



## White matter microstructural abnormalities and their association with anticipatory anhedonia in depression



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### ABSTRACT

Anhedonia is associated with dysfunction of the neural circuitry of reward in patients with major depressive disorder (MDD). However, its neurobiological basis is not fully understood. The present study examined the association between anhedonia and white matter (WM) characteristics in patients with first-episode MDD. We recruited 30 patients with first-episode drug-naive MDD and 28 healthy controls (HC) to undergo diffusion weighted imaging. We examined specifically the correlation between WM characteristics and anhedonia measured with the Temporal Experience of Pleasure Scale (TEPS) in MDD patients. Using Track-Based Spatial Statistics (TBSS), we found that MDD patients exhibited reduced fractional anisotropy (FA) in the left cingulum and the forceps minor. These patients also exhibited increased radial diffusivity (RD) in several major tracts including the bilateral anterior thalamic radiation, the corticospinal tract, the superior longitudinal fasciculus and the uncinate fasciculus in the left hemisphere. Correlational analysis showed that increased RD was significantly correlated with anticipatory anhedonia in the MDD group, while reduced mean FA was correlated with consummatory anhedonia in HC. These preliminary findings suggest that left-sided WM tracts abnormalities may contribute to the development of anhedonia in MDD patients.

### 1. Introduction

Anhedonia is an important symptom of major depressive disorder (MDD) that reflects deficits in reward processing (Buckner et al., 2008), and continues to be present even after reduction in other depressive symptoms (Treadway and Zald, 2011). However, surprisingly few studies have examined the neurobiological basis of anhedonia in depressed patients. Emerging evidence suggests that anhedonia reflects disturbances in the reward circuitry including the orbitofrontal cortex (OFC), the striatum, and in particular the nucleus accumbens (NAcc), when MDD patients process rewarding stimuli (Pizzagalli et al., 2009; Smoski et al., 2009; Wacker et al., 2009). Our previous work (Yang et al., 2016) also found that diminished caudate nucleus responses were correlated with lower motivation in first-episode MDD patients. The present study aimed to extend this line of work by investigating the relationship between white matter (WM) characteristics of first-episode

medication-naive MDD patients and anhedonia severity.

Diffusion tensor imaging (DTI) has been developed to reflect WM microstructure (Song et al., 2002). Fractional anisotropy (FA) is the most widely used measure to quantify white matter anisotropy with different eigenvalues. Other parameters, including mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) can be used to reflect different aspects of WM characteristics (Jones et al., 2013). Only four studies to date have examined the relationship between anhedonia and WM abnormality in MDD. The first study reported that higher levels of anhedonia was correlated with disruption in tracts connecting reward-related regions in depressed adolescents (Keedwell et al., 2012). The second study demonstrated that reduced FA was correlated with anhedonia severity in melancholic MDD patients in segments of the superior-lateral medial forebrain bundle (MFB) (Bracht et al., 2014). Subsequently, they further identified that mean FA of the left superior-lateral MFB was associated negatively with hedonic capacity in

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remitted MDD patients (Bracht et al., 2015). However, another study failed to identify any significant correlation between microstructure of the superior-lateral MFB and anhedonia in MDD patients (Blood et al., 2010). In brief, these findings suggest that altered WM in reward circuitries may be associated with anhedonia. However, these findings might be confounded by medication effects and methodological and sampling differences. Thus, a study of patients with medication-naïve MDD could better address this question.

The present study aimed to use DTI to examine the WM characteristics of first-episode medication-naïve MDD patients. We further assessed relationships between WM characteristics and anhedonia within the MDD group. We used the Temporal Experience of Pleasure Scale (TEPS) to evaluate anhedonia (Chan et al., 2012) and took the FA, AD, RD and MD values from the DTI data as indices of WM characteristics. Given that MDD may be correlated with abnormalities in subcortical reward circuitry (Bracht et al., 2015, 2014), we hypothesized that MDD patients would show disruptions in WM tracts connecting reward-related regions involving the cingulum and the corpus callosum compared with controls. We also hypothesized that disruptions in these WM tracts would be correlated with anhedonia severity in patients with MDD.

## 2. Method

### 2.1. Participants

Thirty medication-naïve patients with first-episode MDD meeting the diagnostic criteria of the DSM-IV (APA, 2000) were recruited from the outpatient clinic of the Second Xiangya Hospital, the Central South University. The inclusion and exclusion criteria were the same as our previous study (Yang et al., 2016). In brief, all patients had a total score of  $\geq 20$  on the Hamilton Rating Scale for Depression (HAM-D) (Williams, 1988), and had no history of drug treatment. Potential participants were excluded if they reported other primary psychiatric disorder symptoms; treatment with psychotropic medications or electroconvulsive therapy, substance abuse, or if they had an IQ of less than 70.

We also recruited 28 matched healthy controls from the local community through advertisement. The exclusion of any psychiatric disorders in healthy controls were the same as our previous study. Moreover, participants with a Beck Depression Inventory (BDI) (Wang et al., 1999) score of  $> 19$  were also excluded. All participants were right-handed as measured by the Annett Handedness Scale (Annett et al., 1970). The present study was approved by the Ethics Committee of the Central South University. Written consent was obtained from all participants.

### 2.2. Measures

The severity of state anhedonia was assessed using the Chinese version of the Snaith-Hamilton Pleasure Scale (SHAPS, Snaith et al., 1995; Liu et al., 2012). This 14-item scale assesses a participant's "in the moment" pleasure experience based on a four-point Likert scale ranging from 1 to 4. Higher scores indicate greater state anhedonia. The severity of trait anhedonia was assessed using the Chinese version of the Temporal Experience of Pleasure Scale (TEPS, Chan et al., 2010, 2012). The Chinese version of the TEPS is a 20-item self-report scale capturing wanting and liking of pleasure experiences in a two-week period. Participants rated the items based on a six-point Likert scale ranging from 1 (very false for me) to 6 (very true for me). The scale captures four factors (contextual consummatory, abstract consummatory, contextual anticipatory and abstract anticipatory). Abstract and contextual factors for both the anticipatory and consummatory facets were also added together separately to obtain factor total scores in anticipatory and consummatory pleasure.

### 2.3. DTI data acquisition and preprocessing

Imaging scans were acquired using a 3-T scanner (TrioTim, Siemens) at the Second Xiangya Hospital, the Central South University. For each participant, DTI data were acquired using a diffusion-weighted interleaved echo planar imaging sequence with the following parameters: 29 axial slices; slice thickness = 5.4 mm; TE = 93 ms; TR = 4000 ms; FOV = 230 mm; matrix =  $128 \times 128$ ; bandwidth = 1395 Hz/Px; voxel size =  $1.8 \times 1.8 \times 5.4$  mm. Diffusion gradients were applied in 30 directions with  $b = 1000$  s/mm<sup>2</sup>. DTI preprocessing was conducted using the FMRIB Software Library (FSL) version 4.1.8 (University of Oxford, UK, <http://www.fmrib.ox.ac.uk/fsl>). First, eddy-current distortions and motion artifacts in the raw diffusion-weighted images were corrected using the FSL Eddy Correction Tool (Jenkinson and Smith, 2001). The corrected images were then skull-stripped to remove non-brain tissues using the FSL Brain Extraction Tool (BET) (Smith, 2002). Then individual images (including FA, MD and three eigenvalues L1, L2 and L3) were generated using the FSL diffusion tensor analysis toolkit (FDT) (Smith et al., 2004). AD was defined as the largest eigenvalue (L1), RD was calculated as the average of the two smaller eigenvalues (L2 and L3), and MD was calculated as the average of the three eigenvalues (L1, L2, and L3). Then we used all the participants' FA images in the Tract-Based Spatial Statistics (TBSS) analysis (Smith et al., 2006) within FSL following the standard pipeline ([www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS](http://www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS)). All FA images were nonlinearly-registered to MNI152 space using the FSL registration tool FNIRT and the mean FA image and mean FA skeleton (threshold was set at 0.3) were created. Participants' FA images were then projected onto this skeleton to generate normalized skeletonized FA images. Similarly, using the nonlinear transformation of FA images, MD, AD and RD images were registered to MNI standard space and individual skeletonized images were generated for further analysis.

### 2.4. Statistical analyses

Voxel-wise statistics across participants were carried out for each voxel of normalized skeletonized FA images. Five thousand permutations and Threshold-Free Cluster Enhancement (TFCE) was used to correct for multiple comparisons. Considering the results of the voxel-wise analyses, we reported the significant clusters containing  $\geq 10$  voxels, labelled them according to the Johns Hopkins University (JHU)-ICBM-tracts probabilistic atlas, and binarized the TFCE corrected statistical maps into masks with corrected  $p < 0.05$ . We then examined the associations between WM measures of the clusters and clinical variables (anhedonia and depression) in SPSS 24.0. Pearson correlation analysis was performed between the SHAPS, TEPS and BDI scores and WM measures of the clusters for the MDD group and healthy controls, with  $p < 0.05$  as the significance threshold (Kriegeskorte et al., 2010). Similarly, we repeated the same analyses for the MD, AD and RD images.

## 3. Results

### 3.1. Demographic information

Demographic and clinical characteristics of the participants are shown in Table 1. The two groups did not differ in age, gender, years of education and IQ (all  $p > 0.05$ ). However, the MDD group reported significantly higher levels of trait anticipatory and consummatory anhedonia measured by the TEPS and higher levels of state anhedonia measured by the SHAPS than healthy controls ( $p < 0.001$ ). As expected, healthy controls reported significantly lower level of depressive symptoms on the BDI than the MDD patients ( $p < 0.001$ ).

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