

Voxel based Analysis of DTI in Depression Patients*

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Abstract. Diffusion tensor imaging (DTI) is a powerful technique for the assessment of white matter structural integrity and connectivity. There is a growing appreciation of the importance of connectivity to brain function. Disruption of this connectivity can result in brain dysfunction manifested in impaired cognitive functioning and the development of clinical symptoms. White matter forms the basis of anatomical connectivity. DTI is a useful tool for examining and quantifying white matter microstructure. Clinical research studies in alcoholism, HIV-1 infection, geriatric depression and schizophrenia using DTI have revealed abnormalities in white matter microstructure. The use of complementary imaging methods may be helpful in further characterizing these abnormalities. Other psychiatric disorders may also have white matter involvement amenable to study with DTI. Advances in acquisition and analysis methods will be necessary to further advance work in this field. In this paper, the voxel-based analysis in DTI is introduced to investigate the whole brain abnormalities between the refractory depression male patients and normal controls. The significant reduction of fractional anisotropy (FA) value is found in frontal lobe, anterior cingulate, Temporal Lobe and other regions in refractory depression patients, and no areas of significantly higher FA in patients compared with healthy volunteers. Our result supports the hypothesis that neuroanatomical circuit abnormality is a key factor in the functional anatomy of refractory depression.

Keywords: diffusion tensor imaging, voxel-based analysis, FA value, refractory depression.

1. Introduction

Diffusion tensor imaging (DTI) is a useful tool for examining and quantifying white matter microstructure and connectivity. The movement of water in brain is hindered by the presence of cell membranes, myelin sheaths surrounding axons, and other structures, particularly so in white matter tracts where the apparent water diffusion (ADC) is highly anisotropic, since diffusion parallel to axons and myelin bundles is considerably faster than that perpendicular to axons [1, 2]. As a new method, DTI technique is undergoing rapid development, and considerable controversies remain over the analysis of DTI data [3].

Major depression is the leading cause of disability worldwide. It is estimated that 5% of American adults are affected each year. While depression can develop at any age, the increasing age of the population in developed countries such as the USA has made late life depression an increasingly important health issue. While the causes of late-life depression are not well understood, imaging studies using MRI have reported increased white matter hyperintensities (WMH) in this population [4]. Tremendous progress have made in therapy of depression, but there are still about 10% patients have no response to antidepressant therapy called refractory depression. An internationally consistent opinion about refractory depression is that a major

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depressive episode with poor response to two adequate trials of different classes of antidepressants with good compliance.

In 2001, a statistical parametric mapping of white matter lesions in late-onset depression found increased lesion density in medial orbital prefrontal white matter [5]. Functional imaging studies have found abnormalities in the prefrontal cortex, anterior cingulate, amygdala and striatum [6, 7]. Dysfunction of one or more corticalbasal ganglia-thalamic neuronal loops has been implicated. Neuropathological evidence of altered neuronal and glial cell morphology and density in the frontal cortex has been reported. In treatment studies of late-life depression, aspects of executive dysfunction appear to be important predictors of treatment response and relapse. Neuropsychological studies of late-life depression have reported disturbances in attention, speed of processing, and executive function, processes which require integrity of front striatal structures [8]. The anatomical connections between the prefrontal cortex and the striatum pass through the frontal white matter, providing an opportunity to assess the integrity of the connectivity using DTI.

There are two principal methods employed in FA maps analysis: region-of-interest (ROI) and whole-brain, voxel-based analysis (VBA) [9]. The majority of studies to date have adopted the former, manually defining ROIs on the unregistered images. This allows a powerful examination of regions selected on the basis of existing information. However, because the placement of ROIs is subjective, this should be guided by unambiguous criteria and with demonstrated intrarater reliability [10]. Even then, there is a risk that the rater will be influenced by gross anatomical group differences into a systematic placement bias.

As an explorative method, the voxel-based analysis could be more helpful in discovering unanticipated or unpredicted areas of neuroanatomical [11]. However, no study has been reported, as far as we know, on the brain of refractory depression patient using whole brain voxel-based analysis of diffusion tensor images. In this paper, the voxel-based analysis in DTI is introduced to investigate the whole brain abnormalities between the refractory depression male patients and normal controls. Eight male patients experiencing refractory depression and twelve normal male healthy subjects are analyzed.

2. Materials and Methods

Nine normal male healthy subjects, with a mean age of 30.75 (22-40, SD: 7.2), were recruited from the general community and evaluated using a series of strict neuropsychological tests as blow: Wechsler Memory Scale-Revised (WMS-R), Warrington Recognition Memory Test and a story recall test, SCOLP, STROOP, Wechsler Adult Intelligence Scale-Revised (WAIS-R), and Cattell's Culture Fair Test. Then, superadd usual MR scan to ensure their qualification. Eight male depression patients, with a mean age of 30.5 (21-37, SD: 5.3) were participant in clinical MR research Center for the Study of the Neuroscience of Depression at West China hospital of Sichuan University. Depressed subjects were, fulfilled DSM-IV criteria for major depression and inherently does not respond satisfactorily to one or more treatments that are optimally delivered (refractory depression).

2.1. Imaging Acquisition

DTI maps were acquired using a 3.0T GE MR scanner (General Electric Medical Systems, EXCITE, Milwaukee, Wisconsin, USA) by employing a single-shot EPI (echo planar imaging) sequence [12]. Head motion was minimized with restraining foam pads provided by the manufacturer. For each slice, 15 images with high diffusion-weighting along 15 noncolinear and noncoplanar directions were collected. Scan parameters were as follows: TR (repetition time) 10 s; TE (echo time) 70.8 ms; slice thickness=3.0 mm, FOV(field of view)=240×240 mm, voxel dimensions were 1×1×3mm, Scan matrix=128×128, b value= 1000 s/mm².

2.2. Imaging Processing

FA maps were generated from each participant's DTI scan, and were calculated by a free software DTIstudio (Department of Radiology, Johns Hopkins University, School of Medicine Baltimore, MD, USA; available at

<http://cmrm.med.jhmi.edu/>), based on the theory mentioned above. Voxel-based analysis was carried out using SPM2 (Wellcome department of Imaging Neuroscience, London UK; available at <http://www.fil.ion.ucl.ac.uk/spm/software/>). Prior to the analysis, all FA images (whether patient or control) were normalized using the parameters determined from the normalization of the b=0 image and standard T2 template in SPM2. All images were re-sampled with a final voxel size of 2×2×2 mm. After normalization, all maps should be smoothed with a 6-mm FWHM isotropic Gaussian kernel [9].

3. Statistical Analysis

Statistical comparisons were performed using two sample *t*-test between patients and normal controls in whole group. Voxels with $T > 3.05$ ($P < 0.005$ uncorrected for multiple comparisons) and clusters of size > 30 voxels (almost 240 mm³) were considered as significant differences between the patients and normal controls. For visualization of the regions, which show significantly different FA values between the two groups, the significant clusters were superimposed onto SPM2's standard template brain.

4. Results

In a voxel-by-voxel contrast, several regions showed significantly lower FA values in the patients than in the controls (uncorrected $P < 0.005$, cluster size > 30 voxels). The coordinates, T scores and Z scores of peak voxels for these regions are briefly listed in Table 1. The white matter areas that showed lower FA values are the left frontal lobe and anterior cingulate (Fig.1A), left sub-lobar of extra-nuclear, (Fig.1B), right middle temporal gyrus, and bilateral middle occipital gyrus (Fig.2C), right temporal lobe (Fig.2D), right frontal lobe, right parietal lobe, Brodmann area 7 and area 44. No FA value was significantly higher in the patients than that in controls.

Table 1. Regions with reduced FA values in refractory depression patients compared with those in normal controls (uncorrected $P < 0.005$).

Description of extent of cluster	L/R	Cluster size (mm ³)	T score	Z score	Peak coordinates (x, y, z)
Parietal Lobe, Precuneus, White Matter	R	744	6.46	4.40	6 -70 44
Sub-lobar, Extra-Nuclear, White Matter, Corpus Callosum	L	240	5.59	4.05	-10 -42 18
Limbic Lobe, Anterior Cingulate, and Frontal Lobe, Sub-Gyral, White Matter	L	472	4.79/4.24	3.68/3.39	-14 42 0 /-14 48 -10
Temporal Lobe, Middle Temporal Gyrus, and Occipital Lobe, Middle Occipital Gyrus, White Matter	R	328	4.68/3.52	3.62/3.02	38 -82 18 /34 -72 12
Temporal Lobe, Middle Temporal Gyrus, White Matter	R	256	4.63	3.59	36 -58 22
Temporal Lobe, Sub-Gyral, White Matter	R	368	4.59	3.57	44 -50 -12
Parietal Lobe, Precuneus, Gray Matter, Brodmann area 7	L	312	4.25/3.51	3.39/2.95	-16 -64 54 /-12 -70 58
Frontal Lobe, Inferior Frontal Gyrus, Gray Matter, and White Matter Brodmann area 44	L	256	4.21/3.05	3.37/2.66	-52 16 18 /-48 12 12
Frontal Lobe, Precentral Gyrus, White Matter	R	280	4.11/3.93	3.31/3.21	32 -20 56 /34 -20 64
Occipital Lobe, Middle Occipital Gyrus, White Matter	L	264	3.77/3.35	3.11/2.85	-26 -86 14 / -28 -82 6

Listed are coordinates corresponding to the voxels with maximum (peak) effects sizes defined in Montreal Neurological Institute (MNI) space.

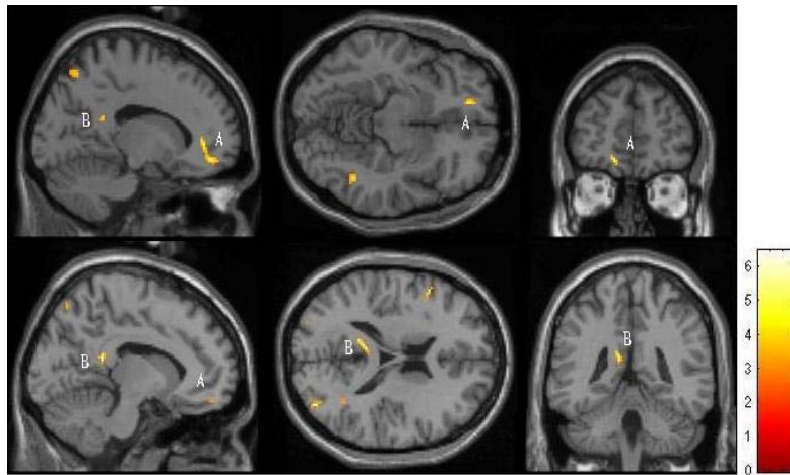


Fig.1: Standardized sagittal, transaxial and coronal statistical parameter maps illustrate two regions with significant reduction of FA values in refractory depression patients' brain. Cluster A: Limbic Lobe, Anterior Cingulate, and Frontal Lobe, Sub-Gyral, Left Cerebrum. Cluster B: Left Cerebrum, Sub-lobar, Extra-Nuclear, White Matter, Corpus Callosum.

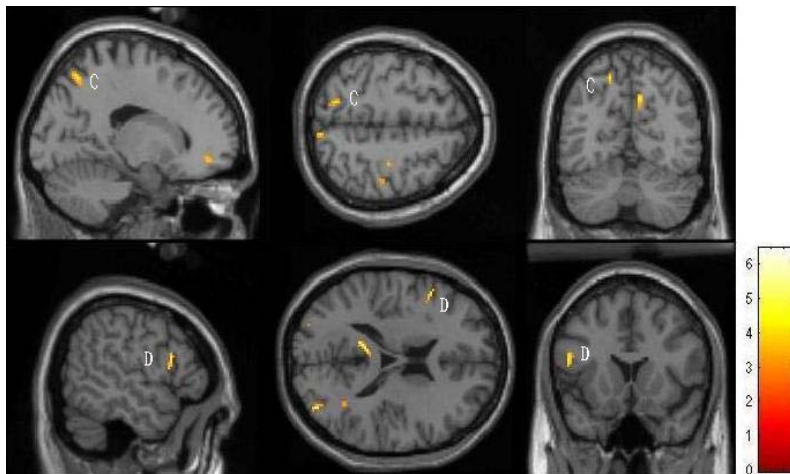


Fig.2: Standardized sagittal, transaxial and coronal statistical parameter maps illustrate two regions with significant reduction of FA values in refractory depression patients' brain. Cluster C: Parietal Lobe, Precuneus, Gray Matter, Brodmann area 7. Cluster D: Frontal Lobe, Inferior Frontal Gyrus, Gray Matter, and White Matter Brodmann area 44.

5. Discussion

Fig.1 shows the statistical parameter map result showing regions of FA reduction in the white matter of the anterior cingulate, and frontal lobe (cluster A) and extra-nuclear (cluster B) for patients with refractory depression compared with normal controls, overlaid on the corresponding T1 image. The obviously different areas between patients with refractory depression and with controls are mainly on the white matter of the frontal brain regions, whose Montreal Neurological Institute coordinates (MNI) is (-14 42 0 /-14 48 -10), $P_{unconnected} < 0.005$, in Fig.1 and Table 1. This result is consistent with previous studies of DTI alterations in late-life depression, which reported that microstructural changes in the white matter of the right superior frontal gyrus [13]. This result is also consistent with Alexopoulos' study which showed that microstructural white matter abnormalities lateral to the anterior cingulate may be associated with a low rate of remission [14].

Structural imaging studies (CT and MRI) in adults with affective disorders in comparison to controls have reported regional cerebral structural differences specifically in the prefrontal lobe, basal ganglia, temporal lobe, and ventricular spaces [15]. These regional structural differences support hypotheses implicating frontal-striatal-limbic circuits in affective disorders [16, 17]. Functional imaging studies with

positron emission tomography (PET) in adults with MDD also support the role of dysfunction in frontal-based ganglia circuits in mood disorders [18, 19].

The reduction of white matter anisotropy observed in our DTI study is suggestive of possible loss of integrity within frontal white matter fiber tracts and sub-lobar of extra-nuclear, and supports the hypothesis that neuroanatomical circuit abnormalities are a key factor in the functional anatomy of refractory depression. The inferior frontal brain regions include the medial orbital prefrontal region and the neural pathways to caudate and other limbic regions [20]. Damage to the orbitofrontal circuit may lead to disinhibition, irritability, and diminished sensitivity to social cues [21]. Our observations in the present study implicate the orbitofrontal circuit in refractory depression.

We also find other significant regions with reduction of FA value in patients compared with controls as: Brodmann area 7 and Brodmann area 44, in Fig.2 and Table 1.

The Brodmann area 7 in the parietal association cortex integrates information from visual, auditory and somatosensory input to locate objects in space. A bundle of nerve fibers (the superior longitudinal fasciculus) communicates this information to area 6 to direct movement. The premotor areas also receive input from part of the limbic cortex (area 24), which is thought to contribute motivational input to motor planning [20].

Area 44 and part of area 45 in the frontal lobe, known as Broca's area is important for language production (spoken or written).

Broca's area is connected to Wernicke's area by a bundle of nerve fibers known as the arcuate fasciculus. Patients with lesions to the arcuate fasciculus show good comprehension of spoken language and reasonably fluent conversational speech, but have great difficulty repeating the spoken language they hear. They show difficulty reading aloud, despite good reading comprehension. The patient is often unable to name objects pointed-to, and writing typically shows errors in spelling and word-order.

With an eye to some depression patients' description about their symptom, we should pay more attention to these regions: Brodmann area 7 and Brodmann area 44. Many patients would mention there was a pair of gray glasses always on their bridge of nose when they open eyes. Because Broca's area is primarily concerned with language production rather than with comprehension, it does seem to play a role in the understanding of grammatical aspects of language. Patients with lesions in Broca's area often have difficulties with questions like "Is it true that my mother's brother's sister is a female?" Patients with Broca's aphasia also often have "tip-of-the-tongue" word-finding problems which can be offset by telling the patient the initial syllable or some other clue.

6. Conclusion

In this paper, the voxel-based analysis in DTI is introduced to investigate the whole brain abnormalities between the refractory depression male patients and normal controls. The significant reduction is found in white matter FA values in medial orbital prefrontal and external capsule in refractory depression patients, and no areas of significantly higher fractional anisotropy in patients compared with healthy volunteers.

Our result supports the hypothesis that neuroanatomical circuit abnormality is a key factor in the functional anatomy of refractory depression. These findings suggest that white matter pathology is present early in the course of refractory depression and may be less pronounced than has been found in previous diffusion tensor imaging studies of patients with depression. The reduction of white matter anisotropy observed in our DTI study is suggestive of possible loss of integrity within frontal white matter fiber tracts and external capsule, and supports the hypothesis that neuroanatomical circuit abnormalities are a key factor in the functional anatomy of refractory depression.

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