Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 126–131

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Morphometric brain characterization of refractory obsessive–compulsive disorder: Diffeomorphic anatomic registration using exponentiated Lie algebra

Wanjie Tang [a], Bin Li [a], Xiaoqi Huang [b], Xiaoyu Jiang [b], Fei Li [c], Lijuan Wang [a], Taolin Chen [b], Jinhui Wang [d], Qiyong Gong [b], Yanchun Yang [a,*]

[a] Department of Psychiatry, West China Hospital, Sichuan University, Chengdu, Sichuan, PR China
[b] Department of Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan, PR China
[c] Huaxi MR Research Center (HMRRC), West China Hospital, Sichuan University, Chengdu, Sichuan, PR China
[d] Center for Cognition and Brain Disorders, Zhejiang Key Laboratory for Research in Assessment of Cognitive Impairments, Hangzhou Normal University, Hangzhou, Zhejiang, PR China

ARTICLE INFO

Article history:
Received 14 May 2013
Received in revised form 10 July 2013
Accepted 11 July 2013
Available online 19 July 2013

Keywords:
DARTEL
MRI
Obsessive–compulsive disorder
Posterior cingulate cortex
Refractory

ABSTRACT

Background: Few studies have used neuroimaging to characterize treatment-refractory obsessive–compulsive disorder (OCD). This study sought to explore gray matter structure in patients with treatment-refractory OCD and compare it with that of healthy controls.
Methods: A total of 18 subjects with treatment-refractory OCD and 26 healthy volunteers were analyzed by MRI using a 3.0-T scanner and voxel-based morphometry (VBM). Diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) was used to identify structural changes in gray matter associated with treatment-refractory OCD. A partial correlation model was used to analyze whether morphometric changes were associated with Yale–Brown Obsessive–Compulsive Scale scores and illness duration.
Results: Gray matter volume did not differ significantly between the two groups. Treatment-refractory OCD patients showed significantly lower gray matter density than healthy subjects in the left posterior cingulate cortex (PCC) and mediodorsal thalamus (MD) and significantly higher gray matter density in the left dorsal striatum (putamen). These changes did not correlate with symptom severity or illness duration.
Conclusions: Our findings provide new evidence of deficits in gray matter density in treatment-refractory OCD patients. These patients may show characteristic density abnormalities in the left PCC, MD and dorsal striatum (putamen), which should be verified in longitudinal studies.

1. Introduction

Obsessive–compulsive disorder (OCD) is a chronic and debilitating neuropsychiatric disorder characterized by persistent intrusive thoughts (obsessions) and/or repetitive behaviors (compulsions). OCD is relatively common, affecting approximately 2–3% of the global population (Michaud et al., 2006; Ruscio et al., 2010). Functional and structural neuroimaging research over the past two decades has implicated specific cortical–striatal–thalamic–cortical (CSTC) circuits in the pathophysiology of OCD (Alexander et al., 1986; Chamberlain et al., 2008; Gillan et al., 2010; Maia et al., 2008; Pujol et al., 2004; van den Heuvel et al., 2005).

Despite advances in OCD treatment, approximately 20% of patients prove refractory to psychological and pharmacological therapies (Husted and Shapira, 2004). Psychosurgery and deep brain stimulation (DBS) is generally used as a "last resort" treatment for such patients. One of the principal obstacles to optimizing treatment for refractory OCD is that little is known about the neural basis of this clinical subtype. Only a handful of functional neuroimaging studies have examined structural abnormalities in refractory OCD (Atmaca et al., 2006, 2008). They have identified volume abnormalities in the orbitofrontal cortex (OFC), thalamus, hippocampus and amygdala, although the findings from these studies do not always agree. In addition, these studies suffer from methodological weaknesses that make it difficult to apply their results to clinical practice. They involve a relatively small number of subjects and they use the region of interest (ROI) method with uncorrected thresholds, which limits statistical power and increases the risk of false-negative and false-positive results.

More extensive neuroimaging studies are needed based on approaches more rigorous than the ROI method in order to improve our

Abbreviations: CSTC, cortical-striatal-thalamic-cortical; DARTEL, diffeomorphic anatomical registration using exponentiated Lie algebra; DBS, deep brain stimulation; FWE, family-wise error; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; MD, mediodorsal thalamus; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PCC, posterior cingulate cortex; ROI, region of interest; VBM, voxel-based morphometry; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

* Corresponding author at: Department of Psychiatry, West China Hospital of Sichuan University, South Dianxin Road #28, Chengdu, 610041, Sichuan, PR China.
E-mail address: yanchunyang1958@gmail.com (Y. Yang).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.07.011

understanding of intractable OCD and improve treatment options. Several OCD studies based on voxel-based morphometry (VBM) have been conducted (Szeszko et al., 2008; Valente et al., 2005), but they have not examined how gray matter in patients with refractory OCD differs from that in patients with conventional OCD or healthy individuals. In addition, the VBM approaches used in these studies can sometimes generate artifacts because of the varying level and type of correction and the inaccuracy of spatial alignment of scans.

A recently developed VBM method based on diffeomorphic anatomical registration using exponentiated Lie algebra (DARTEL) (Ashburner, 2007) not only overcomes some limitations of the ROI method but also is more sensitive than standard VBM and optimized VBM for detecting structural brain abnormalities (Bergouignan et al., 2009; Klein et al., 2009). This approach may provide a more powerful and unbiased tool to study the neural substrates of intractable OCD. Therefore, the aim of the present study was to use VBM-DARTEL to characterize morphological abnormalities in gray matter in patients with refractory OCD relative to healthy controls. The long-term goal of this research is to provide neuroanatomical guidelines for ablation and DBS and thereby make these treatments more precise and effective, as well as increase our understanding of the neurobiology of intractable OCD.

2. Methods

2.1. Sample

2.1.1. Patients with OCD

Twenty-six patients with refractory OCD between 18 and 46 years of age were recruited consecutively between March 2008 and July 2012 from among patients in the Department of Psychiatry at West China Hospital of Sichuan University, Chengdu, China. Four refused to undergo MRI scanning, and another four were excluded because of motion artifacts and magnetic field inhomogeneities. In the end, 18 patients with refractory OCD were included in the study.

All patients were determined by clinicians to be experiencing severe symptoms and functional impairment, based on detailed screening and baseline assessments, record review and self-reports by the patients themselves. In all cases, attending physicians had determined psychosurgery and DBS to be the only available treatment.

Patients with OCD were assessed by two experienced psychiatrists to make sure that they met the diagnostic criteria for OCD based on the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (Sheehan et al., 1998). Patients with OCD were excluded if they had any other DSM-IV axis I or II comorbidities, any current significant medical problems, history of neurological illness or severe head trauma with loss of consciousness, substance or alcohol abuse/dependence within the past 12 months, or any other condition affecting their ability to participate in the study. At the start of the study, patients were assessed by the same two psychiatrists using the Y-BOCS (Goodman et al., 1989), the 14-item Hamilton Anxiety Rating Scale (HARS) (Maier et al., 1988) and the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960, 1967).

To ensure that our patient group contained only those with treatment-refractory OCD, we carefully defined our criteria based on clinical data such as age at OCD onset, duration of OCD and treatment history (Mallet et al., 2008; Pallanti and Quercioli, 2006). In our study, a patient was considered to have refractory OCD if all of the following conditions were met: (1) the OCD had lasted more than 5 years; (2) the patient had an overall score of 24 on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) or a score above 15 (out of 20) on at least one Y-BOCS subscale; (3) the patient did not respond to adequate pharmacotherapy involving at least three serotonin-reuptake inhibitors (clomipramine, fluoxetine, sertraline, paroxetine, fluvoxamine or citalopram), one of which had to be clomipramine, with "adequate pharmacotherapy" defined as administration of the maximum recommended dose for more than 12 weeks, followed by augmentation with at least one atypical antipsychotic (quetiapine, risperidone, olanzapine or aripiprazole) for more than 6 months; and (4) the patient did not respond to cognitive–behavioral therapy involving exposure and response prevention techniques over the course of 1 year of therapy or after 20 sessions with at least two therapists.

Patients went through a 4-week washout period from medications and psychotherapy before the study.

2.1.2. Healthy comparison subjects

Twenty-six healthy subjects were recruited from the local area by poster advertisements and assessed according to the same exclusion criteria above in order to exclude anyone with psychiatric or somatic disorders. Healthy subjects had no history or present diagnosis of any DSM-IV axis I or II condition, no neurological illness, no history of head trauma with loss of consciousness and no history of psychiatric disorders among first-degree relatives.

This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and written informed consent was obtained from all participants. Subject recruitment and MRI scanning were performed between March 2008 and July 2012. All participants were Han Chinese and were assessed by two experienced radiologists as having no abnormalities on conventional MRI.

2.2. Image acquisition

Resting-state functional MRI scanning was performed on all subjects using a 3.0-T magnetic resonance system scanner (GE EXCITE, Milwaukee, Wisconsin) with an 8-channel phased-array head coil. Subjects were fitted with soft ear plugs, positioned comfortably in the coil and instructed to relax and remain still. Head motion was minimized using foam pads. For each slice, 15 images were collected with high-diffusion weighting along 15 non-collinear and non-coplanar directions and the following scan parameters: repetition time, 10,000 ms; echo time, 70.8 ms; slice thickness, 3.0 mm; field of view, 240×240 mm^2; voxel dimensions, $1 \times 1 \times 3$ mm^3; scan matrix, 128×128; b value, 1,000 s/mm^2.

High-resolution, three-dimensional T1-weighted images were acquired using a spoiled gradient recalled sequence with the following parameters: repetition time, 8.5 ms; echo time, 3.4 ms; fractional anisotropy, 12°; number of axial slices, 156; axial slice thickness, 1 mm; axial field of view, 240×240 mm^2; data matrix, 256×256. An experienced neuroradiologist blinded to group allocation (FL) reviewed all scans to exclude any participant with obviously gross abnormalities.

2.2.1. VBM-DARTEL

T1-weighted image registration was achieved using the diffeomorphic registration algorithm implemented in the DARTEL toolbox for SPM8 (Wellcome Trust Centre for Neuroimaging, University College London) running under MATLAB 7.11.0 (The Math Works, Natick, MA, USA) in a Windows 7 Professional environment. This algorithm has been found to increase the registration between individuals and thereby improve localization and increase sensitivity during analyses. In particular, since this technique is more deformable, it improves the realignment of small inner structures. VBM preprocessing involved five steps and followed the standard approach of Ashburner (Ashburner, 2007; Bergouignan et al., 2009). This preprocessing gave smoothed, modulated and normalized data that were used in statistical analysis.

2.3. Statistical analysis

Imaging results for patients with refractory OCD and healthy comparison subjects were compared using two-sample t tests. We used absolute threshold masking at 0.2 to avoid possible edge effects around the border between gray matter and white matter or cerebrospinal fluid, as well as to restrict the analysis to gray matter. Results were assessed using a family-wise error (FWE) threshold of $p < 0.05$,