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·Review·

Review of structural neuroimaging in patients with refractory obsessive-compulsive disorder

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Abstract: The notion that some special brain regions may be involved in the pathogenesis of obsessive-compulsive disorder (OCD) dates back to the beginning of the twentieth century. Structural neuroimaging studies in the past 2 decades have revealed important findings that facilitate understanding of OCD pathogenesis. Current knowledge based on functional and structural neuroimaging investigations largely emphasizes abnormalities in fronto-striatal-thalamic-cortical and orbitofronto-striato-thalamic circuits in the pathophysiology of OCD. However, these neuroimaging studies did not focus on refractory OCD. The present review mainly focused on structural neuroimaging performed in OCD, which had been ignored previously, and highlighted current evidence supporting that orbito-frontal cortex and thalamus are key brain regions, and that the hippocampus-amygdala complex is associated with refractoriness to the available treatment strategies. However, to fully reveal the neuroanatomy of refractoriness, longitudinal studies with larger samples are required.

Keywords: structural neuroimaging; refractory; obsessive-compulsive disorder; orbito-frontal cortex; thalamus

1 Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive unwanted thoughts or images and overwhelming urges to perform ritualistic behaviors or mental acts, leading to obvious impairment in occupational, academic, and social functioning. According to data from the Epidemiological Catchment Area (ECA) survey and other epidemiological studies, the lifetime prevalence of OCD is between 2%–3% in the general population[1]. OCD is a chronic disorder like collagen tissue disorders, with symptoms tending to wax and wane but rarely remitting spontaneously through the course of the disorder. Considering the prevalence, the chronic course, and the functional interference of OCD, it is important to elucidate variables underlying this disorder[2], particularly when considering treatment of refractory ones. A majority of OCD cases (40%–60%) respond to serotonin reuptake inhibitors, alone or in combination with other medications, and cognitive behavior therapy. On the other hand, up to 30%–40% of patients do not respond to the available treatment modalities[3-6]. For OCD, refractoriness to treatment includes a less than 35% decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score at final evaluation as compared to baseline, or a final Y-BOCS score of larger than 16 and being no better than "minimally improved" on the Clinical Global Impression improvement item.

The notion that some special brain regions may be involved in the pathogenesis of OCD dates back to the beginning of the twentieth century. In that period, in patients demonstrating sequela of encephalitis lethargica after in-

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fluenza epidemies, involuntary movements, obsessions and compulsions occurred simultaneously, implying that basal ganglia might be involved in OCD. The functional imaging techniques which indirectly measure activity levels in specific brain areas were used to determine whether the structures thought to be involved in OCD were abnormally active in patients with this disorder[7]. Furthermore, after both pharmacotherapy and behavioral psychotherapy, there showed some changes in the activities of basal ganglia and prefrontal regions[8]. Throughout the past 2 decades, structural neuroimaging studies have revealed important findings that contribute to the understanding of OCD pathogenesis, though neurobiological theories of OCD are largely based on the results of functional neuroimaging studies. However, in refractory OCD, it seems that there have not been enough investigations.

2 Key brain regions

Current knowledge from functional and structural neuroimaging emphasizes abnormalities of fronto-striatal-thalamic-cortical circuits and orbitofronto-striato-thalamic circuits in the pathophysiology of OCD[9,10]. In this context, structural imaging studies have implicated the pathology of basal ganglia and frontal regions[11]. Among these regions, some areas have been determined as "key brain regions", including orbito-frontal cortex (OFC), thalamus, anterior cingulate cortex (ACC) and caudate nucleus. In a recent meta-analysis study, Whiteside *et al.*[7] also emphasized these structures in the pathophysiology of OCD. However, the structural magnetic resonance imaging (MRI) findings regarding these regions are inconsistent. Some studies reported increases in volumes[12-14], while some findings indicated decreased volumes[13-16]. Moreover, some studies even revealed no differences in the volumes of these key brain regions[17-19]. Recently, Pujol *et al.*[20] have found reduced gray matter volumes in the medial frontal gyrus, the medial OFC, and the left insulo-opercular region. Similarly, Choi *et al.*[21] have shown volume reduction of the left anterior OFC in patients with OCD. Most recently, in a voxel-wise meta-analysis of gray matter changes by Radua J and Mataix-Cols D[22], 12 data-sets comprising 401 patients with OCD and 376 healthy controls meeting inclusion criteria were employed and new improved voxel-based meta-analytic method was developed to examine regions of increased or decreased gray matter volume in OCD and control groups. Results showed that OCD patients had larger regional gray matter volumes in bilateral lenticular nuclei, extending to the caudate nuclei, and decreased volumes in bilateral dorsal medial frontal/anterior cingulate gyri, although there was no group difference in global gray matter volume. Moreover, patients with more severe OCD had significantly increased gray matter volumes in the basal ganglia. Another meta-analysis by Rotge *et al.*[23] revealed no volumetric differences for the whole brain, the intracranial region, the gray matter, the prefrontal cortex or the basal ganglia of OCD patients, but reduced volumes of the left ACC, the left and the right OFCs, and increased volumes of the left and the right thalami. In addition, the severity of OCD was determined to be correlated significantly with the effect sizes of the left and the right thalami. Our research group also performed a volumetric MRI study in treatment-naive patients and healthy controls, focusing on the *in vivo* neuroanatomy of the whole brain, total gray and white matter volume, thalamus, caudate nucleus, ACC and OFC concurrently[14]. Results showed that OCD patients without any comorbidity had significantly smaller left and right OFC volumes and significantly greater left and right thalamus volumes, compared with healthy controls, and there was a near-significant difference in left side for anterior cingulate between the 2 groups. Furthermore, significant correlations were found between Y-BOCS scores and left/right OFC volumes, and between Y-BOCS scores and left thalamus volumes in the patients. In addition, some key brain regions were examined in treatment-naive patients, refractory OCD patients, treatment-responding ones and healthy controls[13]. Results showed that as a whole group, OCD patients had increased white matter volume than healthy controls, and that treatment-naive patients had significantly smaller left and right OFC volumes compared with treatment-responding patients and healthy controls. Besides, there were significant differences in both sides between refractory patients and treatment-responding

patients, while no significant difference was detected in volume of either side between treatment-naive and refractory patients. Concerning the anterior cingulate, there was a near-significant difference only between treatment-naive patients and healthy controls in left side. Moreover, treatment-naive patients had significantly greater left and right thalamus volumes compared with treatment-responding patients and healthy controls, and there was a considerable difference in thalamic volumes between refractory patients and treatment-responding patients. These findings suggest that reductions in OFC volumes and increases in thalamic volumes may be associated with refractoriness of OCD, which might not be due to the changes in cingulate or caudate region. Meanwhile, it should be noted that the sample size in this study was small, limiting the strength of statistical power and the generalizability of the study findings. More recently, Cecconi *et al.*[24] have reported a significant regional postoperative increase in gray matter volume in the right inferior frontal gyri in all 5 patients with refractory OCD 1 year after gamma ventral capsulotomy.

3 Hippocampus-amygdala complex

Since hippocampus-amygdala complex has strong connections with OFC, these complexes are included in OCD circuit[25,26] and are thought to connect the brain regions that modulate the information involved in the initiation of behavioral responses implemented with little conscious awareness[10]. Abnormalities in the regions of hippocampus and amygdala have been emphasized in studies involving positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), and researchers have commented that these regions may play an important role in the pathophysiology of OCD, with neglected discussion[27,28]. Moreover, in OCD, there is a loss of normal hemispheric asymmetry of the hippocampus-amygdala complex[16] and differences in amygdala volumes[29].

Furthermore, pharmacological agents that are effective in treatment of OCD (*e.g.* serotonergic reuptake inhibitors) exert their effects on amygdala receptors[30-32]. On one hand, the cybernetic models proposed by Gray[33] and Pitman[34] imply that the hippocampus may play an important role in compulsive behavior. On the other hand, in the study of Van Laere *et al.*[35], PET images obtained before and after high-frequency anterior capsular stimulation in 6 refractory OCD patients showed positive correlations between clinical improvement and the metabolic activity changes in left ventral striatum, left amygdala, and left hippocampus. Despite the above-mentioned importance, the role of hippocampus-amygdala complex in OCD has not been extensively investigated. Moreover, this complex had not been evaluated in refractory OCD patients until we examined the volumes of the hippocampus and the amygdala by MRI in a sample of 14 refractory OCD patients and 14 healthy comparison subjects[36]. In that study, we found that the mean left and right hippocampal and amygdala volumes of the patients were smaller than those of the healthy controls, and OCD severity was correlated with left hippocampal volume. These results suggest that hippocampus and amygdala abnormalities might be implicated in refractoriness to OCD.

4 Deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) techniques in the treatment of refractory OCD

DBS serves as an alternative to neurosurgery methods for movement disorders such as Parkinson's disease (PD), dystonia, and essential tremor. Usage of DBS in psychiatric disorders began by OCD. In 1999, DBS was conducted in 4 patients with refractory OCD by Nuttin and colleagues[37], and 3 of the patients displayed beneficial outcomes. Currently, there are 3 targets for DBS in treatment of OCD: the rostral-caudal dimension of the anterior limb of the internal capsule and ventral capsule/ventral striatum, the subthalamic nucleus, and the inferior thalamic peduncle[38]. TMS is a noninvasive technique that delivers magnetic pulses directly to the scalp. To date, several trials of TMS on OCD patients have been published, with promising results[39-43]. Stimulation of the right and the left prefrontal cortex[41] and of the supplementary motor area[42] has shown beneficial effects in treatment-resistant OCD patients, with response rates ranging from 25% to 60%, as measured by Y-BOCS. On the other hand, Ruffini *et al.*[44] have

assessed the influence of repetitive transcranial magnetic stimulation (rTMS) of the left OFC in drug-resistant OCD patients, and found that low frequency rTMS provides significant but time-limited improvement in OCD patients.

5 Conclusion

The structural imaging differences between refractory OCD and OCD are summarized as follows. First of all, it seems that OFC of the refractory patients is smaller than those of the treatment-responding OCD patients and control subjects, but is comparable to that of treatment-naive patients. Second, treatment-naive patients have significantly larger left and right thalamus volumes compared with treatment-responding patients and healthy controls, while thalamic volumes are considerably different between refractory patients and treatment-responding patients.

Currently, studies on structural neuroimaging in refractory OCD constitue only a small part. Still large numbers of studies need to be done in the future. First, the regions previously ignored in refractory OCD should be examined structurally. Second, the effect of psychopharmacological and psychotherapetic approaches on brain volumes need to be comparatively examined. Third, novel treatment strategies such as DBS and rTMS should be evaluated.

In summary, OFC and thalamus are the key brain regions, and the hippocampus-amygdala complex may be associated with refractoriness to the available treatment strategies. Longitudinal studies with larger sample sizes are required.

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结构神经影像在研究难治性强迫症中的应用

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摘要：关于某些脑区参与强迫症的说法可追溯至20世纪初。在过去20年间，结构神经影像研究得到了很多重大发现，大大促进了对强迫症病因的了解。目前的功能和结构神经影像研究主要强调了额叶－纹状体－视丘－皮层和眶额－纹状体－视丘回路异常在强迫症中的作用。然而，难治性强迫症在研究中常常被忽略。本综述主要回顾了强迫症结构神经影像的一些发现，提示眶额皮层和丘脑是参与强迫症的关键区域，而且杏仁海马复合体也与该病的难治性有关。未来的研究只有增大样本量才能更全面地揭示难治性强迫症的神经结构学基础。

关键词：结构神经影像；难治性；强迫症；眶额皮层；丘脑