Journal of Affective Disorders 208 (2017) 184–190

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Effectiveness of cognitive-coping therapy and alteration of resting-state brain function in obsessive-compulsive disorder☆

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ARTICLE INFO

Keywords:
Obsessive-compulsive disorder
Cognitive-coping therapy
Resting-state fMRI
Treatment

ABSTRACT

Background: Cognitive-coping therapy (CCT), integrating cognitive theory with stress-coping theory, is an efficacious therapy for obsessive-compulsive disorder (OCD). However, the potential brain mediation for the effectiveness remains unclear. We sought to investigate differences of resting-state brain function between OCD and healthy controls and if such differences would be changed by a four-week CCT.

Patients and methods: Thirty-one OCD patients were recruited and randomized into CCT (n=15) and pharmacotherapy plus CCT (pCCT, n=16) groups, together with 25 age-, gender- and education-matched healthy controls. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was scored to evaluate the severity in symptoms. Resting-state functional magnetic resonance imaging was scanned pre- and post-treatment.

Results: For patients, Y-BOCS scores were reduced during four-week treatment for CCT and pCCT ($P < 0.001$), but no group difference was observed. No differences in amplitude of low-frequency fluctuation (ALFF) values were found between CCT and pCCT either pre- or post-treatment. Compared to controls, ALFF in OCD patients was higher in the left hippocampus, parahippocampus, and temporal lobes, but lower in the right orbitofrontal cortex, rectus, bilateral calcarine, cuneus, lingual, occipital, left parietal, postcentral, precentral, and parietal (corrected $P < 0.05$). The ALFF in those regions was not significantly correlated to the severity of OCD symptoms. After a 4-week treatment, the ALFF differences between OCD patients and controls disappeared.

Limitations: The pharmacotherapy group was not included since OCD patients generally do not respond to pharmacotherapy in four weeks.

Conclusions: Our data indicated that resting-state brain function was different between OCD and controls; such differences disappeared after OCD symptoms were relieved.

1. Introduction

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder, affecting up to 2% of the US population (Stein, 2002) with a similar prevalence worldwide (Sasson et al., 1997). Often of early onset, OCD tends to be treatment-resistant (Bjorgvinsson et al., 2007). It is characterized by recurrent intrusive thoughts that cause distress and interfere with psychological function and by repetitive behaviors (overt compulsions), or mental acts (covert compulsions) performed in response to obsessions. These compulsions can be highly time consuming and affect patients throughout their lives, leading to a diminished quality of life, reduced productivity, and higher health care

☆ **Trial Registration:** ChiCTR-IPC-15005969.

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http://dx.doi.org/10.1016/j.jad.2016.10.015
Received 24 February 2016; Received in revised form 27 August 2016; Accepted 17 October 2016
Available online 18 October 2016
0165-0327/

costs (Hollander et al., 1996; Koran, 2000).

It usually takes up to 12 weeks to achieve significant clinical response when OCD patients are treated with pharmacotherapy, including selective serotonin reuptake inhibitors (SSRIs) and antipsychotics as augmenting treatment, or cognitive-behavioral therapy (CBT) (Foa, 2010; Math and Janardhan Reddy, 2007). The brain's response to treatment with serotonin reuptake inhibitor (SRI) medications or CBT in OCD has been intensely investigated. Although the results from many studies are not consistent, functional brain imaging studies have repeatedly found that elevated cerebral glucose metabolism and blood flow in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), basal ganglia, and thalamus are decreases in response to the treatments (Baxter et al., 1992; Feusner et al., 2009; Kwon et al., 2003; Saxena et al., 2001). These findings suggest that OCD symptoms are mediated by hyperactivity along frontal-subcortical circuits connecting the OFC, basal ganglia, and the thalamus (Saxena et al., 1998).

Pharmacotherapy is thought to act primarily by altering serotonin and dopamine synapse function, altering monoaminergic regulation to affect symptom reduction. CBT is thought to directly alter the connectivity in the cortical-striatal-thalamic-cortical-amygdala circuits via emotional learning processes (Ressler and Rothbaum, 2013). The effects of intensive CBT on brain glucose metabolism and cingulate neurochemistry in OCD have been previously reported. Saxena et al. performed [^{18}F]-fluorodeoxyglucose positron emission tomography on 10 OCD patients before and after 4 weeks of intensive individual CBT and found that OCD patients show significant bilateral decreases in normalized thalamic metabolism but have a significantly increase in right dorsal anterior cingulate cortex activity (Saxena et al., 2009). O'Neill and colleagues performed proton magnetic resonance spectroscopic imaging in 10 OCD patients before and after 4 weeks of intensive CBT. Their data implicate the pregenual anterior cingulate cortex and anterior middle cingulate cortex as the loci of the metabolic effects of CBT in OCD (O'Neill et al., 2013).

Recently, it was found that cognitive-coping therapy (CCT) (Hu, 2010; Hu and Ma, 2011; Hu et al., 2015, 2012; Ma et al., 2013), a new treatment for OCD integrating cognitive theory with stress-coping theory, achieved higher response and remission rates in 4-week treatment regimen with lower rates of relapse and drop-off during a 12 month follow-up, and higher levels of social-occupational function recovery. Also, CCT is similarly efficacious for both drug-resistant and non-drug-resistant OCD (Ma et al., 2013). However, very little is known about the brain's response to CCT in OCD.

Resting-state functional magnetic resonance imaging (rs-fMRI) has been increasingly used to understand the resting-state brain function in psychiatric disorders. The rs-fMRI has the advantage of identifying neurophysiologic mechanisms that are not specific to an employed task, which will complement and extend findings from task-based studies, because the diversity of tasks used may lead to controversial results (Lee et al., 2013). For example, while dysfunction in orbital, medial frontal, and striatal areas are found to be contribute to the pathogenesis of OCD (Feusner et al., 2009; Kwon et al., 2003), other evidence indicates there is a broader cortical dysfunction in the disorder, including abnormality of dorsolateral prefrontal cortex, anterior insula, lateral and medial temporal lobe regions, and parietal cortex (Menzies et al., 2008; Stern et al., 2012; Ursu and Carter, 2009). The rs-fMRI focuses on spontaneous low frequency fluctuations (< 0.1 Hz) in the BOLD signal, which can be used to detect the brain rest network (Lee et al., 2013). Established in 2007 (Zang et al., 2007), amplitude of low-frequency fluctuation (ALFF) has been reported as a marker of brain function, able to characterize various abnormal conditions, such as migraine (Li et al., 2016), subcortical ischemic vascular disease (Lampit et al., 2015) and Alzheimer's disease (Sacco et al., 2016). ALFF has also been used to investigate mental disorders including OCD (Hou et al., 2012; Zang et al., 2007). Most recently, ALFF was used as a way of evaluating brain plasticity (Lampit et al., 2015; Li et al., 2016; Sacco et al., 2016). ALFF measures the deviation, rather than the mean of a period, of BOLD. Therefore, it is not a parameter of hyper- or hypo-activation; it represents regional spontaneous neuronal activity (Zang et al., 2007). Several studies show the test-retest of ALFF analysis is overall moderate-to-high in 2.5 to 16 months (Turner et al., 2012; Yan et al., 2013; Zou et al., 2015). Although only a few studies investigate the ALFF in OCD (Hou et al., 2012; Li et al., 2011; Zhu et al., 2016, 2015), none of them are involved in interventions and no consistent conclusion has been reached (Supplemental Table 1 for more rs-fMRI studies in OCD).

In this study, we sought to investigate whether there were differences in resting-state brain function between OCD and healthy controls and whether such difference would change after the severity of OCD symptoms was reduced by CCT. We hypothesized that the resting-state brain activation would be different between OCD and healthy controls and that such differences would be altered in OCD patients after the severity of OCD symptoms was reduced.

2. Methods

2.1. Participants

This study was approved by the Committee on Human Research of the Xinxiang Medical University. OCD patients were recruited at the Second Hospital of Xinxiang Medical University and via the medical centers located in Zhengzhou City and Kaifeng City, Henan Province, from May 2013 to June 2014. All patients met DSM-IV diagnostic criteria for OCD. All potential recruits undertook a semi-structured clinical interview to screen for current axis-I disorders. Patients were recruited on the basis of an OCD diagnosis and a Yale-Brown Obsessive Compulsive scale (Y-BOCS) score≥16, and those with axis-I comorbidities (including schizophrenia, substance abuse, developmental disabilities, or severe cognitive dysfunction) were excluded. All participants were right-hand dominant and reported no history of head trauma, neurological disease, or contraindications for MRI. All participants provided written informed consent prior to participation.

Thirty-one eligible patients completed resting state functional resonance imaging (rs-fMRI) scans. Twenty-five completed the second scanning. Twenty-five healthy age-, gender- and education-matched controls were recruited and completed the scans of rs-fMRI. The Y-BOCS was evaluated before treatment and after a 4-week treatment with CCT or pharmacotherapy plus CCT (pCCT). Two trained psychiatrists who had no other contact with participants evaluated the Y-BOCS. The inter-rater reliability was greater than 0.85 ($P < 0.001$).

2.2. Resting state functional magnetic resonance imaging (rs-fMRI) scanning

All scans were done on a 3 T MR imaging system (TIM Verio, Siemens, Germany) using a twelve-channel phased array head coils. After conventional localizer and T2 anatomic scans, resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence with the following parameters: 33 axial slices with a slice thickness/gap=4 mm/0.4 mm, repetition time (TR)=2000 ms, echo time (TE)=30 ms, flip angle (FA)=90°, field of view (FOV)=240×240 mm^2, in-plan matrix=64×64, resulting in a voxel size of 3.8×3.8×4 mm^3, total volumes=240. For each participant, a high resolution structural T1-weighted anatomical sequence was scanned in a sagittal orientation using a three-dimensional magnetization-prepared rapid gradient-echo (3D MP-RAGE) with the following parameters: TR=1900 ms, TE=2.52 ms, FA=15°, slice thickness=1 mm, data matrix=256×256, isotropic voxel 1×1×1 mm^3. To minimize the motion of the subject's head during the study, foam padding was utilized. Each patient completed rs-fMRI scanning before and after a 4-week treatment. During the scanning, participants were instructed simply to remain relaxed with their eyes closed and think of nothing in particular.