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Review

# Diffusion tensor imaging in first degree relatives of schizophrenia and bipolar disorder patients

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ABSTRACT

*Objectives:* White matter (WM) abnormalities are one of the most widely and consistently reported findings in schizophrenia (SZ) and bipolar disorder (BD). If these abnormalities are inherited determinants of illness, suitable to be classified as an endophenotype, relatives of patients must also have them at higher rate compared to the general population. In this review, we evaluate published diffusion tensor imaging (DTI) studies comparing first degree relatives of SZ and BD patients and healthy control subjects.
*Methods:* We searched PubMed, Embase and PsychInfo for DTI studies which included an unaffected relative and a healthy comparison group.
*Results:* 22 studies fulfilled the inclusion criteria. WM abnormalities were found in many diverse regions in relatives of SZ patients. Although the findings were not completely consistent across studies, the most implicated areas were the frontal and temporal WM regions and the corpus callosum. Studies in relatives of BD patients were fewer in number with less consistent findings reported across studies.
*Conclusions:* Our review supports the concept of WM abnormalities as an endophenotype in SZ, with somewhat weaker evidence in BD, but larger and higher quality studies are needed to make a definite comment.


## 1. Introduction

Despite Kraepelin's original division of schizophrenia (SZ) and bipolar disorder (BD) into different clinical categories (Kraepelin, 1920), increasing evidence suggests that these two conditions share similarities or overlap in symptoms (Keshavan et al., 2011), cognitive functions (Schretlen et al., 2007), brain structure (Ellison-Wright and Bullmore, 2009), and risk genes (Potash, 2006). Furthermore, as would be expected in disorders with prominent genetic determinants, many structural and functional abnormalities seen in these conditions can also be seen in unaffected relatives of probands (McDonald et al., 2004; McIntosh et al., 2004; Glahn et al., 2010). These observations raise the possibility of identifying endophenotypes related to underlying disease mechanisms. Endophenotypes are measurable illness-related traits that may be more sensitive than diagnosis to the underlying genetic variation of the disorder. One important test for candidate endophenotypes is whether the abnormality can be identified in unaffected biological relatives of patients at a higher rate compared to the general population (Gottesman and Gould, 2003; Braff et al., 2007). If so, further studies can lead to identification of the genes associated with the endophenotype.

White matter (WM) integrity has been proposed as a candidate endophenotype because it is abnormal in BD and SZ, and highly heritable in the two conditions (van der Schot et al., 2009; Bertisch et al., 2010). WM integrity is commonly examined using diffusion tensor imaging (DTI). DTI noninvasively quantifies water molecule diffusion in vivo, reflecting organization of tracts in the WM. DTI experiments provide several measures of relevance to WM integrity: Fractional anisotropy (FA) reflects the overall integrity of nerve fibers. A reduction in FA can reflect a decrease in myelination and/or decrease in axonal organization of fibers. In addition, measurements of radial, axial and mean diffusivity (RD, AD, and MD) are calculated from DTI data (Hasan, 2006). The importance of RD and AD has been debated, but there isn't sufficient evidence to interpret their biological meaning clearly. Mean diffusivity (MD, or the directionally averaged apparent diffusion coefficient (ADC)), reflects global water molecule diffusion independent of fiber directionality. In addition to these multiple measures, multiple types of analyses are possible with DTI data: region of interest (ROI) analyses including the use of tractography, whole brain analyses such as voxel-based analysis (VBA), and tract-based spatial statistics (TBSS) which registers the FA map of each subject to a white matter skeleton representing the centers of white matter (Shizukuishi et al., 2013).

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**Table 1**
DTI studies of healthy relatives of SZ and related disorders.

| Authors | Sample | Mean age (years) ± SD | Field strength | Analysis method | Abnormalities in relatives compared to healthy controls | Additional modalities | Comments/limitations |
|---|---|---|---|---|---|---|---|
| DeLisi et al. (2006) | 15 relatives<br>25 HC<br>15 SZ | 19.3 ± 4.6<br>23.7 ± 3.7<br>34.3 ± 10.7 | 1.5 T | VBA | • ADC didn't differ in the region of the body of the CC | Gray matter<br>Volumetric quantification | • Several of the patients and relatives were biologic relatives<br>• Relatives were still in the peak age of risk for SZ (defined as ages 12–30)<br>• Only psychotic disorders excluded for relatives and HC<br>• Family history of psychotic disorders excluded for HC<br>• None of the relatives or HC were on antipsychotic or antidepressant medications |
| Hoptman et al. (2008) | 22 relatives<br>37 HC<br>23 DSM-IV SZ + SZAF | 20.1 ± 4.1<br>23.1 ± 4.0<br>36.8 ± 11.0 | 1.5 T | VBA | Reduced FA in:<br>• Left inferior frontal gyrus WM<br>• Bilateral left posterior cingulate WM<br>• Bilateral angular gyral WM<br>Increased FA in:<br>• Left subgenual anterior cingulate<br>• Bilateral pontine tegmental WM<br>• Right middle/superior frontal gyri | – | • Most of the patients and relatives were biologic relatives<br>• Relatives were still in the peak age of risk for SZ (defined as ages 12–30)<br>• Fourteen relatives satisfied criteria for the prodrome, of those without the prodrome seven satisfied criteria for schizotypal personality disorder or had some schizotypal traits and five had a history (but not current) of major depression<br>• Relatives have never experienced acute psychotic symptoms<br>• Psychotic disorders and family history of psychotic disorders excluded for HC<br>• None of the HC were currently taking medication for any psychiatric condition<br>• There was a significant difference in sex distribution across groups<br>• In this study some of the participants were recruited from the study DeLisi et al. (2006), but the sample size was enlarged. |
| Munoz Maniega et al. (2008) | 22 relatives<br>51 HC<br>31 DSM-IV SZ | 30 ± 3<br>35 ± 11<br>37 ± 10 | 1.5 T | VBA<br>ROI | • VBA showed that FA didn't differ significantly<br>• Automatic ROI analysis showed that FA was reduced in the ALIC | – | • Relatives had at least two or more first or second degree relatives with SZ<br>• None of the relatives and patients were related<br>• Not specified whether relatives or HC have another psychiatric illness, other than SZ or are taking medicine. |
| Hao et al. (2009) | 34 siblings<br>32 HC<br>34 DSM-IV SZ | 25.8 ± 7.1<br>26.6 ± 6.0<br>25.4 ± 5.9 | 1.5 T | VBA | Reduced FA in:<br>• Left hippocampus<br>• Left PFC | – | • All of the patients and relatives were biologic relatives<br>• All of the psychiatric disorders excluded for relatives and HC<br>• First degree relatives of HC didn't have a history of any psychiatric disorder |
| Camchong et al. (2009) | 22 relatives<br>30 HC<br>18 healthy MZ twin pairs | 48.5 ± 8.2<br>43.8 ± 11.4 | 3 T | ROI<br>VBA<br>TBSS | • ROI analysis and TBSS showed decreased FA in right genu of CC<br>• VBA showed no differences | Correlation of FA values between healthy MZ twin pairs | • Current alcohol or drug abuse, drug dependence, major depressive episode, current or previous use of anti-psychotic medications, a personal history of psychosis or BD, or an Axis II Cluster A personality disorder was excluded for all subjects<br>• HC were excluded if they have a family history of psychosis or BD |
| Clark et al. (2011) | 20 Relatives<br>32 HC<br>31 DSM-IV SZ | 41.1 ± 13.0<br>34.8 ± 14.0<br>32.7 ± 9.3 | 1.5 T | ROI | Decreased FA in:<br>• The bilateral IFOF<br>• The left ILF<br>• The left tSLF<br>Age was not significantly different among these groups, but post-hoc analysis (age as a covariate) showed only decreased FA in the left ILF remained significant<br>There were no significant differences in ADC values | Genetic liability effects<br>Correlation with BPRS scores | • None of the relatives were biologic relatives of the patients<br>• No individual with a schizophrenia spectrum disorder or a psychotic disorder was included in relatives or HC<br>• Six control and eight patient relatives met diagnostic criteria for additional Axis I or II diagnoses (mood disorders, anxiety disorder, attention-deficit/hyperactivity disorder, conduct disorders, antisocial personality disorder)<br>• HC or relatives were not taking psychiatric medicine<br>• HC were excluded if they had any evidence of drug abuse or alcoholism within six months |
| Phillips et al. (2011) | 49 relatives (P + S)<br>21 HC<br>54 HCR (P + S)<br>26 DSM-IV SZ | P: 54.4 ± 8.3<br>S: 30.1 ± 11.5<br>25.9 ± 6.7<br>P: 55.7 ± 8.5<br>S: 26.9 ± 9.8<br>29.5 ± 7.4 | 1.5 T | VBA | Decreased FA in:<br>• bilateral temporal lobe<br>• bilateral occipital lobe<br><br>Results didn't withstand permutation correction | Genetic liability effects | • All of the psychiatric disorders were excluded for HC and HCR subjects<br>• Recent or past history of significant and habitual drug abuse or alcoholism were excluded for all subjects<br>• Age was similar between HC and patient siblings, HC and patient parents, and between patients and their siblings |