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REVIEW ARTICLE

Functional and Structural Neural Changes in Obsessive-compulsive Disorder after Pharmacotherapy

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Abstract: Obsessive-compulsive disorder (OCD) is an important disorder which is disturbing the quality of life and is characterized by repetitive thoughts and behaviors, now in a different category in the Diagnostic and Statistical Manual for Mental Disorders Fifth Edition (DSM 5). Neuroimaging investigations are very useful to reveal a neurobiological model of the OCD. Studies conducted in the last quarter century have shown clear results and revealed that specific cortico-subcortical circuits could be involved in the occurrence of OCD symptomatology. These neuroimaging studies pointed out some important findings for OCD patients. Our present information implicates some problems in some cortico-subcortical in the pathophysiology of OCD. In the present paper, final information on the neuroanatomy and neurochemistry of OCD was reviewed, revising the effects of anti-obsessional drugs on the structural and functional neuroimaging studies. As can be seen in the review, drug treatments can generally affect the brain structurally and functionally, suggesting that brain of OCD tends to neuroplasticity. However, it is not clear that these effects of pharmacotherapy are related to anti-obsessional drugs per se or impact on the improvement of the disorder.

Keywords: OCD, functional, structural, pharmacotherapy, neural, changes.

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is under a new diagnostic category, one being the Obsessive-Compulsive Disorder and Related Disorders in the Diagnostic and the other being the Manual of Mental Disorders Fifth Edition (DSM 5) [1]. It is well-established that OCD has two main symptoms, obsessions and compulsions. Obsessions are defined as intrusive thoughts, beliefs, or imaginations that are not solely restricted to intensive daily problems and that need to be suppressed by alternative imaginations or behaviors, and finally, that is recognized as a product of the person's mind. Compulsions are defined as urges to show repetitive behaviors or mental activities, intending to impede or reduce patient's distress. The Epidemiological Catchment Area (ECA) survey and other epidemiological studies have revealed the lifetime prevalence of OCD to be 2% to 3% [2]. OCD shows two different peak periods, teenage years and over the third decade. The ratio of female to male is close to 1/1 [3, 4]. In fact, OCD looks like a long-standing organic illness, with a variable course throughout the course of the disorder. When these patients are treated, this dimension of the disorder should be pointed out as some patients expect rapid and stable improvements throughout the progress of the disorder like infectious disorders. When considering the psychopharmacological treatment of OCD, selective serotonin reuptake inhibitors (SSRIs) and serotonin reuptake inhibitor (SRI) clomipramine are first agents to come into the mind. A considerable portion of patients with OCD is responsible to first use SRI or SSRIs. Nevertheless, it is well-established that 30% to 40% of patients do not respond to the available first treatment alternatives [5-8]. It has been described that refractoriness to OCD implicated less than 25% decreases in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score at final evaluation compared to beginning of the treatment.

In the treatment of OCD, patients who do not respond to the first line treatments, increase in doses, switching to another treatment option or augmentation strategies are preferred. The first strategy is to increase the doses [9]. In a double-blind study, it was showed that 250 to 400 mg for a day might be more effective [9, 10]. Another method is to change to the duloxetine treatment. Changing to the duloxetine was reported to be efficacious [10, 11]. Another augmentation strategy is to add clomipramine to ongoing SSRI treatment [12] or SSRI augmentation to ongoing clomipramine treatment [9, 13]. Intravenous clomipramine compared to placebo was reported efficacious in non- responsible patients to clomipramine orally [14]. Some other, not well-studied alternatives are Pindolol. It was useful to reduce Y-BOCS scores in 2.5 mg, 3 times daily, in patients who were not responsible to ≥3 serotonin reuptake inhibitor (SRI) trials in

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a double-blind, placebo-controlled study [9, 15]. Ondansetron, A 5-HT3 receptor antagonist was detected to be able to use in refractory OCD patients [9, 16].

Neuroimaging investigations are very useful to reveal a neurobiological model of the OCD. Studies conducted in the last quarter century have shown clear results and revealed that specific cortico-subcortical circuits could be involved in the occurrence of OCD symptomatology. These neuroimaging studies pointed out some important findings for OCD patients. Our present information implicates some problems in some cortico-subcortical pathways in the pathophysiology of OCD [5, 17]. Some regions have been defined as "key brain regions", including orbitofrontal cortex (OFC), thalamus, anterior cingulate cortex (ACC) and caudate nucleus. We previously conducted an MRI study in treatment-naive patients and healthy controls [18]. The results of that study showed that OCD patients had considerably reduced left and right OFC and considerably greater left and right thalamus, indicating that thalamus and OFC could be related to refractoriness to treatment in OCD. There are neuroimaging studies on other neuroanatomic regions in the OCD. Now, we can deal with the influences of the pharmacotherapy on structural and functional neuroimaging.

2. STRUCTURAL NEUROIMAGING STUDIES

Gilbert *et al*. [19] examined morphological alterations of the thalamus in pediatric OCD patients. They found thalamus to be considerably greater in the patient group, reducing after paroxetine treatment. Authors commented that volume alterations might not be related to paroxetine itself but treaty influences of it. Hoexter *et al*. [20] conducted an investigation to evaluate influences of psychopharmacological agents and cognitive-behavioral therapy (CBT) on brain volumes of OCD patients, using fluoxetine and CBT. The authors found that fluoxetine, treated patients showed increased grey matter volumes of the left putamen whereas CBT-treated ones did not show any volumetric changes, with a contrary notion that improvement itself could be affecting the volumetric changes aforementioned. In another investigation on child and adolescent OCD patients after a follow-up of six months, authors found comparable volumes for gray matter volumes [21]. One other region seems as the amygdala. It is a very critical area for all anxiety disorders since it has modulatory effects on fear conditioning. In addition, the amygdala is a region with an intensive serotonergic innervation. For these reasons, it seems that it is important for the occurrence and maintenance of OCD. With regard to amygdala, it has been performed on a study in which OCD patients showed a considerable asymmetry towards left side before the treatment period whereas after the treatment period, especially left amygdala volumes of patients with OCD statistically significantly reduced, with a correlation between decrease in left amygdala volumes and paroxetine dosage, indicating that left amygdala seemed to be important in the neuroanatomy of OCD and that paroxetine might affect neuroplasticity of amygdala in the treatment of disorder [8]. Our study team also examined two of the key brain regions, OFC and thalamus, in regard to the effects of anti-obsessional medication, and measured volumes of these regions before and after twelve weeks of the period in patients with OCD [22]. Thalamus volumes were found to reduce considerably by the treatment period while OFC volumes not to change by anti-obsessional medication, suggesting that thalamus region could have a neuroplasticity when treating OCD with drugs. On the other hand, we recently examined the effect of drugs which are used in the OCD treatment on hypophysis volumes in the OCD patients and revealed that pituitary volumes were considerably reduced in patients with OCD compared to healthy comparisons at baseline whereas they significantly changed to larger volumes throughout three months of period of treatment with selective serotonin reuptake inhibitors or clomipramine [23]. Yun *et al*. [24] studied the relationship between cortical surface and thickness, and treatment response to anti-obsessional treatment and reported cortical morphology to predict response to psychopharmacological medication in OCD patients.

3. FUNCTIONAL NEUROIMAGING STUDIES

In brief, we can say that functional neuroimaging studies performed in patients with OCD revealed these patients to have an increased activity of brain circuits consisting of the ACC, thalamus, OFC, and striatum, with some similar findings being shown same regions in childhood period OCD patients [25, 26]. In fact, our knowledge on the neuroanatomy of the OCD considerably comes from the neuroimaging investigations. Functional neuroimaging studies utilize various techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and single-photon emission tomography (SPECT), and magnetic resonance spectroscopy (MRS) techniques. These methods have implicated that the pathophysiology of OCD might have been related to wide brain areas particularly important parts of frontal cortex such as OFC, ACC, and the dorsolateral prefrontal cortex (DLPC), caudate nucleus, and thalamus [5, 27, 28]. In a review, Menzies *et al*. [29] commented that the orbito-fronto-striatal model might not be enough to explain the neural base for the OCD. Moreover, in a study evaluating OCD patients and their OCD-free relatives, it was shown that there were considerably reduced activity of some cortical areas like lateral OFC, suggesting an underlying endophenotype for OCD [27]. Most recently, Bhikram *et al*. studied the effect of an intravenous serotonin reuptake inhibitor, citalopram, on the neural substrates of OCD, to test its efficacy in OCD treatment compared to conventional psychopharmacotherapy in a small number of OCD patients and healthy comparisons during fMRI investigation. They reported that OCD patients exhibited meaningful alterations in neural activity at prefrontal region after citalopram administration intravenously than those who received placebo, and these alterations were correlated with reductions in subjective anxiety [30]. By using proton magnetic resonance spectroscopic imaging, Jang *et al*. studied regional N-acetylaspartate (NAA) levels before and after twelve weeks of period in patients being treated with citalopram and demonstrated that OCD patients had significantly reduced NAA values in some cortical areas such as prefrontal cortex, frontal white matter, and anterior cingulate at the beginning of the study compared to healthy controls, with particular raises in NAA values in the prefrontal cortex and frontal white matter in OCD patients after medication period [31]. Han *et al*. [32] reported that patients with OCD had increased ven-

tral frontal-striatal circuit activity after a treatment period. Yoo *et al*. [33] reported OCD patients to exhibit meaningful elevations of fractional anisotropy (FA) values in the corpus callosum, internal capsule and white matter in the area superolateral to the right caudate than healthy controls and that the elevations of FA were mostly no longer seen after twelve weeks of treatment with citalopram, considering that white matter changes might be reversed by pharmacotherapy. In an study, it was studied the effect of psychotropic agents on the regional cerebral blood flow (rCBF) by using 99mTc-HMPAO single photon emission computed tomography (SPECT) before and after twelve weeks of medication and was found that values of rCBF were reduced considerably in some regions including left caudate nucleus and both sides of putamen in both treatment responders and non- responders whereas in the right thalamus solely in responders, showing that thalamus could be important region to indicate treatment response, with enhanced activitity in the cerebellum and parietal lobe, and reduced activity in OFC, middle frontal gyrus, and temporal regions after clinical improvement of the OCD [34]. Lazaro *et al*. reported the patients with OCD to show considerably increased activity of middle frontal gyrus at the beginning of their study whereas the activity of left side of insula and putamen significantly decreased after six months of pharmacotherapy [21]. Ho Pian and colleagues showed pre-treatment cerebellar and whole brain HMPAO uptake to be increased in patients with OCD who were responders to fluvoxamine treatment compared to those who were not responders [35]. Wen *et al*. analyzed the correlational relationship between treatment response and features of regional cerebral blood flow (rCBF) before treatment period in OCD patients and found that higher rCBF in the anterior part of the brain and reduced rCBF in posterior part before treatment of OCD patients were a potentially signs of treatment response to OCD [36]. Shin *et al*. evaluated influences of SSRIs on brain network in 25 patients with OCD, who were not taking any treatment suffering resting-state functional MRI at the beginning of the study and after a period of sixteen weeks in seventeen ones who took SSRI treatment [37]. The authors concluded that the phenomenology of OCD might be the outcome of disturbed balance in the brain networks and that improvement in that balance by drugs could be leading to clinical improvement. Shin *et al*. evaluated the effects of selective serotonin reuptake inhibitor (SSRI) treatment on the whole-brain functional network in twenty-five drug-free OCD patients suffering resting-state functional MRI at the beginning of the study and after a period of sixteen weeks in seventeen ones who took SSRI treatment [37]. The authors concluded that OCD phenomenology might be the outcome of disrupted optimal balance in the brain networks and that improvement in that balance by drugs could be leading to clinical improvement.

CONCLUSION

In this paper, we reviewed general knowledge on the occurrence of OCD, the effects of i-obsessional drugs on the structural and functional neuroimaging studies. As observed in the review, drug treatments can generally affect the brain structurally and functionally, suggesting that brain of OCD tends to neuroplasticity. However, it is not clear that these effects of pharmacotherapy are related to anti-obsessional drugs per se or impact on the improvement of the disorder.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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