucleus in schizophrenia. Supporting these results, VBA (31) and ROI (48) (but see 49) studies found reduced middle cerebellar peduncle FA and superior cerebellar peduncle (50) in chronic, medicated patients with schizophrenia. The majority of results provides support for compromised integrity of white matter connections in the cortical-thalamic-cerebellar-cortical circuit.

Since visual processing abnormalities have been observed in schizophrenia, one study investigated the white matter integrity of visual processing regions in schizophrenia through ROI analyses (51). Subjects with schizophrenia were taking antipsychotic medications but the illness duration was not specified. Results revealed reduced FA in the optic radiations but not in the striate, inferior parietal, or fusiform regions. The authors argue that the results support the notion that visual deficits occur during early and not later stages of processing. These results are supported by a study that also found FA reductions in the optic radiation of chronic, medicated patients with schizophrenia (22), but are inconsistent with others (26). Reduced FA in other occipital regions has also been reported (42, 43) (illness duration not specified).

First-Episode and Early Schizophrenia

DTI studies of first-episode schizophrenia provide an important indication of white matter alterations that occur early in the disease course with minimal antipsychotic medication exposure. The majority of results revealed reduced FA in various white matter regions, but the reduction is less than that observed in chronic schizophrenia.

One DTI study examined white matter integrity with VBA in antipsychotic-naive, first-episode patients (52). Results showed FA reductions in small regions throughout the brain in first-episode schizophrenia. Specific areas affected include a frontal region within the left fronto-occipital fasciculus, a temporal region within the left inferior longitudinal fasciculus, CC (splenium), left cerebral peduncle, right parietal region, and white matter near the substantia nigra and posterior limb of the internal capsule. These results are consistent with other VBA studies that reported similar widespread findings in first-episode schizophrenia (53-55). The combination of results suggest compromised integrity of small white matter regions throughout the brain in the first episode that are apparent early in the illness but are not as extensive as those observed in chronic schizophrenia. These changes cannot be fully explained by an antipsychotic drug effect.

Several studies investigated associative and interhemispheric fiber connections using ROI and fiber tractography methods. Karlsgodt et al. (56) found reduced FA in the superior longitudinal fasciculus in recent-onset (mean illness duration: fifteen months) antipsychotic-treated patients, but

Table 2 Summary of DTI Studies in Schizophrenia

Study	Subjects	Analysis	General Findings
Agartz et al., 2001	20 CS, 24 HC	VBA	▼FA in corpus callosum (splenium) and forceps major
Ardekani et al., 2003	14 SZ (not specified), 14 HC	VBA	▼FA in widespread regions
Begre et al., 2008	11 FE, 11 HC	VBA	Intervoxel coherence correlated with ERP parameters across multiple regions
Buchsbaum et al., 1998	5 CS, 6 HC	VBA	▼Relative anistropy in corpus callosum, internal capsule, frontal & temporal lobes; PET metabolic findings consistent with fronto-striatal disconnectivity
Buchsbaum et al., 2006a	63 CS, 55 HC	VBA	▼FA in widespread regions
Buchsbaum et al., 2006b	103 CS, 41 HC	FT	▼FA anterior thalamic radiation/anterior limb of internal capsule
Butler et al., 2006	17 SZ (not specified), 21 HC	ROI	▼FA in optic radiations
Burns et al., 2003	30 SZ (not specified), 30 HC	VBA	▼FA in uncinate and superior longitudinal fasciculus
Carpenter et al., 2008	76 mixed SZ, 77 HC	FT	▼FA in corpus callosum (genu, splenium) that is inversely correlated with duration of illness
Cheung et al., 2008	25 drug-naive FE, 26 HC	VBA, ROI	VBA: ▼FA in widespread regions; ROI: ▼FA in corpus callosum (splenium)
Federspiel et al., 2006	12 FS, 12 HC	VBA	▼Intervoxel coherence (similar to FA) in widespread regions
Foong et al., 2000	20 CS, 25 HC	ROI	▼FA, ▲MD in corpus callosum (splenium)
Friedman et al., 2008	40 FE, 39 HC; 40 CS, 40 HC	ROI	▼FA in forceps major & minor, inferior longitudinal fasciculus, & corpus callosum in CS, ▼FA (trend level) in inferior longitudinal fasciculus in FE
Fujiwara et al., 2007	42 CS, 24 HC	FT	▼FA in cingulum; inverse correlation with positive symptoms
Garver et al., 2008	13 mixed SZ off medication, 14 HC	VBA	▲MD in widespread regions; MD decreased following antipsychotic treatment in good responders
Hao et al., 2006	21 FE, 21 HC	VBA	▼FA in widespread regions
Hoptman et al., 2008	23 CS, 22 HR, 37 HC	VBA	HR: ▼FA in frontal, parietal, posterior cingulate; CS: ▼FA in widespread regions
Hubl et al., 2004	13 CS with hallucinations, 13 CS without hallucinations, 13 HC	VBA	▼FA in the superior longitudinal fasciculus, cingulum and corpus callosum in patients with hallucinations vs. without hallucinations
Jones et al., 2006	14 CS, 14 HC	FT	▼FA in superior longitudinal fasciculus; FA difference diminished with age
Karlsgodt et al., 2008	12 FE, 17 HC	FT	▼FA in superior longitudinal fasciculus; correlated with working memory
Kim et al., 2008	30 CS, 22 HC	FT	▼FA in cortical-thalamus; correlation with positive and negative symptoms
Kitamura et al., 2005	6 CS, 6 HC	ROI	▼FA in frontal lobe
Kubicki et al., 2002	Male only: 15 CS, 18 HC	ROI and segmentation to extract fiber tract	No FA differences; no left>right cingulum FA asymmetry in CS as observed in HC
Kubicki et al., 2004	Male only: 16 CS, 18 HC	ROI and segmentation to extract fiber tract	▼FA in cingulum; correlated with Wisconsin Card Sorting Test
Kubicki et al., 2005	21 CS, 26 HC	VBA	▼FA in widespread regions
Kubicki et al., 2008	32 CS, 42 HC	FT	▼FA in anterior corpus callosum
Kunimatsu et al., 2008	Male only: 19 CS, 20 HC	FT	▼FA and ▲MD in superior fronto-occipital fasciculus
Kuroki et al., 2006	Male only: 24 CS, 31 HC	ROI	▼FA and ▲MD in fornix; MD inversely correlated with hippocampal volume and antipsychotic dosage
Leitman et al., 2007	19 CS, 19 HC	VBA	▼FA in widespread regions correlated with voice emotion recognition performance; frontal FA correlated with executive function
Lim et al., 1999	Male only: 10 male SZ, 10 HC	ROI	▼FA frontal and parietal-occipital regions
Magnotta et al., 2008	12 CS, 10 HC	FT	▼FA in superior cerebellar peduncle
Manoach et al., 2007	17 CS, 19 HC	ROI	▼FA in anterior cingulum; ▼FA in anterior cingulum, frontal eye field, and posterior parietal regions correlated with longer saccadic latencies
McIntosh et al., 2008a	25 SZ, 49 HC, 40 Bipolar	FT	▼FA in uncinate and anterior thalamic radiation
McIntosh et al., 2008b	NRG1 SNP8NRG243177 genotype: 14 TT (high risk), 32 CT, 41 CC	VBA	▼FA in anterior limb of internal capsule in high risk
Minami et al., 2003	12 mixed SZ, 11 HC	ROI	▼FA in frontal, parietal, temporal, and occipital lobes; frontal FA was directly correlated with antipsychotic dosage

Table 2 Summary of DTI Studies in Schizophrenia (continued)

Study	Subjects	Analysis	General Findings
Mitelman et al., 2006	51 good outcome CS, 53 poor outcome CS, 41 HC	VBA	▼FA in widespread regions, but more extensive in poor outcome
Mitelman et al., 2007	51 good outcome CS, 53 poor outcome CS, 41 HC	ROI	▼FA in widespread regions, but more extensive in poor outcome; correlated to positive and negative symptoms
Miyata et al., 2007	40 CS, 36 HC	FT	No difference in corpus callosum FA
Mori et al., 2007	42 CS, 42 HC	VBA, ROI	▼FA in widespread regions; inversely correlated with duration of illness
Muñoz Maniega et al., 2008	31 SZ (not specified), 22 HR, 51 HC	VBA	▼FA in anterior limb of the internal capsule in SZ & HR; ▼FA in uncinate and superior longitudinal fasciculi in SZ
Nestor et al., 2004	14 CS, 14 HC	ROI	Uncinate fasciculus and cingulum FA correlated with memory and executive function performance
Nestor et al., 2007	21 CS, 24 HC	ROI	Fornix FA correlated with memory performance
Nestor et al., 2008	25 CS, 28 HC	FT	▼FA in cingulum; FA in cingulum and uncinate fasciculus correlated with executive function and memory performance and illness duration
Okugawa et al., 2004	25 CS, 21 HC	ROI	▼FA in middle cerebellar peduncles; directly correlated with antipsychotic dosage
Okugawa et al., 2006	21 CS, 21 HC	ROI	▼FA in superior cerebellar peduncles; inversely correlated with Positive and Negative Syndrome Scale (PANSS) cognitive cluster
Peters et al., 2008	10 FE, 10 HR, 10 HC	FT	No differences among groups; anterior cingulum FA, and MD in the uncinate and CC (splenium) were correlated with positive symptoms in combined FE & HR
Price et al., 2005	20 FE, 29 HC	ROI	No group differences in corpus callosum FA or MD
Price et al., 2007	18 FE, 21 HC	FT	▼FA in corpus callosum
Price et al., 2008	19 FE, 23 HC	ROI	No difference in uncinate FA; spread of FA distribution was reduced indicating a reduction in the number of voxels with high FA in the core of the tract
Rosenberger et al., 2008	27 SZ, 34 HC	FT	▼FA in cingulum and longitudinal occipito-frontal fasciculus; FA in uncinate and cingulate inversely correlated with age in SZ
Rotarska-Jagiela et al., 2008	24 CS, 24 HC	ROI	▼FA, ▲MD, and reduced volume in the corpus callosum
Schlosser et al., 2007	18 SZ, 18 HC	VBA	▼FA in temporal and frontal lobe; frontal FA correlated with fMRI activity in frontal and occipital cortex
Seal et al., 2008	Male only: 14 CS, 14 HC	VBA	▼FA and ▲radial diffusivity in widespread regions
Seok et al., 2007	15 hallucinating CS, 15 non-hallucinating CS, 22 HC	VBA, ROI	▼FA in superior longitudinal fasciculus, cingulum, middle cerebellar peduncle in combined CS; ▲FA in superior longitudinal fasciculus and cingulum in hallucinating CS compared to non-hallucinating CS
Shergill et al., 2007	33 CS, 40 HC	VBA	▼FA in corpus callosum (genu) & superior longitudinal fasciculus; direct correlation between auditory hallucinations and FA in anterior cingulum and superior longitudinal fasciculus
Skelly et al., 2008	25 CS, 25 HC	VBA	▼FA in widespread regions; correlations with positive symptoms
Steel et al., 2001	10 CS, 10 HC	ROI	No frontal FA differences; no correlation with proton magnetic resonance spectroscopy measures of frontal N-acetyl-aspartate (NAA)
Sun et al., 2003	30 CS, 19 HC	ROI	▼FA in anterior cingulum
Szeszko et al., 2005	10 FE, 13 HC	VBA	▼FA in middle frontal, superior temporal, and internal capsule regions
Szeszko et al., 2008	32 FE, 30 HC	VBA	▼FA in uncinate, fronto-occipital & superior longitudinal fasciculi; correlations with positive (fronto-occipital) and negative symptoms (uncinate) and memory impairment (uncinate)
Takei et al., 2008	31 CS, 65 HC	FT	▼FA, ▲MD in fornix and correlated with memory impairment
Tang et al., 2007	40 CS, 42 HC	ROI	▼FA in medial temporal lobe; correlated with proton magnetic resonance spectroscopic measures of N-acetyl-aspartate (NAA), a marker of neuronal integrity
Wang et al., 2003	Male only: 29 CS, 20 HC	ROI	No FA differences in middle & superior cerebellar peduncle
Wang et al., 2004	Male only: 21 CS, 20 HC	ROI	▼FA in anterior cingulum
Winterer et al., 2008	NRG1 SNP8NRG221533 genotype: 19 TT, 24 CT, 7 CC (high risk)	VBA	▼FA in medial prefrontal region in high risk
Zhou et al., 2008	17 FE, 14 HC	ROI	▼FA in fornix; functional disconnectivity of hippocampus was supported by fMRI findings
Zou et al., 2008	21 FE, 18 HC	ROI	▼FA in anterior limb of the internal capsule

CS=chronic schizophrenia; FE=first episode; SZ=schizophrenia, duration of illness not specified; HC=healthy control; FT=fiber tracking; ROI=region of interest; VBA=voxel-based analyses; FA=fractional anisotropy; MD=mean diffusivity; ▼=decreased; ▲=increased

another study did not (57). Friedman et al. (39) investigated widespread white matter areas that included forceps minor (frontal callosal fibers) and major (occipital callosal fibers), inferior longitudinal fasciculus, and the CC (genu and splenium) in first-episode and chronic patients with ROI analyses. Subtle FA reductions were noted in all regions except the forceps minor in first episode, but a statistical trend difference was observed only in the left inferior longitudinal fasciculus. FA reductions were observed in all regions in the chronic group, but a statistical difference was observed only in the left inferior longitudinal fasciculus and right forceps minor. The lack of FA reduction in the CC is consistent with previous studies of first-episode schizophrenia (57, 58). Another study of first-episode schizophrenia found no differences in FA or MD in the cingulum, uncinate fasciculus, or superior longitudinal fasciculus (57).

Connections between frontal and thalamic regions were also investigated in early schizophrenia. A DTI study of the anterior limb of the internal capsule using ROI analyses showed reduced FA in antipsychotic-naive/minimally treated first-episode patients (59). A VBA study supports this finding (55). These studies suggest that the integrity of fibers connecting prefrontal/anterior cingulate to the thalamus may be compromised early in the disease and not arise from the deleterious effects of antipsychotic medications.

Despite some inconsistencies, these studies suggest compromised white matter integrity in early schizophrenia that progresses with disease duration. These findings are especially evident in fiber tracts connecting the frontal lobe.

High Risk

One study investigated the integrity of the anterior limb of the internal capsule, and several association fibers including the uncinate fasciculus, cingulum, and arcuate fasciculus (part of the superior longitudinal fasciculus) in subjects at high risk for schizophrenia and with schizophrenia (18). High-risk subjects had two or more first- or second-degree relatives with schizophrenia but did not have prodromal or psychotic symptoms. FA was investigated with VBA and ROI analyses. Results showed that high-risk subjects, similar to the subjects with schizophrenia, had reduced FA of the anterior limb of the internal capsule when compared to control subjects. FA levels of the association fibers fell in-between subjects with schizophrenia and controls but were not statistically significant, which is consistent with another study (57). Consistently, reduced FA in the anterior limb of the internal capsule was observed in subjects with a neuroregulin 1 (NRG1) risk-associated genotype for schizophrenia (60). NRG1 contributes to neurodevelopment, myelination and axonal guidance (61). White matter abnormalities may occur in association with genetic modifications of this gene. Another study reported reduced FA in medial frontal regions in subjects with a NRG1 risk-associated genotype for schizophrenia (62). These results suggest that compromised integrity of the frontal white matter connections may be associated with a higher vulnerability for developing schizophrenia.

Another VBA study investigated high-risk, chronic, and control subjects (63). High-risk subjects had a first-degree relative with schizophrenia, the majority had prodromal symptoms, and one-third met criteria for schizotypal personality disorder. The main findings included reduced FA in the white matter of the left inferior frontal gyrus, posterior cingulate and bilateral angular gyrus and elevated FA in the subgenual anterior cingulate, right middle/superior frontal, and bilateral pontine tegmental regions in the high-risk group compared to the control group. FA alterations observed in subjects with schizophrenia were widespread and included frontal, temporal, occipital, cingulate, insula, and basal ganglia.

These studies suggest that white matter alterations may be detectable before psychosis onset or are associated with genetic vulnerability for developing schizophrenia. However, longitudinal studies are necessary to determine this with greater certainty. Similar to chronic and early schizophrenia, those at high risk show that their frontal white matter connections are the most affected.

Relation to Symptoms

Are the white matter alterations in schizophrenia clinically meaningful? Research to address this question investigated the associations between DTI measures and psychiatric symptom severity, cognitive impairments, and disease outcome.

Psychiatric Symptoms

Several studies have reported significant associations between psychiatric symptom severity and DTI indices but the direction of the relationship is inconsistent. Some studies found a direct relationship between FA and positive symptoms, where greater FA corresponded to greater severity of positive symptoms. One VBA study found that higher FA in the inferior fronto-occipital fasciculus within the temporal lobe corresponded to greater severity of hallucinations and delusions in early schizophrenia (64). Similarly, a fiber tractography study found anterior cingulum FA, and MD in the uncinate and CC (splenium) to be directly correlated with positive symptoms in a combined sample of first-episode and high-risk subjects (57). In contrast, an inverse relationship between posterior cingulum FA and positive symptom severity was found in previous studies of chronic, medicated patients with fiber tractography (65). Similarly, a fiber tractography study found reduced FA in tracts connecting the thalamus to left orbitofrontal and right dorsal prefrontal re-

gions was related to greater severity of positive symptoms in chronic, medicated patients with schizophrenia (28). VBA studies of chronic, medicated schizophrenia also found that the greater the severity of positive symptoms the lower the FA in the sagittal stratum, uncinate and superior longitudinal fasciculus (23), and the CC (genu), anterior cingulum, and inferior longitudinal fasciculus (22).

Several studies have investigated the differences in white matter integrity between patients with and without hallucinations. VBA studies have shown that chronic patients with hallucinations had greater FA in the superior longitudinal fasciculus, cingulum (31, 37, 66) and CC (66) compared to chronic patients without hallucinations. Seok (31) also showed that FA in the superior longitudinal fasciculus was positively correlated with severity of hallucinations.

The relationship between DTI measures and negative symptoms has also been explored. One VBA study found greater negative symptom severity to be associated with lower FA in the anterior and posterior limb of the internal capsule and superior longitudinal fasciculus, CC, anterior thalamic radiation, fronto-occipital fasciculus, and white matter in the temporal lobe (22). Reduced FA in the uncinate fasciculus was associated with increased alogia and affective flattening in early schizophrenia (64).

The relationship of white matter integrity to clinical outcome in patients with schizophrenia has also been investigated. Mitelman et al. (22) found greater FA reductions in poor versus good outcome patients (criteria described by Keefe [67]) in multiple, widespread regions using ROI analyses on previously published VBA data (68). Severe widespread reductions in white matter tract integrity are likely to adversely affect patient clinical outcome.

Cognitive Symptoms

Learning and memory are especially impaired in schizophrenia. Medial temporal lobe function, instrumental for learning and memory, is known to be impaired in schizophrenia. One study assessed the integrity of the fornix, the major white matter connection between the hippocampus and the cerebrum, in chronic, antipsychotic-medicated patients with schizophrenia with fiber tractography (69). The relationships between fornix FA and MD and memory performance were examined. Results revealed reduced FA and elevated MD in patients compared to controls, and increased MD was associated with poorer memory organization performance in patients. These results are consistent with other studies reporting fornix FA to be directly related to impaired learning and memory function in chronic schizophrenia (70). Other studies found a similar relationship between reduced FA in the uncinate fasciculus and impaired learning and memory performance in early and chronic schizophrenia (70, 71). These results suggest that compromised connectivity of the medial temporal lobe contributes to diminished memory function in schizophrenia.

Executive function and working memory deficits are also commonly observed in schizophrenia. Reduced FA in the cingulum was associated with executive function deficits in chronic, medicated patients with schizophrenia; this was assessed with fiber tractography (70, 71) and a similar method (25). Another fiber tractography study reported FA of the left superior longitudinal fasciculus predicted working memory performance in recent-onset schizophrenia (56). Reduced FA was associated with poorer performance; this suggests that compromised connectivity has behavioral implications.

Emotional processing impairments are commonly observed in schizophrenia and were investigated in one DTI VBA study of chronic, medicated patients (72). Poor performance on voice emotion identification was predicted by FA reductions in primary and secondary auditory pathways, orbitofrontal, CC, and white matter near the amygdala.

Impaired ocular motor control is also related to reduced FA in chronic schizophrenia. Manoach (30) reported reduced FA in the right hemisphere anterior cingulate, frontal eye field, and posterior parietal white matter regions. Reduced FA was related to longer saccadic latencies in schizophrenia. These findings suggest that impaired ocular motor control in schizophrenia may be influenced by compromised connectivity.

Drug Response

Few studies have investigated the effects of antipsychotic medication on white matter changes in schizophrenia. One VBA study investigated white matter integrity before and following twenty-eight days of antipsychotic medication (risperidone, haloperidol, or ziprasidone) in good and poor treatment-responding patients with mixed-illness duration (73). White matter MD was elevated in both patient groups compared to control subjects prior to treatment. In the good responders, MD declined following treatment. Some studies have reported relationships between antipsychotic dose and DTI indices but with no consistency regarding brain region. For example, antispychotic medication dosage was directly correlated with FA in the left middle cerebellar peduncle (48) and frontal lobe (74).

Integration with Other Neuroimaging Techniques

Diffusion tensor imaging has been used in conjunction with five other imaging methods: volumetric measurements, functional magnetic resonance imaging (fMRI), positron emission tomography (PET), proton magnetic resonance spectroscopy (1H-MRS), and electrophysiological (ERP) assessments. With each combination the investigators make an

effort to advance a fundamental question by gaining complementary information. We expect this approach will become routine over the next five years.

Structural MRI and DTI

Rotarska-Jagiela and colleagues (75) have provided a systematic analysis of the anatomical and diffusion properties of the CC in subjects with chronic schizophrenia. Results showed patients to have diminished FA, elevated MD, and reduced volume in the whole CC. These indices were also correlated with one another in both groups. Because the CC has been a structure of substantial interest to the neurobehavioral scientific community for many years, this report provides a useful reflection of the field's anatomical research progress (76). The developmental characteristics of the CC, especially as it applies to schizophrenia, will likely be an active area of future investigations.

Kuroki and colleagues (77) examined the volume of the hippocampus and diffusion indices of the fornix in subjects with chronic schizophrenia. Clear differences were found between the two groups on both measures. FA was significantly diminished and MD was significantly greater in the patient group. As expected, the patient group also had lower hippocampal volumes. Correlations between measures were noteworthy. In the patient group, fornix MD correlated negatively with hippocampal volume, and fornix cross-sectional area correlated positively with hippocampal volume. Also in patients, medication dosage was negatively correlated with FA and cross-sectional area of the fornix and positively correlated with MD. This carefully constructed study robustly demonstrates the relationship between volumetric and water diffusion alterations that occur in the medial temporal lobe in chronic, medicated schizophrenia.

fMRI and DTI

Zhou and colleagues (78) examined the relationship between functional and anatomical medial temporal lobe connectivity in first-episode subjects with schizophrenia. The authors predicted that diminished hippocampal functional connectivity assessed with resting fMRI and reduced fornix FA assessed with fiber tractography would characterize the patient group. Resting fMRI data showed that visual, parahippocampal, and superior temporal regions differed significantly in their correlations to the left anterior hippocampi between groups. The healthy controls showed stronger associations than the patient group. DTI measures showed significantly lower fornix FA in the patient group. This study helps to integrate research showing compromised hippocampal functional and anatomical connectivity in schizophrenia.

Schlosser and colleagues (79) made an effort to determine whether the neural response during a working memory task assessed with fMRI reflected the anatomical integrity of frontal and medial temporal white fiber tracts using VBA in schizophrenia (illness duration not specified). Results revealed reduced FA in frontal white matter tracts in patients, and this FA reduction correlated with the reduced fMRI response in prefrontal cortex. These findings suggest that compromised integrity of frontal white matter tracts is related to dysfunctional frontal neural activity in schizophrenia (5).

PET and DTI

Buchsbaum and colleagues (80) provided an early examination of brain interregional functional relationships. By using 18-F-2-deoxyglucose to measure cerebral metabolism and DTI to assess anisotropy, the investigators were able to demonstrate complementary differences between unmedicated, chronic subjects with schizophrenia and healthy control subjects. The anisotropy of the groups differed significantly in anterior (superior fronto-occipital fasciculus) and posterior (inferior fronto-occipital fasciculus) white matter tracts. In an effort to clarify the relevance of these differences, the investigators looked at brain metabolism regional correlations. They show strong correlations between the basal ganglia and the medial frontal cortex in healthy volunteers but no such correlations in the schizophrenia group. This brief report is noteworthy for being the first DTI study of schizophrenia, and an early application of multiple neuroimaging techniques to address the problem of functional and anatomical connectivity in schizophrenia.

1H-MRS and DTI

Tang and associates (81) have provided an important update to the line of investigation published ten years earlier by Buchsbaum (80). By combining 1H-MRS measures of N-acetyl-aspartate (NAA; a marker of neuronal integrity) with DTI measures of the same white matter regions, this group has convincingly demonstrated strong relationships between neurochemical and DTI indices of fiber tract integrity. Results showed a selective reduction in NAA and FA in the left medial temporal lobe in the schizophrenia group. There were no differences in frontal regions. These measures were also correlated in patients but not in the controls. Because NAA is located mainly in the neurons, these results suggest that the health of the axonal projections in the medial temporal lobe is specifically compromised in schizophrenia. This creative study goes a long way toward showing how integrating neuroimaging techniques can help elucidate the interacting components of pathology.

In a smaller study, Steel and colleagues (82) examined NAA and FA in white matter tracts localized to the frontal lobe. Though significant NAA reductions were confirmed in the frontal white matter of subjects with schizophrenia, no significant FA alterations were found. This is consistent with

the previously mentioned study that emphasized abnormalities in the medial temporal regions in schizophrenia (81). These two studies taken together suggest that the DTI and 1H-MRS findings do not always correlate in all brain regions in schizophrenia. They do, however, support the strategy for combining these complementary methods.

Electrophysiology and DTI

An unusual study aimed to show a relationship in evoked response potential (ERP) pattern and white matter anisotropy in first-episode schizophrenia (83). Using a Go/No-Go paradigm that assessed inhibitory control, the investigators expected to find a correlation between intervoxel coherence values and No-Go ERP parameters. In both groups, correlations were found between ERP parameters and intervoxel coherence in widespread white matter regions. However, the patient group had significant correlations in many other white matter regions as well. The authors interpret these findings as neural activity correlates of extended white matter circuits for inhibitory control in first-episode schizophrenia.

Conclusions and Interpretations

The DTI research reviewed here indicates that the integrity of brain white matter is compromised in schizophrenia. These studies support the hypothesis that diminished brain connectivity contributes to the pathophysiology of schizophrenia (4, 5). Abnormal DTI indices are routinely found in multiple brain regions of schizophrenic subjects and white matter fibers connecting regions throughout the brain. Diminished anisotropy is observed across the course of schizophrenia. Patients experiencing their first episodes and those studied early in the disease course have fewer, less extensive DTI abnormalities than chronic patients. High-risk, genetically vulnerable samples also exhibit FA abnormalities. A common theme found in these three groups is compromised white matter tract integrity of a network connecting the frontal lobe with subcortical and posterior cortical systems. Chronic schizophrenia is clearly afflicted with widespread and extensive white matter alterations, but is especially affected in frontal, temporal, and subcortical connections. Clinical manifestations of the disease, like hallucinations and cognitive deficits, appear to be correlated with diffusion aberrations. A consistent finding is that patients with chronic auditory hallucinations have greater anisotropy in areas of the superior longitudinal fasciculus. It is plausible that this reflects aberrant connectivity between language and auditory regions, areas activated during auditory hallucinations (84). Antipsychotic treatment may affect white matter integrity in schizophrenia, but further research is needed to determine the relationship.

Volumetric MRI, fMRI, and 1H-MRS studies applied in conjunction with DTI often show strong associations. The biological basis of the relationship between white matter diffusion and other biological measures, such as fMRI activity, NAA, or gray matter volume, is not known. But, it is the hope that basic science investigations will elucidate these relationships. Future research integrating neuroimaging techniques should provide better insight into the pathophysiological mechanisms in schizophrenia.

DTI is a new methodology that appears to reflect multiple biological components of white matter integrity. Water diffusion in white matter fiber bundles reflects the health of the tissue. This review shows that several important aspects of schizophrenia are associated with alterations in DTI measures. Alterations in anisotropy measures may partially reflect dysmyelination, which are problems with the production or structure of myelin. This is consistent with postmortem findings in schizophrenia (85-88) and supported by a DTI study that revealed increased radial diffusivity in schizophrenia (19). Altered fiber organization or aberrant axon morphology may also affect anisotropy in schizophrenia. Postmortem findings of axonal atrophy support this notion (89). With further advances in DTI acquisition and analysis techniques, future research may be able to deconvolve the components of white matter biology affected in schizophrenia. This could prove extremely fruitful for the development of therapeutic drug targets.

White matter alterations change with disease course, clinical characteristics, and antipsychotic treatments associated with schizophrenia. DTI may prove to be a potent instrument for predicting disease outcome, identifying treatment targets, and elucidating the biological nature of white matter pathophysiology in schizophrenia.

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