**REVIEW**

Diffusion Tensor Imaging Analysis for Psychiatric Disorders

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The pathophysiology of psychiatric disorders is complex and cannot be easily assessed by laboratory studies. Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique increasingly used for noninvasive and quantitative evaluation of abnormalities of the cerebral white matter because it provides exquisite details on tissue microstructures and also can perform sophisticated computer-based analyses. We review basic principles of DTI; methods of diffusion tensor analysis; recent DTI findings in major psychiatric diseases, such as schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorder; and factors to keep in mind when interpreting the results of DTI analysis. We recommend the frequent use of DTI as a routine clinical protocol to assess white matter abnormalities in patients with psychiatric disorders.

**Keywords:** cerebral white matter, diffusion tensor analysis, neuroimaging

**Introduction**

Diffusion tensor imaging (DTI) is an informative examination based on modification of conventional magnetic resonance (MR) imaging that allows noninvasive quantification of the diffusion characteristics of water molecules in vivo. DTI was first reported by Basser in 1994.1 Water molecules diffuse freely along nerve fiber tracts, but diffusion is restricted in other directions. This directional dependence, called anisotropic diffusion, is described mathematically by a tensor, which is often represented as an ellipsoid. The directions of the main axes of the ellipsoid are given by eigenvectors ($e_1$, $e_2$, $e_3$), and their lengths are represented by the corresponding eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$) of the diffusion tensor.2

Diffusion tensor analysis enables reconstruction of nerve fiber tracts and quantification of the anisotropy of white matter. Diffusion tensor tractography (DTT) is the assessment of fiber tracts based on DTI and provides attractive tools for visualizing white matter tracts, such as color mapping and fiber assignment by continuous tracking.3 Images of nerve fibers obtained by DTT show good correspondence with clinical symptoms or histological changes, and white matter areas related to psychiatric diseases, such as the cingulum, uncinate fasciculus, cerebral fornix, and corpus callosum, can be identified relatively easily using DTT.

The 4 parameters of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) are quantified by eigenvalues ($\lambda_1$, $\lambda_2$, $\lambda_3$). The $\lambda_1$ value corresponds to AD and decreases when axons are damaged by ischemia or other insults, whereas the average value of $\lambda_2$ and $\lambda_3$ corresponds to RD and increases in demyelinating diseases like multiple sclerosis.4 FA is quantified by a specific square root of $\lambda_1$, $\lambda_2$, and $\lambda_3$ values and reflects pathological conditions that affect the integrity of nerve fibers.

Diffusion tensor analysis has been applied to clinical examination and research since the mid–1990s. In 1999, Lim and associates confirmed lower anisotropy of white matter by this technique in 10 patients with schizophrenia despite the absence of a deficit in white matter volume.5 There were few reports about diffusion tensor analysis in the 1990s, but the number increased to over a thousand ones in 2010. Thus, diffusion tensor analysis is now well established as an analytical tool for brain imaging.
Methods of Diffusion Tensor Analysis

Two principal methods are widely used for diffusion tensor analysis—region-of-interest (ROI) analysis and whole brain voxel-based analysis (VBA) (Table 1). ROI analysis, used when a study focuses on a particular brain region, allows detailed examination of selected regions with measurement of absolute values and targeting of specific tracts drawn by DTT. However, the placement of ROIs should be guided by clear criteria based on anatomical information to minimize intra- and inter-rater variability. In addition, ROI analysis is time-consuming and requires practice to achieve adequate reliability. VBA is useful for identifying regions with different diffusion parameters among groups when researchers do not have a working hypothesis regarding a specific brain region, even though validation is required for spatial normalization, segmentation, smoothing of kernel size, correction for multiple comparisons, and the extent threshold. In statistical parametric mapping (SPM) (Wellcome Department of Cognitive Neurology, London, UK), the most widely used VBA package, a subject’s diffusion images are registered in a standard space, and the registered data is smoothed for group or correlational analysis. However, VBA is less sensitive than ROI analysis for quantification because spatial normalization can be imperfect and some residual morphometric differences may persist. These differences are not seen with tract-based spatial statistics (TBSS) (Oxford University, Nuffield Department of Clinical Neurosciences, UK), another software package, that attempts to avoid such problems completely by using a “mean FA skeleton” to represent the centers of fibers that are common to all humans.

Diffusion Tensor Imaging in Psychiatric Disorders

Over the past few decades, the rapid growth of MR imaging research into psychiatric disorders has resulted in the linking of signs and symptoms of various psychiatric diseases with specific structural or functional brain abnormalities, as discussed hereafter for schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders.

Schizophrenia

Schizophrenia is a neuropsychiatric disorder associated with structural abnormalities of the brain that are detectable by MR imaging. Pooled analysis of 15 voxel-based morphometric studies revealed a decrease in the volume of the left superior temporal gyrus and left medial temporal lobe in patients with schizophrenia as well as a reduction in the volume of the right anterior cingulate gyrus in patients with their first episode. In patients with recurrent schizophrenia, a voxel-based morphometric study identified alterations extending into the left superior temporal gyrus and left medial temporal lobe in addition to bilateral loss of gray matter in the prefrontal cortex, hippocampus, amygdala, and basal ganglia, suggesting a progression of the brain abnormalities over time. Moreover, DTI revealed severe white matter disruption in the temporolimbic region, including the cingulum, as well as in the frontotemporal region (uncinate fasciculus), parietotemporal region (arcuate fasciculus), and corpus callosum region. The fornix houses major projections of the hippocampus to and from other brain regions. DTI has detected a significant reduction of FA in the fornix of the left hemisphere and a significant increase in the MD of the fornix bilaterally in patients with schizophrenia, suggest-

Table 1. Methods for quantitative diffusion tensor imaging (DTI) studies

<table>
<thead>
<tr>
<th>Method</th>
<th>Region of interest (ROI) (Manually placed ROIs)</th>
<th>Voxel-based analysis (VBA) (statistical parametric mapping [SPM]/tract-based spatial statistics [TBSS])</th>
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<tbody>
<tr>
<td>Advantages</td>
<td>Specific absolute value measured Specific tracts drawn by diffusion tensor tractography (DTT)</td>
<td>Entire brain evaluation Avoids operator bias</td>
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<td>Disadvantages</td>
<td>Low intra-/inter-rater reliability Only assesses areas set by a hypothesis Manual tracing is time-consuming</td>
<td>SPM: validation is required for spatial normalization, segmentation, smoothing kernel size, correction for multiple comparisons, and extent threshold TBSS: fewer anatomical data on the white matter bundle (45)</td>
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Magnetic Resonance in Medical Sciences
ing a correlation between the disrupted integrity of the fornix and memory organization. In the early stage of the first episode of schizophrenia, MD shows a significant increase in the left parahippocampal gyrus, left insula, and right anterior cingulate gyrus without any reduction of brain volume or abnormalities of FA, so MD seems to be a useful marker for early schizophrenia. This hypothesis is consistent with the result of another DTI investigation of a large cohort of patients with first-episode schizophrenia, which confirmed a reduction of FA in the inferior longitudinal fasciculus alone. Patients with schizophrenia also demonstrate abnormalities of the semantic network, which are identified by DTI analysis as a decrease of significant FA in the left inferior frontal white matter and are revealed by functional MR imaging as weaker connectivity between the left inferior frontal gyrus and left middle temporal gyrus. Furthermore, in a 15-month study of youths (mean age: 17.02±3.37) at high risk for psychosis, TBSS-based ROI analysis revealed a significant relationship between lower baseline FA values in the medial temporal lobe and inferior longitudinal fasciculus and deterioration of social and role functioning, whereas the normal progressive increase of FA with age was not seen. In a multimodal imaging study of patients with chronic schizophrenia, DTI revealed a significant reduction of FA in the anterior part of the corpus callosum, DTT analysis detected a significant difference of connectivity between the genu of the corpus callosum and the medial prefrontal cortex, and functional MR imaging showed significant failure of deactivation in the medial prefrontal cortex compared with healthy controls. Thus, the medial prefrontal cortex has been identified as a prominent site of abnormalities in chronic schizophrenia.

Bipolar Disorder

Pooled analysis of the results of 141 MR imaging studies of structural brain abnormalities has shown increased volumes of the lateral ventricles and the third ventricle and decreased cross-sectional area of the corpus callosum in patients with bipolar disorder. Volumetric studies have generally revealed regional abnormalities in the prefrontal cortex, medial temporal cortex, and limbic structures. A common and important change seen in bipolar disorder is a decrease in the volume of the anterior cingulate cortex. Medial temporal structures, such as the amygdala, hippocampus, basal ganglia, and striatum, have extensive connections to the prefrontal cortex. Increased volume of the amygdala and striatum and normal hippocampal volume have been reported in patients with bipolar disorder. Another study found enlargement of the striatum in adolescents with bipolar disorder with either their first or multiple episodes. DTI studies employing ROI methods have revealed a significant decrease of FA in the prefrontal white matter, increased FA in the midline of the genu of the corpus callosum, and an increase of the apparent diffusion coefficient (ADC) in the bilateral orbital frontal white matter of patients with bipolar disorder. These changes suggest the presence of anatomic disconnectivity in the frontal-subcortical circuits. In addition, a DTT study has revealed a significant increase of reconstructed fibers in the subgenual cingulate and amygdalo-hippocampal complex of patients with euthymic bipolar disorder relative to controls, suggesting alteration of the white matter pathway between the left subgenual cingulate and the amygdalo-hippocampal complex. The first DT analysis performed by TBSS in subjects with bipolar disorder revealed that an increase of FA in the left uncinate fasciculus and a decrease of FA in the right uncinate fasciculus probably reflected abnormal right versus left asymmetry with regard to the alignment of fibers in the orbitomedial prefrontal cortex, which might be associated with mood dysregulation. A meta-analysis of DTI studies of bipolar disorder identified 2 clusters of decreased FA in the right brain. The first is located in the right parahippocampal white matter crossed by the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and posterior thalamic radiations. This might be associated with alterations in the identification of facial emotion. The second cluster of decreased FA is near the right anterior and subgenual cingulate cortex, and this might account for functional abnormalities underlying abnormal emotional processing and altered functional connectivity in bipolar disorder.

Major Depressive Disorder

Most MR imaging features of bipolar disorder and major depression overlap, so interpretation is difficult. The prefrontal cortex and anterior limbic structures are important brain areas in relation to altered emotional processing and cognitive disturbances that occur in major depression as well as in bipolar disorder. The majority of volumetric MR studies have revealed loss of gray matter and volume reduction in subregions of the prefrontal cortex, medial temporal lobe, amygdala, and hippocampus in patients of all ages. Alterations of
limbic-cortical-striatal-pallidal-thalamic circuits underlie the onset of depression in both bipolar disorder and major depression. The decrease of hippocampal volume in patients with major depression is considered to arise from increased apoptosis of glutamatergic neurons, which is caused by hypercortisolemia due to hyperfunction of the hypothalamic-pituitary-adrenal axis to induce depression. A DTI study showed that treatment-naïve young adults with their first episode of major depressive disorder had significantly lower FA in the white matter of the right middle frontal gyrus and left lateral occipitotemporal gyrus as well as in the subcortical white matter of the right parietal lobe and white matter of the right angular gyrus. This was the first exploration of the white matter of the whole brain by VBA with SPM2 software, and the results suggested that white matter abnormalities are present early in the course of major depressive disorder. A similar study by VBA with the TBSS software package of treatment-naïve young adult patients (mean age: 20.55 ± 1.86) with their first episode of major depression revealed a decrease of FA in the left anterior limb of the internal capsule, right parahippocampal gyrus, and left posterior cingulate cortex and showed that FA values for the left anterior limb of the internal capsule were negatively correlated with the severity of depressive symptoms. Geriatric patients with major depression demonstrate a decrease of FA in the dorsolateral prefrontal cortex, anterior cingulate, and diffuse frontal and temporal regions compared with non-depressed controls. This report is consistent with the results of another study comparing geriatric patients with or without remission of depression. Also, a DTI study of patients with major depression who had attempted suicide found a significant decrease of FA in the left anterior limb of the internal capsule relative to those patients without suicide attempts and normal subjects, a finding which might eventually assist with the development of effective strategies for suicide prevention in patients with major depressive disorders. The first study that simultaneously compared cerebral volume and diffusion data between patients with major depression and normal controls by VBA with SPM5 software revealed that compared with controls, the depressed subjects had significantly smaller volumes of the right parahippocampal gyrus, hippocampus, and prefrontal cortex as well as higher MD values in the bilateral parahippocampal gyri, prefrontal cortices, left uncus, pons, and cerebellum. In addition, FA in the bilateral prefrontal areas showed a weak negative correlation with the total duration of depression, so these findings suggested that volumetric and diffusional abnormalities occur in distinct tissue compartments of specific brain subregions, especially in the frontal areas, in patients with depression. A recent meta-analysis of DTI studies identified 4 consistent sites of decreased FA in patients with major depressive disorder—the white matter in the right frontal lobe, the right fusiform gyrus, the left frontal lobe, and the right occipital lobe. Fiber-tracking studies showed that the main fascicles involved were the right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right posterior thalamic radiation, and interhemispheric fibers running through the genu and body of the corpus callosum.

**Anxiety Disorders**

Anxiety disorders are classified into 5 main subgroups according to the National Institute of Mental Health: generalized anxiety disorder (GAD), panic disorder, phobia, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder. Volumetric MR imaging studies have revealed a decrease in the volume of the anterior cingulate cortex, insula, amygdala, and hippocampus in patients with anxiety disorders, although these volumes are influenced by medication status, disease duration/severity, MR imaging technique, post-processing method, age, and gender. In particular, a decrease in the volume of gray matter in the left cingulate cortex has been found in persons with PTSD as a result of the Tokyo subway sarin terror attack compared with subjects without PTSD, and this reduction of the cingulate gray matter volume is significantly associated with the severity of PTSD symptoms. In addition, VBA has revealed an increase of FA in the left anterior cingulum in persons with PTSD after the sarin attack. Another study of workers with PTSD after a coal mining accident found an increase of FA values in the left superior frontal gyrus compared with age-matched healthy controls, whereas GAD was associated with elevation of FA in the right postcentral gyrus relative to control levels, and FA was reduced in the right anterior cingulate gyrus of patients with PTSD compared with patients with GAD. In young adults exposed to parental verbal abuse, analysis with TBSS identified 3 white matter tract regions with significantly reduced FA: the left superior temporal gyrus and fibers from the arcuate fasciculus, the left fusiform gyrus adjacent to the
posterior part of the tail of the hippocampus and fibers from the cingulum bundle, and the left body of the fornix. In these areas, FA was strongly associated with the average parental verbal abuse scores and level of maternal verbal abuse.

Discussion

DTI is a sophisticated MR imaging technique increasingly used to evaluate abnormalities of the white matter to make a differential diagnosis of psychiatric diseases, such as schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorder, all of which feature abnormalities of FA. Table 2 summarizes DTI findings in these diseases. DTI is also used for quantitative evaluation of disease status or severity and to monitor response to treatment. The application of DTI in these areas is likely to expand in the future. However, several factors can produce heterogeneity of MR imaging data that subsequently leads to incorrect results. First, patient characteristics, such as gender, medications, IQ, social status, age at disease onset, family history, comorbidities, and substance abuse, can interfere with meaningful interpretation of results. Second, the severity of psychiatric symptoms is extremely variable, so it is important to identify symptom clusters as rigorously as possible based on symptom severity, duration of illness, and presence of other psychiatric diseases. Third, the magnetic field strength of the MR imaging unit is an important determinant of spatial and contrast resolution. Intensifying the strength of a static magnetic field to improve spatial and contrast resolution leads to spatial distortion and inhomogeneity of signal intensity, so it is important to correct such biases prior to analyzing imaging data. There are 2 methods to correct spatial distortion—the 3-dimensional (3D) measurement of geometric displacement using specially designed phantoms and the 3D calculation of geometric displacement from the spherical harmonics of the gradient, grad unwarp, which is the method adopted by the Alzheimer’s Disease Neuroimaging Initiative (ADNI). There are a few sources of signal intensity inhomogeneity. B0 inhomogeneity is difficult to eliminate, even using high order shimming, whereas B1 inhomogeneity is caused by a heterogeneous dielectric constant in vivo. These issues are difficult to overcome at the time of acquisition, making it necessary to correct signal intensity inhomogeneity with post-processing. The N3 software package (nonparametric nonuniform intensity normalization) is reported to be one of the most robust intensity correction algorithms. Fourth, post-processing is a crucial step that enables manipulation of images and extraction of useful data. Several sophisticated computerized and manual methods are available that involve the use of different thresholds, filters, and templates. Therefore, it must be noted that the results obtained with different methods of analysis are not directly comparable. Fifth, group average results have not been validated for individual subjects.

Conclusion

DTI studies of patients with psychiatric disorders have clearly identified white matter abnormalities and should become part of the routine clinical assessment of patients with such disorders. Despite several limitations, DTI offers clues that help eluci-

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<tr>
<th>Disorder</th>
<th>DTI findings</th>
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<tr>
<td>Chronic schizophrenia</td>
<td>Decreased fractional anisotropy (FA) in the cingulate, corpus callosum, and frontal lobes</td>
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<tr>
<td>First episode of schizophrenia</td>
<td>Increased MD in the left parahippocampal gyrus, left insula, and right anterior cingulate gyrus without any reduction of brain volume or abnormalities of FA</td>
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<tr>
<td>Bipolar disorder</td>
<td>Various FA findings in the prefrontal white matter (21–23, 33) and subgenual cingulate cortex (24, 26)</td>
</tr>
<tr>
<td>Treatment-naïve young adult major depressive disorder</td>
<td>Decreased FA in the right middle frontal gyrus, left occipitotemporal gyrus, subgyral and angular gyrus of the right parietal lobe, left anterior limb of the internal capsule, right parahippocampal gyrus, and left posterior cingulate cortex (31–33)</td>
</tr>
<tr>
<td>Geriatric major depressive disorder</td>
<td>Decreased FA in the dorsolateral prefrontal cortex, anterior cingulate, and diffuse frontal and temporal regions (33, 34, 37)</td>
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<tr>
<td>Anxiety disorders</td>
<td>Decreased or increased FA in the cingulum bundle (33, 40–42)</td>
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date the pathophysiology of psychiatric disorders.

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