

Left Amygdala Functional Connectivity Decreased after Fear of Negative Events was Disregarded in Obsessive-Compulsive Disorder

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ABSTRACT: Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental disorder that affects patients throughout their lives, leading to a diminished quality of life for patients and families, reduced productivity, and higher health care costs. It is of clinical and theoretical importance to investigate a more efficacious therapeutic approach for OCD and the neurophysiological mechanism underlying the efficacy of treatment, potentially associated with the etiology of OCD. Recently, a novel psychotherapy designated cognitive-coping therapy (CCT) has been reported to have a large effect size in OCD treatment. CCT hypothesizes that fear of negative events plays a crucial role in OCD. The study entitled “Decreased left amygdala functional connectivity by cognitive-coping therapy in obsessive-compulsive disorder” attempted to investigate the potential neurophysiological mechanism underlying the efficacy of CCT for OCD. The study provides crystal evidence showing that 4-week pharmacotherapy plus CCT decreases the left amygdala seed-based functional connectivity (LA-FC) with the right anterior cingulate gyrus and the left paracentral lobule/the left superior parietal/left inferior parietal, and 4-week CCT decreases the LA-FC with the left middle occipital gyrus/the left superior parietal. The alteration of the LA-FC with the right anterior cingulate gyrus positively correlates to the reduction of the Yale-Brown obsessive-compulsive scale (Y-BOCS) score. Therefore, it provides new insights into understanding the neurophysiology and neuropsychology behind the onset and treatment of OCD.

KEYWORDS: Obsessive-compulsive disorder, cognitive-coping therapy, Amygdala, fMRI, functional connectivity

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Background

Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental disorder characterized by recurrent, unwanted, intrusive thoughts and by repetitive behaviors or mental acts performed in response to obsessions. The lifetime prevalence of OCD affects up to 3.3% of the U.S. population and the 12-month prevalence estimate is 1.2%.¹ Often early-onset and highly comorbid with other psychiatric disorders, OCD affects patients throughout their lives, leading to diminished quality of life for patients and families, reduced productivity, and higher health care costs.²

The treatment outcomes for OCD are not ideal at present. Only 20% of individuals with OCD who accept treatment experience a complete absence of symptoms for at least 5 years.³ Currently, selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) are the first-line treatment for OCD, because they provide the most promise. Even so, around 60% of OCD patients do not respond adequately to pharmacotherapy.⁴ Although CBT has an effectiveness rate ranging from 60% to 85%, approximately 25% of patients refuse exposure and response prevention (ERP). Among those who accept ERP, 15% do not respond and up to 12% drop out.⁵ For those with severe symptoms of OCD refractory to treatment, deep brain stimulation (DBS) is a therapeutic option. The response rate of DBS is around 53%⁶ and DBS has a surgical site infection rate of 4.5% in OCD.⁷

Recently, novel psychotherapy, cognitive-coping therapy (CCT), has proved to yield quick effectiveness in OCD treatment with a super large effect size.^{8–11} Its effectiveness is not related to the symptom severity, the subtype of OCD, age of onset, or duration of illness, but it is significantly correlated to how much individuals with OCD tangle themselves with the fear of negative events. In line with these results, a recent study on contamination-based OCD demonstrates that within-session fear decline predicts post-treatment symptom reduction.¹² In CCT, fear of negative events is hypothesized to play a key role in the onset of OCD (Figure 1). From the view of this hypothesis, OCD may be considered a specific situation-induced mental disorder, in which individuals struggle to control the effects of fear on themselves. Therefore, CCT focuses on helping individuals with OCD recognize why and how fear is involved in the disorder and then teaching them to cope with (ie, discard) the fear rather than habituate it, which is the main difference between CCT and the exposure and response prevention of CBT.

Previous neuroimaging studies on OCD

Currently, the functional neuroimaging studies mainly include task-based functional magnetic resonance imaging and resting-state functional magnetic resonance imaging (rs-fMRI). The rs-fMRI has been more frequently used to understand the brain



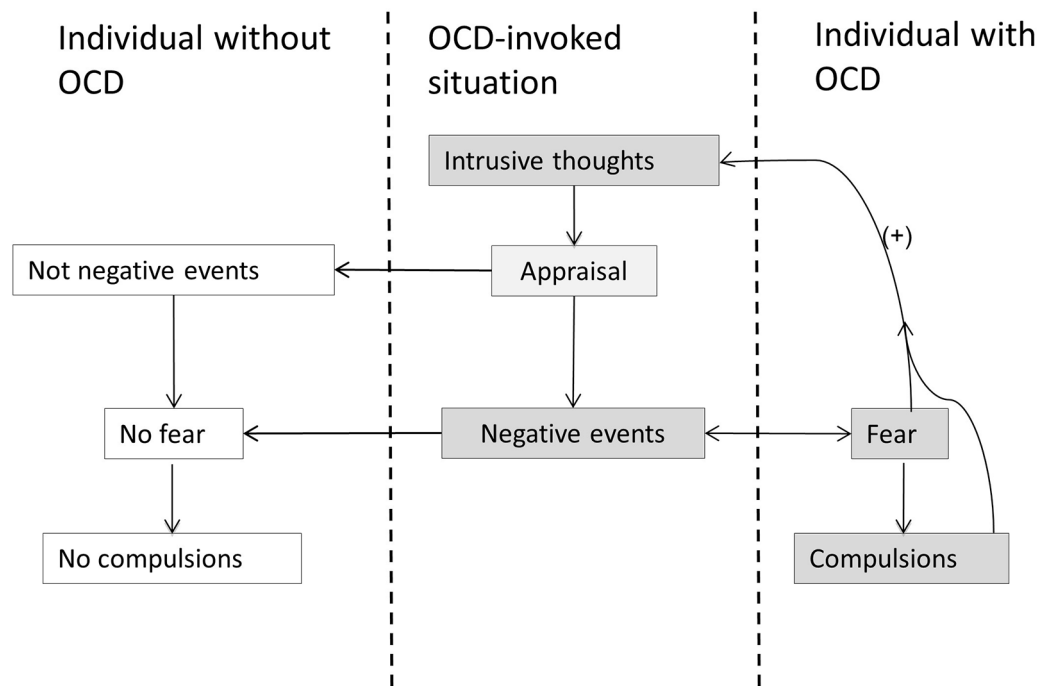


Figure 1. Role of fear of negative events in OCD.

function in psychiatric disorders because the diversity of tasks used may lead to controversial results. It is advantageous in identifying neurophysiologic mechanisms that are not specific to an employed task, which will complement and extend findings from task-based studies. The rs-fMRI focuses on spontaneous low-frequency fluctuations (<0.1 Hz) in the BOLD signal to detect the brain rest network. Also, the amplitude of low-frequency fluctuation (ALFF) is gradually accepted to investigate mental disorders including OCD and is reported to have excellent discrimination between drug-naïve OCD and healthy controls.

Accumulating evidence from neuroimaging studies suggests dysfunction of the cortico-striato-thalamo-cortical (CSTS) circuit and abnormalities in functional connectivity within this circuit in individuals with OCD. Further studies indicate limbic structure involvement beyond CSTC, such as the amygdala and hippocampus, and other areas including insular, orbital, and cingulate. Abnormalities in these regions include not only the gray and white matter volume, but functional activation as well.

The neurophysiology underlying the response to CBT in OCD has been investigated. Previously, positron emission tomography (PET) scans on OCD patients after a 4-week intensive CBT demonstrates significant bilateral decreases in normalized thalamic metabolism, but a significant increase in right dorsal anterior cingulate cortex activity.¹³ Another PET scan before and after an 8 to 12 weeks CBT shows that the patients who responded to CBT have significant decreases in normalized right caudate glucose metabolism.¹⁴ Lately, accumulating data demonstrate a potential for rs-fMRI to forecast OCD after CBT and the effects of CBT on rs-fMRI in OCD. It is reported that there is decreased resting-state functional

connectivity (rs-FC) between the amygdala subregions and the visual associated cortices, and there is increased rs-FC between the amygdala and the right inferior parietal lobe in patients with OCD who responded to 12-week of CBT.¹⁵

Recently, the study entitled “Decreased left amygdala functional connectivity by cognitive-coping therapy in obsessive-compulsive disorder” attempted to investigate the potential neurophysiological mechanism underlying the efficacy of CCT for OCD.

Description of the study

The before-and-after study was designed to investigate the effectiveness of CCT and the potential neurophysiological mechanism underlying the efficacy of short-term CCT in OCD treatment.¹⁶ This study recruited 107 individuals with OCD, who were partially randomized into 3 treatment groups: pharmacotherapy (the serotonin reuptake inhibitors) only, pharmacotherapy plus CCT (pCCT), and CCT only. Based on the cognitive theory and the stress-coping theory, CCT is developed to be an emotion- and motivation-focused psychotherapy, in which fear of or worry about negative events (eg, fear of contamination) are attributed to the onset and maintenance of OCD. In CCT, fear of negative events, obsessions, and a motivation to perform compulsions are considered stressors. The effects of these stressors on compulsions will be reduced if they are coped with properly. The findings of the study demonstrate that, after a 4-week treatment, the scores on the Yale-Brown obsessive-compulsive scale (Y-BOCS) were reduced in pCCT and in CCT. The reduction rates in pCCT and CCT which were significantly higher than those in

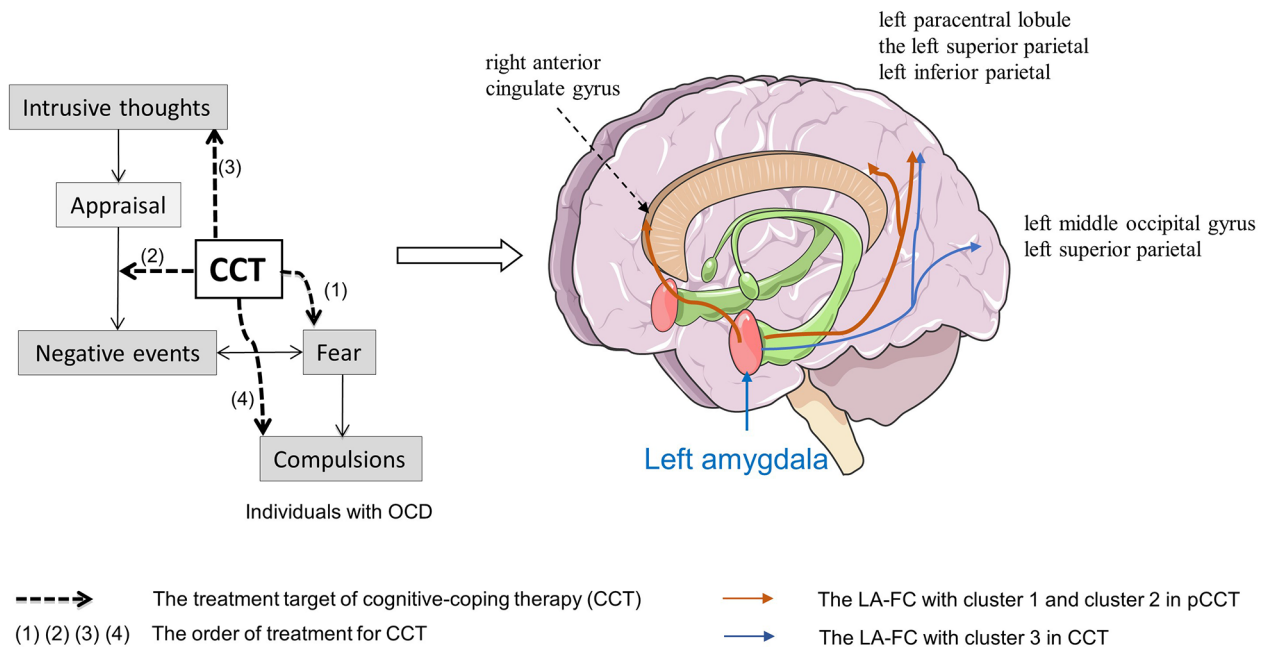


Figure 2. The targets and the effects of CCT.

pharmacotherapy. There was no difference in the Y-BOCS score between pCCT and CCT. Four-week pCCT and 4-week CCT achieved a higher response rate (>92.3%, reduction on Y-BOCS score $\geq 35\%$) and remission rate (73.1%, reduction on Y-BOCS score $\geq 80\%$ or less than 8) than pharmacotherapy. The effect sizes were 4.1 and 3.9 for pCCT and CCT, respectively. These clinical findings corroborate that CCT is an efficacious approach for OCD treatment and that it is a clinically rational intervention against the fear of negative events.

The amygdala has been found to modulate fear response and anxiety in humans.¹⁷ It is an important part of the circuit that allows the brain to detect and respond to threats. Based on the effectiveness of CCT and the hypothesis that fear of negative events plays a key role in OCD, the study further examined whether the different treatments would change the amygdala-seeded functional connectivity compared to the baseline. The study found that pCCT-treated patients showed decreased L-amygdala FC (LA-FC) with 2 clusters (1 and 2). Cluster 1 included the right anterior cingulate gyrus and cluster 2 included the left paracentral lobule and the left parietal lobe. CCT-treated patients showed decreased LA-FC with the left middle occipital gyrus, the left superior parietal, and the left inferior parietal lobe (cluster 3) (Figure 2). The LA-FC values (*z*-value) were analyzed in the study. The alteration of the *z*-value in LA-FC with cluster 1 was positively related to the reduction of the Y-BOCS score. The decreased LA-FC with the right ACC (cluster 1) after OCD symptoms were improved was positively correlated with the improvement of symptoms, suggesting that LA-FC with the ACC might be involved in OCD.

In addition, while the *z*-value of FC with cluster 2 in patients with covert compulsions (repetitive mental acts)

exhibited no significant difference between pre- and post-treatment, the *z*-values of LA-FC with the 3 clusters were significantly decreased after the treatments of pCCT or CCT in patients with covert compulsions, patients with overt compulsions (repetitive behaviors), non-remission patients, and remission patients. These findings suggest that LA-FC with the left paracentral/parietal lobe might be a potential marker to distinguish the 2 subtypes of OCD. Cluster 2 in pCCT and cluster 3 in CCT had overlapped the brain region of the left parietal lobe, probably suggesting the common neurophysiological pathway for these 2 approaches to OCD.

There are several limitations to this study. First, the sample size was relatively small, especially for rs-fMRI, which limited the ability to perform further analysis across groups. Second, 74% of patients with pharmacotherapy and 81% of patients with pCCT were taking SSRIs when they entered this study and the rs-fMRI analysis, which might affect the FC as a confounding factor. Third, this study did not exclude the patients who had comorbidities with depression or anxiety. It should be noted that OCD patients with comorbidities of depression or anxiety have different neuroimaging results compared with those without the comorbidities.¹⁸⁻²⁰

Conclusion

It is of great clinical importance to improve the treatment outcomes in neuropsychiatric disorders, including OCD. The rationale of this study was to investigate the effectiveness of CCT on OCD treatment outcomes and the potential neurophysiological mechanism underlying the efficacy of CCT for OCD. The study provides crystal evidence showing that CCT for OCD is a highly efficacious approach and that a 4-week pharmacotherapy plus CCT decreases the left amygdala

seed-based functional connectivity (LA-FC) with the right anterior cingulate gyrus and the left paracentral lobule/the left superior parietal/left inferior parietal, and 4-week CCT decreases the LA-FC with the left middle occipital gyrus/the left superior parietal. The alteration of the LA-FC with the right anterior cingulate gyrus is positively correlated to the reduction of the Yale-Brown obsessive-compulsive scale (Y-BOCS) score. Therefore, the study corroborates the hypothesis that the fear of negative events plays a role in OCD. Also, it provides new insights into the understanding of the neurophysiology and neuropsychology in the onset and treatment of OCD.

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Author Contributions

The idea was conceptualized by XH, who was involved in drafting the manuscript.

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