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Research report

Improvements in white matter micro-structural integrity of right uncinate fasciculus and left fronto-occipital fasciculus of remitted first-episode medication-naïve panic disorder patients

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ABSTRACT

Objective: We designed this study to investigate neural correlates of white matter micro-structural integrity of remitted patients with first-episode, medication-naïve and very late-onset panic disorder
Method: Twenty-one remitted patients with panic disorder completed treatment course with treatment of escitalopram (dose range around 10–15 mg/d). Twenty-one healthy controls were also enrolled into this study. Patients and controls all received 3-Tesla magnetic resonance imaging diffusion tensor imaging scanning at baseline and 6th week. We utilized FDT (FMRIB's Diffusion Toolbox v2.0) function of FSL (FMRIB Software Library) to calculate fractional anisotropy (FA). We compared FA values of patients and controls at baseline and 6th week to estimate the changes of FA of remitted patient group and inter-scan bias of controls. FA outputs of remitted patients and controls were compared by independent *t* test.
Results: We found increased FA in some regions of right uncinate fasciculus and left fronoto-occipital fasciculus after remission in patient group (corrected $p < 0.05$). Reduced FA of other regions of right uncinate fasciculus was still observed in remitted patients when they were compared to the control group.
Conclusion: Subtle changes of white matter micro-structural integrity after remission might represent neural correlates of treatment effects for first-episode, medication-naïve and very late-onset panic disorder.

1. Introdution

Panic disorder (PD) will cause diminished well-being of qualities of life, poor sense of health, frequent utilization of medical services, occupational deficiency, financial dependency and marital strife and impairments of functions due to recurrent panic attacks, state anxiety and accompanying psychiatric symptoms (Barrera et al., 2013; Culpepper, 2004; Rubin et al., 2000). The groups of different onset age might represent distinct illness pattern and clinical characteristics (Ramsawh et al., 2011). According to Gorman et al. (2000) fear network model of PD, the components include frontal cortex, insula, amygdala, hippocampus and sensory cortex. PD patients usually have visuospatial dysfunction and false threat alarm from fear network (de Carvalho et al., 2010; Gorman et al., 2001; Kent et al., 2005; Pillay et al., 2006; Uchida et al., 2008; Windmann, 1998). There are few reports mentioning the white matter (WM) structural abnormalities in PD. Several studies of PD reported that frontal deep WM hyperintensity and higher fractional anisotropy (FA) values of left anterior cingulate and right posterior cingulate regions, which were related to the clinical severity (Bae et al., 2010; Han et al., 2008). Our previous study also showed that patients with PD had FA alterations of right inferior fronto-occipital fasculi, left body of corpus callosum and left superior longitudinal fasciculus (Lai and Wu, 2012). However, there are still no consensus due to limited studies and different modalities for WM structural analysis of these studies. Therefore it is an intriguing point for research due to limited documents about the WM tracts in patients with first-episode, drug-naïve and very late-onset PD.

Patients with PD have difficulties in inhibiting the interference of nonverbal stimuli. They also have reduced verbal cognitive ability to express abstraction and symbolization (Galderisi et al., 2008). Difficulties in integrating sensory information through the visuospatial system and attention have also been reported (Uchida et al., 2008). In the WM tract system, the fronto-occipital fasciculus (FOF) is the component of subcortical language network, which

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is important for language semantics and verbal ability (Mandonnet et al., 2007). Besides, FOF plays a role in the recognition of facial emotion. FOF can interact with other language-related WM tracts to connect the visual cortex and emotion-related regions (Tusa and Ungerleider, 1985). Besides, frontal system might connect with sensory regions, such as occipital lobes, through the FOF. Frontal and occipital lobes are also the components of fear network model (Gorman et al., 2000). According to the hypothesis of fear network model, frontal can control amygdala-related fear response, which is also important for PD pathogenesis. Uncinate fasciculus (UF) connects frontal lobe and amygdala. Reduced FA of bilateral UF has been reported in social anxiety disorder. It suggests that deficient connectivity of UF might involve the connection between orbitofrontal cortex and amygdala (Baur et al., 2011a). Similar findings of reduced FA of UF and limbic system are also found in generalized anxiety disorder (Hettema et al., 2011; Tromp do et al., 2012; Zhang et al., 2013). The results also correspond to the gray matter deficits of orbitofrontal cortex and amygdala in previous studies of PD (Lai et al., 2010; Sobanski et al., 2010). Besides UF and FOF, our previous report of PD patients found altered FA of corpus callosum and superior longitudinal fasciculus (Lai and Wu, 2012). The above studies show that these WM tracts might be important for pathophysiology and treatment of PD.

Serotonin is associated with the micro-structural integrity of fronto-limbic WM pathway and variations of FA of the WM tract between amygdala and prefrontal cortex. The polymorphisms of the serotonin transporter seem to influence the WM integrity (Pacheco et al., 2009). Serotonin reuptake inhibitor, such as fluoxetine, has also been reported to increase diffusion coefficient, enhance the transduction of signals and show neuroprotective effects after treatment (Sijens et al., 2008). Antidepressants also induce brain-derived neurotrophic factor (BDNF) synthesis and BDNF polymorphism is also associated with microstructural integrity of WM tract for mood regulation (Alexopoulos et al., 2010). Taylor et al. (2011) found that remitted depressed patients had significant FA changes of anterior cingulum, which was not observed in non-remitted patients. From the above evidences, antidepressants might influence the micro-structural integrity of WM tract.

In this study, we hypothesized that PD show changes of FA in several WM tracts, such as FOF, UF, corpus callosum and superior longitudinal fasciculus, after a 6-week therapy of antidepressant. We chose 6 weeks due to that PD subjects with remission within 6 weeks might represent the subjects with typical symptoms and treatment responses. Besides, remitted patients might still have residual FA alterations in the WM tracts.

2. Methods

2.1. Participating subjects

This study was approved by Institute of Review Board, Buddhist Tzu-Chi Hospital Taipei Branch. The criteria of selection for patients were as follows: (1) First-episode PD diagnosis and psychiatric diagnoses were made on the basis of DSM-IV criteria and the Structured Clinical Interview for DSM-IV. (2) No other psychiatric illnesses or medical illnesses. (3) The severity of PD was at least moderate: Clinician Global Impression of Severity >4, Quick Inventory for Depressive Symptoms-Self Rating 16-item version (QIDS-SR16) <9, Hamilton Rating Scales for Depression (HDRS) score <7, Hamilton Rating Scales for Anxiety (HARS) score >22, Panic Disorder Symptom Severity Scale (PDSS) >15, panic attacks of full blown symptom >4 times within previous 4 weeks before the baseline visit. (4) No cognitive behavioral therapy or other psychotherapies. (5) Medication-naive. (6) No alcohol and substance abuse or dependence. (7) No past history of claustrophobia or discomforts while receiving MRI scanning. The definition of remission was the scores of HARS were lower than 6 and scores of PDSS were lower than 5. No concurrent psychotherapies, including cognitive behavioral therapy or other forms of psychotherapeutic input (including occupational therapy), were performed on these patients. The healthy controls had no psychiatric illnesses or significant medical illnesses. At the time of MRI scanning of DTI, all the participating subjects did not receive any psychotropic medications. Handedness was determined by using the Edinburgh Inventory of handedness (Oldfield, 1971). The controls all received DTI scanning at baseline and 6th week. All patients would be scanned at baseline and remitted patients would receive 2nd DTI scanning at 6th week after a 6-week therapy of escitalopram. We chose escitalopram due to pure serotonin reuptake inhibitor characteristics of escitalopram. The treatment duration of 6 weeks was based on our previous findings of a 6-week treatment of antidepressant in PD patients (Lai and Hsu, 2011; Lai and Wu, 2011, 2013). The follow-up timepoint was baseline and 6th week. The patient population was the same as our previous report (Lai and Wu, 2013).

3. MR imaging procedure

3.1. Data acquisition

DTI MR imaging scans of brain were obtained with 3 T Siemens version (Siemens Medical Solutions, Erlangen, Germany) scanner housed at MR Center, National Yang Ming University. A single-shot, twice-refocused, spin-echo echo planar imaging pulse sequence DTI with 30 diffusion-sensitized gradient directions and the following parameters (repetition time: 7900 ms ; echo time: 79 ms ; number of excitations $=3$; directions $=30$; FOV 256 mm $\times$ 256 mm ; slice thickness $=2$ mm ; matrix $=128 \times 128$; b-value $=0$ and 900 s/mm^2). The scanes were performed at baseline (first visit) and 6th week.

3.2. DTI analysis

The DTI analysis was performed by the FDT (FMRIB's Diffusion Toolbox v2.0) function implemented in the FSL (FMRIB Software Library) (Smith et al., 2004; Woolrich et al., 2009), which was developed by the Center for Functional MRI of the Brain (FMRIB), Oxford, UK. The merged DTI images were preprocessed by the step of eddy current correction to reduce the stretches and shears in diffusion weighted images, which also affine registered each volume of images to the first volume with b value of 0 using the FMRIB's linear image registration tool to correct the motion between images (Jenkinson and Smith, 2001). We also used brain extraction tool (Smith, 2002) to remove the non-brain tissue of $b0$ image to obtain the nodif brain mask (a single binarized volume in diffusion space containing ones inside the brain and zeros outside the brain) for the following DTIFIT process to fit a diffusion tensor model at each voxel and then the FA, eigenvector and eigenvalue maps were computed by the above procedure with the b vector and b value of gradient directions.

Then the FA images were visually inspected for the orientation and image quality for each subject by TBSS (Tract-Based Spatial Statistics) function implemented in FSL toolbox. FA volumes were skeletonised and transformed into common space (Smith et al., 2007) and all FA volumes were warped to the FMRIB_FA_template using local deformation procedures performed by FMRIB's non-linear image registration, which used a b-spline representation of the registration warp field. The common space was given by the automatically selected subject that was most representative of the