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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 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 definitive comment.

Keywords

Psychosis; white matter; endophenotype; at risk; DTI

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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 (Glahn et al., 2010; McDonald et al., 2004; McIntosh et al., 2004). 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 (Braff et al., 2007; Gottesman et al., 2003). 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 (Bertisch et al., 2010; van der Schot et al., 2009). 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 have 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).

Substantial evidence suggests that SZ patients show abnormal WM FA in multiple brain regions. In a meta-analysis, (Ellison-Wright and Bullmore, 2009) identified 15 studies and indicated significant FA reductions in two regions: 1. Left frontal deep WM and its WM connections with the frontal lobe, thalamus and cingulate gyrus. 2. The left temporal deep WM and its WM connections with the frontal lobe, insula, hippocampus-amygdala, temporal and occipital lobe. Related WM abnormalities are seen in first episode SZ patients (Szeszko et al., 2005), early onset SZ (Kumra et al., 2005; Szeszko et al., 2008), and in individuals at ultra high risk for psychosis (UHR) some of whom were drug naive (Karlsgodt et al., 2009). These findings suggest that WM abnormalities are not due to long term medication effects, and that they emerge at an early or even a prodromal stage of the illness.

Neuroanatomical WM abnormalities may play an important role in BD as they do in SZ (Hajek et al., 2005). WM hyperintensities and volume deficits are reported in BD in the literature (Altshuler et al., 1995; Beyer et al., 2009; McDonald et al., 2005). A meta-analysis of DTI studies in BD patients revealed two clusters of reduced FA: near the right parahippocampal WM and near the right anterior and subgenual cingulate cortex (Vederine et al., 2011). Thus, it appears that reduced WM integrity is, at least in part, a shared abnormality between SZ and BD and is also seen in other disorder such as Alzheimer's Disease, major depressive disorder, anxiety disorders and autism (Shizukuishi et al., 2013; Thomason and Thompson, 2011).

In this paper, we reviewed DTI studies which provide data on unaffected relatives of patients with SZ or BD compared to healthy controls. We sought to determine whether the WM abnormalities studied by DTI commonly reported in patients are also observed in unaffected relatives of ill probands. If so, this finding may support WM integrity to be an endophenotype in these conditions. We also wanted to evaluate whether relatives of patients with SZ and BD had similar patterns of WM integrity.

2. Methods

Articles were identified on PubMed, Embase and PsychInfo. When we started the research, we found 32 articles using keywords “psychosis” “schizophrenia” “bipolar disorder” “first degree relatives” “at risk” “diffusion tensor imaging” “dti” from January 2005 to October 2014. We also searched the reference lists of published studies. The studies were included if they met the following criteria: (a) used DTI (b) included a group of unaffected first degree relatives of patients with SZ or BD (or unaffected individuals with two second degree SZ or BD relatives) and compared the groups in terms of diffusion measures, (c) were written in English. Note that many of these studies also included an SZ or BD patient group, but this was not required for inclusion.

3. Results

We identified 22 studies that fulfilled the inclusion criteria. 13 studies compared DTI measures in unaffected relatives of SZ patients and healthy controls (Boos et al., 2013; Camchong et al., 2009; Clark et al., 2011; DeLisi et al., 2006; Domen et al., 2013; Goghari et al., 2014; Hao et al., 2009; Hoptman et al., 2008; Knöchel et al., 2012a, 2012b; Muñoz Maniega et al., 2008; Phillips et al., 2011; Prasad et al., 2014) while 8 did the same in unaffected relatives of BD patients and healthy controls (Chaddock et al., 2009; Emsell et al., 2013; Frazier et al., 2007; Linke et al., 2013; Mahon et al., 2013; Sprooten et al., 2013, 2011; Versace et al., 2010). One study used DTI in comparing unaffected relatives of both SZ and BD patients and healthy controls (Skudlarski et al., 2013). See Tables 1, 2, and 3 for details of these studies. We included one study that enrolled not only unaffected but also prodromal relatives (Hoptman et al., 2008). We excluded otherwise relevant studies if they didn't compare the groups in terms of DTI values (Bertisch et al., 2010), only focused on individuals at UHR or clinical high risk for psychosis (Carletti et al., 2012; Jacobson et al., 2010; Karlsgodt et al., 2009; Peters et al., 2008; Pettersson-Yeo et al., 2013; von Hohenberg et al., 2014), applied DTI to measure ADC in grey matter (Narr et al., 2009), were not

written in English (Kang et al., 2012) or was a poster presented at a meeting and not a published manuscript (Contet et al., 2011).

3.1. Studies of SZ relatives

All but two of the fourteen studies found some abnormalities in the relative group compared to healthy controls (Boos et al., 2013; Camchong et al., 2009; Clark et al., 2011; Goghari et al., 2014; Hao et al., 2009; Hoptman et al., 2008; Knöchel et al., 2012a, 2012b; Muñoz Maniega et al., 2008; Phillips et al., 2011; Prasad et al., 2014; Skudlarski et al., 2013). Ten of these studies found decreased FA (Camchong et al., 2009; Clark et al., 2011; Hao et al., 2009; Hoptman et al., 2008; Knöchel et al., 2012a, 2012b; Muñoz Maniega et al., 2008; Phillips et al., 2011; Prasad et al., 2014; Skudlarski et al., 2013), four found increased FA (Boos et al., 2013; Goghari et al., 2014; Hoptman et al., 2008; Knöchel et al., 2012a), one found increased ADC (Knöchel et al., 2012b), and one found decreased RD (Prasad et al., 2014). In general, the findings were of reduced FA. This is consistent with more abnormal WM integrity in the relative group than controls. One large, apparently well-done study at 3 Tesla which used VBA and TBSS approaches and measured FA values was negative (Domen et al., 2013). Another study used VBA and found elevated ADC in gray matter, but not in the WM (DeLisi et al., 2006). Five other studies reported nonsignificant differences between relative and control groups in some analyses, but they also found significant differences using other analysis methods or different anisotropy measures (Camchong et al., 2009; Clark et al., 2011; Goghari et al., 2014; Knöchel et al., 2012a; Muñoz Maniega et al., 2008). Among these five studies four used VBA and one used ROI and studied ADC (Clark et al., 2011). Just one of these studies specified that the participants had no psychiatric disorder. The remainder did not specify disease conditions or reported that the subjects had psychiatric illnesses other than psychotic disorders. In many publications, some participants were taking psychotropic medications. There was a relatively broad age range across these studies (although all included adults) and some had relatively small sample sizes.

Among three studies reporting significant findings in whole brain analyses, FA reductions were found in the left inferior frontal gyrus WM, left posterior cingulate WM, bilateral angular gyrus WM (Hoptman et al., 2008), left prefrontal cortex (PFC) and left hippocampus (Hao et al., 2009), and superficial WM of bilateral temporal and occipital lobes (Phillips et al., 2011). Hovewer, one of these studies also reported increased FA in the left subgenual anterior cingulate, bilateral pontine tegmental WM, and the right middle/superior frontal gyrus (Hoptman et al., 2008).

The literature using ROI approaches is larger. Of the six published studies, four used FA (Camchong et al., 2009; Knöchel et al., 2012a; Muñoz Maniega et al., 2008; Skudlarski et al., 2013) and two used a combination of FA and ADC (Clark et al., 2011; Knöchel et al., 2012b). FA reductions were reported in the anterior limb of internal capsule (ALIC) (Muñoz Maniega et al., 2008), left inferior longitudinal fasciculus (ILF) (Clark et al., 2011), inferior frontooccipital fasciculus (IFOF), left superior longitudinal fasciculus (SLF), (Clark et al., 2011; Knöchel et al., 2012a), left uncinate fasciculus (UF), cingulum bundles (Knöchel et al., 2012a) and different parts of the corona radiata (Skudlarski et al., 2013). Four studies showed decreased FA in corpus callosum (CC), especially in the genu (Camchong et al.,

2009; Knöchel et al., 2012a, 2012b; Skudlarski et al., 2013). One showed increased ADC in the entire CC and isthmus (Knöchel et al., 2012b). The same study design issues discussed above (wide age range, small sample sizes, inclusion of some participants with psychiatric disorders and taking medications) also applied to these papers. One of the ROI based studies reporting widespread FA reductions in relatives also found increased FA in the arcuate fasciculus (AF) (Knöchel et al., 2012a).

There are two studies where the findings went in the opposite direction from this pattern of FA reductions. One of them used an along-tract analysis approach and found increased FA in the right fimbria of fornix (Goghari et al., 2014). The other is a large study was done at 1.5 Tesla and used TBSS. Elevated FA was reported in the left and right AF in relatives compared to controls (Boos et al., 2013). This study allowed non-psychotic psychiatric disorders in the relative group. Another recent study using TBSS also found decreased FA in forceps minor and decreased RD in the SLF and forceps minor in relatives compared to control (Prasad et al., 2014).

3.2. Studies of BD relatives

The literature on BD relatives was smaller and the DTI techniques, age range and clinical characteristics of relatives and healthy comparison subjects tended to be more diverse. Although we examined the studies for factors that might explain the partially discrepant findings reported below, we did not identify a clear pattern in this small number of publications. Of the nine studies we identified in which relatives of BD patients were compared with healthy controls on DTI measures, two did not report any group differences (Chaddock et al., 2009; Emsell et al., 2013). These two studies apparently used the same sample with different DTI techniques. One was a whole brain FA study (Chaddock et al., 2009) while the other examined both FA and RD using tractography (Emsell et al., 2013). Although these two studies tended to study older relatives, there were two other studies which recruited similarly aged relatives, but found significant abnormalities (Mahon et al., 2013; Skudlarski et al., 2013). One other study reported a trend level reduction in FA in the forceps and the posterior thalamic radiations in relatives of BD using ROI, and a significant FA reduction in the same regions using TBSS (Sprooten et al., 2013).

Another paper (Sprooten et al., 2011) used both VBA and TBSS and found that relatives had significantly reduced FA in a large widespread cluster extending over most of the WM skeleton, including the genu and parts of the splenium of CC, internal capsules, ILF, SLF, IFOF, AF, UF, parts of the corticospinal tract and subcortical WM mainly in the parietal and frontal lobes in VBA results.

There were three studies reporting significant findings using an ROI approach for the analysis. Significantly reduced FA was found in the bilateral SLF I (Frazier et al., 2007), right ALIC, UF (Linke et al., 2013) and superior aspect of the right posterior corona radiata (Skudlarski et al., 2013). By contrast, RD was found increased in the right ALIC (Linke et al., 2013).

Five studies used a TBSS analysis and all of them reported significant findings. FA reductions were found in a large widespread cluster extending over most of the WM

skeleton, including internal and external capsules (including the anterior thalamic radiation), ILF, IFOF, UF, parts of the corticospinal tract and subcortical WM around the central sulci (Sprooten et al., 2011), right temporal WM (Mahon et al., 2013), posterior thalamic radiation (Sprooten et al., 2013) the posterior corona radiata (Skudlarski et al., 2013; Sprooten et al., 2013) CC and SLF (Sprooten et al., 2013, 2011). By contrast, one study found a complex pattern in which relatives of BD probands had increased FA in the region of CC, decreased RD in the region of CC and right ILF in the temporal pole, and increased AD in the region of the right ILF in the visual cortex (Versace et al., 2010). Note that these studies had different age ranges, clinical characteristics and sample sizes. For example one study found FA increases in 8-17 age range offspring who were still at the risk for developing BD (Versace et al., 2010). Another study (Sprooten et al., 2011) also had the same design, but recruited an older sample. Several studies did not mention whether probands had psychotic symptoms during affective episode (Mahon et al., 2013; Sprooten et al., 2011; Versace et al., 2010). Only one study (Sprooten et al., 2013) specified that the relatives recruited may have had other psychiatric disorders.

Finally, one study also applied a probabilistic tractography approach and found decreased FA in the right IFOF (Mahon et al., 2013).

4. Discussion

In this study, we reviewed the literature on DTI measures of WM in the brains of unaffected relatives of SZ and BD patients. This literature is relatively small and there are multiple important methodological, clinical, and sample size differences between studies. We note that the findings we reviewed are not completely consistent across publications, with some important papers providing discrepant results. Nonetheless, we conclude that most of the significant findings in the literature show abnormalities in WM integrity in relatives of SZ patients in the frontal, temporal WM and related bundles and in the corpus callosum when compared with healthy controls. Four studies found significant differences in DTI parameters in CC, especially in the genu (Camchong et al., 2009; Knöchel et al., 2012a, 2012b; Skudlarski et al., 2013). All of these studies applied ROI techniques at 3T, studied in the same age range. All but one excluded all axis I psychiatric disorders according to DSM-IV for relatives and HC group (Camchong et al., 2009). Also one of these studies had a particularly large sample size (Skudlarski et al., 2013). This conclusion is resonant with findings from recent meta-analyses showing abnormal WM integrity in the genu of the CC, ACC/medial frontal WM, the right ALIC and right external capsule/corona radiata, left temporal WM and left retrolenticuler internal capsule and external capsule in SZ patients (Bora et al., 2011). WM disintegrity in CC also found in individuals at clinical high risk for psychosis in a recent study (von Hohenberg et al., 2014) and in first episode SZ (Wang et al., 2011). Others (Knöchel et al., 2012b) also found decreased volume of the CC in relatives compared to healthy controls. Findings indicated significantly reduced total CC volume in offspring of schizophrenia patients compared to healthy controls (Francis et al., 2011). In addition, another study found decreased N-acetylaspartate (NAA) concentrations and prolonged T2B in UHR individuals and in first-episode patients (Aydin et al., 2008). Even though the current evidence base is not adequate for making a strong statement we suggest that disrupted connectivity of CC fibers may be an endophenotype for SZ.

A large literature implicates the frontal and temporal regions as well as the corpus callosum in the pathophysiology of SZ (Bora et al., 2011; Ellison-Wright and Bullmore, 2009). Our current analysis of frontal or temporal regions in unaffected relatives of SZ patients is limited by differences in DTI technique locations of significant findings. But we can say that many significant abnormalities are indeed reported in frontal and temporal regions in relatives of SZ patients. This pattern suggests that the findings in unaffected relatives likely represent similar biological abnormalities as those seen in patients. Since unaffected relatives do not carry the confounds of medication effects and chronic effects of mental illness, these findings may be related to the genetic determinants of disease risk, supporting a role for WM abnormalities as an endophenotype in SZ. For example, two studies replicated significant FA reductions in the left SLF and IFOF (Clark et al., 2011; Knöchel et al., 2012a). Consistent with these findings, FA reductions are also found in SLF in UHR individuals for psychosis (Karlsgodt et al., 2009). The same group (Karlsgodt et al., 2008) also found correlations between FA reductions in the left SLF and performance on a verbal working memory task in recent onset SZ patients.

In addition to the collection of brain regions with known WM abnormality in SZ, we highlight two other sets of brain regions with implications for pathophysiology of SZ. The first is language-related regions. One study found decreased FA in the bilateral angular gyrus WM and left inferior frontal gyrus WM in relatives of SZ patients (Hoptman et al., 2008). This is consistent with the previous fMRI studies that show reduced lateralization of activation in language related areas in patients with SZ and in high risk individuals (Li et al., 2007). Another study also showed ADC increases in these regions (DeLisi et al., 2006). However two other studies found FA increases in the AF (one with large sample size, (Boos et al., 2013; Knöchel et al., 2012a)). AF is a fiber connection that lies between Wernicke's and Broca's area and associated with speech and language. Increase in FA of this fiber tract may be explained as a compensatory change or a defect in regional axonal pruning during neurodevelopment. The literature on relatives of SZ patients and language functions is also inconsistent (Francis et al., 2012; Oertel-Knöchel et al., 2013) The second brain region of interest is the hippocampus and its connection with PFC, a pathway particularly implicated in cognitive deficits of SZ (Szeszko et al., 2008; White et al., 2007). One study (Hao et al., 2009) found decreased FA in left hippocampus and left PFC in healthy relatives and this pattern of disruption of WM integrity is consistent with the neuronal disconnectivity hypothesis of SZ and with the finding of healthy relatives sharing similar cognitive deficits with patients (Snitz et al., 2006).

The literature in unaffected relatives of BD patients was smaller and more discrepant. We note that many of the studies we reviewed do indicate reductions in measures of WM integrity. Therefore, there may be a signal of WM abnormalities in BD relatives. However, no single brain region provided replicable abnormalities across studies. In addition, there were too many differences in technical and demographic details of the studies for us to make strong statements. With this caveat in mind, we discuss some of the findings below.

A recent meta-analysis concluded that there are regions of significant WM abnormality in BD (in the right temporoparietal WM and in the right anterior and subgenual cingulate cortex). This literature on BD, has some similarities with SZ patients, especially in ILF and

FOF (Vederine et al., 2011). By contrast, the DTI studies of unaffected relatives of BD patients we review here are not consistent enough to indicate replicable WM abnormalities in this group. We have found nine studies comparing unaffected relatives and HC subjects in DTI measures. Some of the studies provide intriguing data suggesting abnormalities in the CC, SLF, right IFOF, right UF and right ALIC (Frazier et al., 2007; Linke et al., 2013; Mahon et al., 2013; Sprooten et al., 2013, 2011). These fibers are associated with identification in recognition of facial expression of the emotion, regulation of emotion (Phillips et al., 2008, 2003a, 2003b), attention (Corbetta and Shulman, 2002; Umarova et al., 2010), response inhibition (Forstmann et al., 2008) and executive functions like set shifting and risk taking (Bora et al., 2009; Linke et al., 2013). Abnormalities in each of these processes have been reported in BD patients (Green et al., 2007; Linke et al., 2013; A. M. McIntosh et al., 2008; McIntosh et al., 2005; Wang et al., 2009). On the other hand the literature on neurocognitive functions in relatives of BD patients is still unclear (Balanzá-Martínez et al., 2008) in comparison to the SZ literature. Cognitive deficits may not be present in the premorbid phase but they certainly are present by illness onset and worsen with exacerbations and illness burden. Another interesting lead is that some of the findings in BD relatives were right lateralized and models of BD emphasize disruption in cognitive reappraisal partially mediated by the right DLPFC. Nonetheless, the findings, as noted, were not consistent across studies. The wide age range across studies adds to our caution in interpreting this literature, since WM integrity is known to change throughout life and most rapidly in childhood and adolescence.

The literature on WM abnormalities in SZ and BD is large and rapidly growing. WM integrity is critical for normal signal transduction and subtle abnormalities of WM are likely to have nontrivial impact on information processing in the brain (Nave, 2010). As a result, it has been speculated that WM abnormalities may constitute part of the core pathophysiology of these conditions and indeed an endophenotype (Hasler et al., 2006). Our findings are consistent with such a role in SZ. Since there are also abnormalities in WM-related genes (Duncan et al., 2014) and abnormalities in myelin-related gene expression, it is possible that this biological system is one path of vulnerability to SZ. Neurogulin-1 and it's receptor ERBB4 has been indicated as associated genes in SZ and BD (Badner and Gershon, 2002; Green et al., 2005; Mei and Nave, 2014; Munafò et al., 2006; Prata et al., 2009; Stefansson et al., 2002). Some studies identified that variants of Neurogulin 1 have been also associated with FA reduction in the medial frontal regions (Winterer et al., 2008), anterior frontal cortex (Wang et al., 2009) and anterior limb of internal capsule (a M. McIntosh et al., 2008). ERBB4 also showed associations with decreased FA in the anterior limb of internal capsule (Zuliani et al., 2011). Although indirect these results may indicate a genetic relationship between these two disorders and WM integrity.

Our review has several limitations. First, because the pattern of findings is not robust we cannot make any comparisons between findings in SZ and BD relatives. Second, there are multiple inconsistencies across studies related to technical approaches, sample sizes, clinical and demographical profiles. The different methodological approaches across studies included VBA, ROI, TBSS, tractography, probabilistic tractography, along-tract analyses. There were also differences in MRI magnetic field strength, DTI direction numbers, and slice thickness. Many studies included small samples. The participant ages ranged from

childhood to adulthood. Since myelination continues during childhood, adolescence and into adulthood this may be a confound in our interpretations. Also studies including child or young adult relatives who are still in the risk window for developing SZ or BD may be challenging. Third, most of the studies in BD relatives did not specify whether BD probands have psychotic features. This is important because there may be genetic and other biological features specific to this subgroup. Some of the reviewed studies did not specify whether the BD probands had type 1 or another subtype. Fourth, most of the studies did not specify whether relatives of patients or healthy controls had psychiatric illnesses, excluding psychosis or BD. Future studies with large and standardized samples are needed to conclusively nominate WM integrity as an endophenotype in SZ and BD.

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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 25 HC 15 SZ	19.3 ± 4.6 23.7 ± 3.7 34.3 ± 10.7	1.5 T	VBA	• ADC didn't differ in the region of the body of the CC	Gray matter Volumetric quantification	• Several of the patients and relatives were biologic relatives • Relatives were still in the peak age of risk for SZ (defined as ages 12-30) • Only psychotic disorders excluded for relatives and HC • Family history of psychotic disorders excluded for HC • None of the relatives or HC were on antipsychotic or antidepressant medications
Hoptman et al., 2008	22 Relatives 37 HC 23 DSM-IV SZ+ SZAF	20.1±4.1 23.1±4.0 36.8±11.0	1.5 T	VBA	Reduced FA in: • Left inferior frontal gyrus WM • Bilateral left posterior cingulate WM • Bilateral angular gyral WM Increased FA in: • Left subgenual anterior cingulate • Bilateral pontine tegmental WM • Right middle/ superior frontal gyri	---	• Most of the patients and relatives were biologic relatives • Relatives were still in the peak age of risk for SZ (defined as ages 12-30) • 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 • Relatives have never experienced acute psychotic symptoms • Psychotic disorders and family history of psychotic disorders excluded for HC • None of the HC were currently taking medication for any psychiatric condition

Authors	Sample	Mean age (years) ±SD	Field strength	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
							• There was a significant difference in sex distribution across groups • In this study some of the participants were recruited from the study De Lisiet al., 2006, but the sample size was enlarged.
Munoz Maniega et al., 2008	22 Relatives 51 HC 31 DSM-IV SZ	30±3 35±11 37±10	1.5 T	VBA ROI	• VBA showed that FA didn't differ significantly • 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 • None of the relatives and patients were related • Not specified whether relatives or HC have another psychiatric illness, other than SZ or are taking medicine.
Hao et al., 2009	34 Siblings 32 HC 34 DSM-IV SZ	25.8±7.1 26.6±6.0 25.4±5.9	1.5 T	VBA	Reduced FA in: • Left hippocampus • Left PFC	---	• All of the patients and relatives were biologic relatives • All of the psychiatric disorders excluded for relatives and HC • First degree relatives of HC didn't have a history of any psychiatric disorder
Camchong et al., 2009	22 Relatives 30 HC 18 healthy MZ twin pairs	48.5 ±8.2 43.8 ±11.4	3 T	ROI VBA TBSS	• ROI analysis and TBSS showed decreased FA in right genu of CC • 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 • HC were excluded if they have a family history of psychosis or BD

Authors	Sample	Mean age (years) ±SD	Field strength	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Clark et al., 2011	20 Relatives 32 HC 31 DSM-IV SZ	41.1 ±13.0 34.8 ±14.0 32.7 ±9.3	1.5 T	ROI	Decreased FA in: • The bilateral IFOF • The left ILF • The left tSLF 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 There were no significant differences in ADC values	Genetic liability effects Correlation with BPRS scores	• None of the relatives were biologic relatives of the patients • No individual with a schizophrenia spectrum disorder or a psychotic disorder was included in relatives or HC • 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) • HC or relatives were not taking psychiatric medicine • HC were excluded if they had any evidence of drug abuse or alcoholism within six months
Phillips et al., 2011	49 Relatives (P+S) 21 HC 54 HCR (P+S) 26 DSM-IV SZ	P: 54.4 ± 8.3 S: 30.1 ± 11.5 25.9 ± 6.7 P: 55.7 ± 8.5 S: 26.9 ± 9.8 29.5 ± 7.4	1.5 T	VBA	Decreased FA in: • bilateral temporal lobe • bilateral occipital lobe Results didn't withstand permutation correction	Genetic liability effects	• All of the psychiatric disorders were excluded for HC and HCR subjects • Recent or past history of significant and habitual drug abuse or alcoholism were excluded for all subjects • Age was similar between HC and patient siblings, HC and patient parents, and between patients and their siblings
Knöchel et al., 2012b	16 Relatives 15 HC 16 DSM-IV SZ	41.9± 8.6 39.3 ± 11.0 37.6 ± 7.8	3 T	ROI	Decreased FA in: • The whole CC • The inferior genu • The superior genu(p=0.051) • The isthmus	Volumetric quantification Correlation between clinical characteristics and FA values and volume	• The patients and the relatives weren't biologic relatives • Any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV were excluded for relatives and HC

Authors	Sample	Mean age (years) ±SD	Field strength	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
					Increased ADC in: • The Whole CC • The isthmus (p=0.053)		
Knöchel et al., 2012a	18 Relatives 22 HC 28 DSM-IV SZ	39.4 ± 10.8 41.9 ± 10.5 40.8 ± 12.0	3 T	VBA ROI TBSS	• VBA showed that FA didn't differ significantly • ROI analysis showed that FA was significantly reduced in: **1** commissural fibers(including CC) **2** Association fibers(IFOF, left SLF, left IC,UF) **3** Cingulum bundles • ROI analysis showed that FA was significantly increased in AF	Correlation between FA values and clinical characteristics	• Any psychiatric disorder including Axis I and Axis II disorders according to DSM-IV were excluded for relatives and HC • Family history of SZ excluded for HC
Boos et al., 2013	123 Siblings 109 HC 126 DSM-IV SZ+SZAF+S ZFM	26.7± 6.4 27.3± 8.2 26.6± 5.6	1.5 T	TBSS	FA was increased in the left and right AF	Age × illness interaction Correlation between FA values and clinical characteristics	• Siblings who met DSM-IV criteria for (related diagnoses of) SZ or substance dependence were excluded from the study. • Some of the siblings had bipolar disorder (n= 3), major depression (n=22) or other psychiatric disorders (n= 5). • None of the HC met the criteria for any DSM-IV axis I disorder at the time of inclusion • Groups differed significantly in sex distribution and WAIS IQ

Authors	Sample	Mean age (years) ±SD	Field strength	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Domen et al., 2013	93 Siblings 80 HC 85 DSM-IV SZ and related disorders	29.4± 8.8 30.8± 10.8 28.3± 7.0	3 T	VBA TBSS	Although mean FA values of siblings were generally lower than HC, these differences were not signifficant	Cannabis and other drug use AP medication History of affective disorder	• Most of the patients and relatives were biologic relatives • Some of the HC subjects were biologic relatives • Relatives and HC didn't have a lifetime diagnosis of any non-affective psychotic disorder • Family history of psychotic disorders were excluded for HC • 18 relatives and 12 HC had a history of major depressive disorder • Three siblings and three HC used antidepressants and one HC used benzodiazepines. • None of the siblings or HC met the criteria for a current depressive episode
Goghari et al., 2014	24 Relatives 27 HC 25 SZ +SZAF	40.2± 15.0 40.7± 11.1 41.3± 10.8	3 T	VBA Along-tract analysis	• VBA showed that FA didn't differ significantly • Along-tract analysis showed increased FA in the right fimbria of the fornix	Relationship between DTI metrics and clinical characteristics	• Some of the patients and relatives were biological relatives • None of the participants had a current drug/alcohol dependence/abuse • Relatives and HC didn't have a lifetime diagnosis of a psychotic disorder or bipolar disorder or history of antipsychotic medication use • But some of the relatives and HC were receiving antidepressants, antianxiety or other psychiatric medications • No relatives or HC met criteria for a Cluster A disorder

Authors	Sample	Mean age (years) ±SD	Field strength	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Prasad et al., 2014	21 Relatives 29 HC 39 SZ +SZAF	23.0± 4.1 27.1± 6.8 26.8± 8.5	3T	TBSS	• FA was decreased in forceps minor • RD was decreased in the left SLF and forceps minor**	Cognitive measures and diffusion metrics	• Substance abuse in the previous • month or dependence 6 months prior to enrolment were excluded for all groups • Not specified whether relatives or HC have another psychiatric illness, other than SZ or are taking medicine.

* presumed typo in the publication;

** results shown here are taken from the tables in this manuscript;

HC, healthy controls; HCR, relatives of healthy controls; SZ, schizophrenia; SZAF, schizoaffective disorder; SZFM, schizophreniform disorder; BD, bipolar disorders; P, parents; S, siblings; MZ, monozygotic; DTI, Diffusion tensor imaging; ROI, region of interest; VBA, voxel based analysis; TBSS, tract-based spatial statistics; FA, fractional anisotropy; ADC, apparent diffusion coefficient; WM, white matter; CC, corpus callosun; PFC, prefrontal cortex; IC, internal capsule; ALIC, anterior limb of internal capsules; AF, arcuate fasciculus; UF, uncnate fasciculus; SLF, superior longitudinal fasciculus; tSLF, temporal superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; BPRS, Brief Psychiatric Rating Scale; AP, antipsychotic; WAIS, The Wechsler Adult Intelligence Scale; IQ, intelligence quotient.

Table 2

DTI study of healthy relatives of SZ and related disorders and bipolar disorders

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Skudlarski et al., 2013	119 Relatives (SZ +SZAF depression) 83 Relatives (pBD+SZAF manic) 104 HC 125 SZ+SZAF (depression) 82 pBD+SZAF (manic)	42.5±1.5 40.6±2.5 38.9±1.3 33.8±1.0 36.4±1.4	3 T	TBSS ROI	Relatives of SZ+SZAF depression had significantly decreased FA in: • Genu of CC • Left ACR • Right ACR • Right PCR • Left PCR superior aspect • Right ACR superior aspect • Left ACR superior aspect • Right ACR inferior aspect • Left ACR inferior aspect • Right ACR middle frontalgyrus WM Relatives pBD+SZAF (manic) had significantly decreased FA in right PCR superior aspect	Cluster A or B traits in relatives Heritability Correlation with Schizo-Bipolar Scale Demographic measures Medication	• Relatives and HC were free of current Axis I disorders • Relatives were classified by the presence or absence of symptoms of DSM-IV-TR cluster A and cluster B personality disorders

HC, healthy controls; SZ, schizophrenia; SZAF, schizoaffective disorder; pBD, psychotic bipolar disorder; DTI, diffusion tensor imaging; ROI, region of interest; TBSS, tract-based spatial statistics; FA, fractional anisotropy; WM, white matter; CC, corpus callosum; ACR, anterior corona radiata; PCR, posterior corona radiata; DSM-IV-TR; Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision

Table 3

DTI studies of relatives of bipolar disorders

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Frazier et al., 2007	7 Relatives 8 HC 10 DSM-IV BD-I	8.9±3.0 9.2±2.4 9.2±3.0	1.5 T	ROI	Reduced FA in the bilateral SLF I	Clinical characteristics	• The patients and the relatives weren't biologic relatives • The participants were aged 4 to12 years old. • HC had no history of DSM-IV axis I diagnosis • HC had no family history of psychiatric disorders in first degree relatives • Exclusion criteria for all groups were: learning disabilities, history of claustrophobia, autism, schizophrenia, anorexia or bulimia nervosa, alcohol and drug dependence/abuse (during2 months prior to scan, ortotal past history of more than12 months), history of ECT • All of the relatives had ADHD and/or CODD and/or diagnosis of anxiety disorder • One child in the relatives group was taking stimulant treatment • Not indicated whether the proband of relatives had psychotic symptoms during affective episodes or type of bipolar disorder
Chaddock et al., 2009	21 Relatives 18 HC 19 DSM-IV BD-I	42.5±13.6 41.7±12.2 43.3±10.2	1.5 T	VBA	There were no significant FA differences	Genetic liability	• All of the patients had experienced psychotic symptoms during episode of illness exacerbation • Patients and relatives were biologically related • Substance or alcohol dependence in the 12 months

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
							prior to assessment was the exclus(X00131)on crite prior to assessment was the exclus(X00131)on crite prior to assessment was the exclus(X00131)on crite • None of the relatives or HC had ever experienced a psychotic illness • Four of the relatives fulfilled criteria for a non-psychotic Axis I disorder during their lifetime • None of the relatives were taking psychotropic medication at the time of scanning • In HC group, one participant fulfilled lifetime DSM-IV criteria for major depressive disorder, and one participant for alcohol misuse (both recovered) • None of the HC had ever received psychotropic medication.
Versace et al., 2010	20 healthy offspring (BD) (HBO) 25 HC offspring (HC) (CONT)	13.2±2.5 13.9±2.6	3 T	TBSS	• In the region of CC HBO had greater FA and decreased RD • In the region of the right ILF in the temporal pole HBO had decreased RD • In the region of the right ILF in the visual cortex HBO had greater AD	Age related analysis	• Participants didn't endorse any current DSM-IV Axis I diagnosis or a history of depression or BD • Parents of the HBO were diagnosed with BD-I, BD-II,BD NOS. • Parents of the CONT didn't have any current Axis I disorder or history of mood disorder or psychotic disorder • Participants in this study were aged 8 to 17 • Not indicated whether the parents of the HBO had psychotic symptoms during affective episodes

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
Sprooten et al., 2011	117 Relatives 79 HC	21.0±2.8 20.8±2.3	1.5 T	VBA TBSS	VBA showed reduced FA in: • The genu and parts of the splenium of the CC • Internal and external capsules • ILF • SLF • IFOF • AF • UF • Parts of the CS tract • Subcortical WM mainly in the parietal and frontal lobes TBSS showed reduced FA in: • CC • Internal and external capsules (including anterior thalamic radiations) • ILF • SLF • IFOF • UF • Parts of the CS tract • Subcortical WM around	Cyclothymic temperament	• Relatives had at least one first-degree or two second-degree relatives with BD-I (diagnosed with DSM-IV) • No participant had an Axis I disorder • To optimize matching on key confounds, control subjects were recruited from the social networks of the high risk subjects themselves • Not indicated whether the proband of relatives had psychotic symptoms during affective episodes

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
					the central sulci the central sulci		
Mahon et al., 2013	15 Siblings 27 HC 26 DSM-IV BD (I-II)	42.0±11.7 40.8±12.5 40.6±12.4	3 T	TBSS Probabilistic Tractography	TBSS showed reduced FA in the right temporal WM Probabilistic tractography indicated reduced FA along the right IFOF	Impulsivity measures	• Some of the siblings were biologically related to patients in the study • Patients were diagnosed with BD-I or BD-II (diagnosed with DSM-IV) • Siblings and HC were free from current Axis I major mood or psychotic disorders • Siblings were at least 25 years of age and were past the age of onset in their affected sibling • One sibling met criteria for a single postpartum depressive episode that remitted without treatment, two other siblings met criteria for prior substance use disorders, and one of these siblings also met criteria for Anxiety Disorder NOS • One sibling was being treated with a SSRI for anxiety; all other siblings and HC were free from psychotropic medication • Not indicated whether the proband of relatives had psychotic symptoms during affective episodes
Linke et al., 2013	22 Relatives 22 HC	28±11 28±10	3 T	ROI	Reduced FA in: • The right ALIC • The right UF Increased RD in the right ALIC	Executive functions Correlations between FA values and executive functions	• Relatives and HC had no Axis I or Axis II disorder • HC had no mental disorder in their first degree relatives • Eleven relatives were from simplex families (one case of BD-I in the family), there maining eleven were from multiplex families (two or

Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
							more cases of BD-I in the family) more cases of BD-I in the family) • Not indicated whether the proband of relatives had psychotic symptoms during affective episodes
Emsell et al., 2013	21 Relatives 18 HC 19 DSM-IV BD-I	42.5±13.6 41.7±12.2 43.3±10.2	1.5 T	Tractography	There were no significant FA or RD differences.	Genetic liability	• This study is an extention of a previously published study(Chaddock et al, 2009) • All of the patients had experienced psychotic symptoms during episode of illness exacerbation • Patients and relatives were biologically related • Substance or alcohol dependence in the 12 months prior to assessment was the exclusion criteria for all groups • None of the relatives or HC had ever experienced a psychotic illness • Four of the relatives fulfilled criteria for a non-psychotic Axis I disorder during their lifetime • None of the relatives were taking psychotropic medication at the time of scanning • In HC group, one participant fulfilled lifetime DSM-IV criteria for major depressive disorder, and one participant for alcohol misuse (both recovered) • None of the HC had ever received psychotropic medication.
Sprooten et al., 2013	60 Siblings 46 HC	30.4±12.5 30.1±10.6 31.7±11.4	3 T	TBSS ROI	TBSS indicated reduced FA in:	Correlations with clinical measures and potential confounds	• Patients and relatives were biologically related

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Authors	Sample	Mean age (years) ±SD	DTI method	Analysis method	Abnormalities in relatives compared to healthy controls	Additional modalities	Comments/limitations
	64 DSM-IV BD-I 64 DSM-IV BD-I				• Splenium/ body of CC • Posterior tatamic radiations • Posterior corona radiata • Left SLF ROI didn't indicate significant differences		• Some of the patients had episodes with psychotic features • Sibling were mostly past the typical age of BD onset • Siblings were not excluded for anxiety disorders, a single episode of major depression, or past substance abuse or dependence • HC subjects had no lifetime history of axis I psychiatric disorder or family history of mood or psychotic disorders • Participants were excluded for alcohol or drug abuse or dependence within the past six months

HC, healthy controls; BD, bipolar disorder; BD NOS, bipolar disorder not other specified; HBO, healthy offspring with a parent diagnosed with bipolar disorder; CONT; healthy control offspring of healthy parents; ADHD, attention deficit hyperactivity disorder; CODD, conduct/oppositional defiant disorder; DTI, diffusion tensor imaging; ROI, region of interest; VBA, voxel based approach; TBSS, tract-based spatial statistics; FA, fractional anisotropy; RD, radial diffusivity; AD, axial diffusivity, WM, white matter; SLF, superior longitudinal fasciculus; CC, corpus callosum; ILF, inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ALIC, anterior limb of internal capsule; AF, arcuate fasciculus; UF, uncinate fasiculus; CS, cortico-spinal; DSM-IV; Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; SSRI, selective serotonin reuptake inhibitor; ECT, electro-convulsive therapy.