Review Article

Neuroimaging Studies in Obsessive Compulsive Disorder: A Narrative Review

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ABSTRACT

Obsessive compulsive disorder (OCD) is a relatively common psychiatric illness with a lifetime prevalence of 2–3% in general population. The pathophysiology of OCD is not yet fully understood, however over the last few decades, evidence for abnormalities of cortico-striatal-thalamic-cortico (CSTC) circuitry in etiopathogenesis of OCD has accumulated. Recent brain imaging techniques have been particularly convincing in suggesting that CSTC circuits are responsible for mediation of OCD symptoms. Neuroimaging studies, especially more recent studies using functional neuroimaging methods have looked for possible changes seen in the brain of patients with OCD, the specificity of the findings (as compared to other psychiatric illnesses) and the effects of treatment (pharmacotherapy/psychotherapy) on such changes were observed. This narrative review discusses the neuroimaging findings seen in patients with OCD with a special focus on relatively more recent neuroimaging modalities such as magnetic resonance spectroscopy and magnetoencephalography.

Key words: *Functional-magnetic resonance imaging, magnetic resonance spectroscopy, neuroimaging, obsessive compulsive disorder, positron emission tomography scan, single-photon emission computed tomography scan*

INTRODUCTION

Obsessive compulsive disorder (OCD) is characterized by recurrent intrusive thoughts (obsessions) and repetitive behavior (compulsions), often as an attempt to neutralize anxiety and distress caused by the obsessions. The lifetime prevalence in the general population is estimated at 2–3%.[1] It has considerable direct and indirect costs and has a detrimental impact on many factors of quality of life, including level of education, employment status, and financial independence of the patients and their family members.[2,3]

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The pathophysiology of OCD is not yet fully understood, however over the last few years, evidence for abnormalities of fronto cortico-striatal-thalamic circuitry has accumulated.[4-6] This narrative review discusses the neuroimaging findings seen in patients with OCD with a special focus on relatively more recent neuroimaging modalities such as magnetic resonance spectroscopy (MRS) and magnetoencephalography (MEG).

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OBSESSIVE COMPULSIVE DISORDER PATHOPHYSIOLOGY

Although OCD was considered a primarily psychiatric disorder initially, recent evidence suggests that structural and functional changes occurs in specific areas of the brain in patients with OCD leading to conceptualization of OCD as a neuropsychiatric disorder.[7] Apart from the role of serotonin system in the development of OCD, evidence also suggests a possible role of dopaminergic mechanisms in OCD manifestation.[8] Furthermore, there is growing evidence suggesting the role of gamma amino butyric acid (GABA) as well as glutamate (Glu) in the OCD expression.[9]

Clinical observation suggests that OCD has a neuro-developmental basis. There is evidence which links neurological dysfunction to OCD, such as OCD developing after head trauma, streptococcal infection, encephalitis as well as comorbid tic disorders such as Tourette's syndrome.[10] Further evidence of neurological involvement in OCD comes from the fact that these patients show increased levels of neurological soft signs as compared to healthy people.[11,12] In addition, these patients show a significant impairment in neurological function including abnormalities of motor circuits as compared to healthy controls.[13] A neuro-degenerative hypothesis has also been postulated which suggests that neuronal loss in the inhibitory pathways leads to functional hyperactivity in the cortico-limbic loop (a primary circuit implicated in OCD pathophysiology).[14]

FUNCTIONAL NEUROANATOMY OF OBSESSIVE COMPULSIVE DISORDER

In the last few decades, improvement in imaging technology has led to advancement in our understanding of neural basis of OCD pathophysiology. Recent brain imaging techniques have been particularly convincing in suggesting that specific brain circuits are responsible for mediation of OCD symptoms.[5] Pathophysiological abnormalities in the prefrontal-basal ganglia-thalamic-prefrontal circuits are believed to underpin OCD.[15] Dysfunction in these circuits may be associated with implicit processing deficits and intrusive symptoms.[16]

Orbitofrontal and cingulate cortex sends robust excitatory (glutaminergic) projections to ventral striatum and caudate nucleus. The caudate nucleus sends GABA-ergic projections to globus pallidus which, in turn, sends inhibitory projections to thalamus. Two serial inhibitory outputs suggest the possibility of reverberating circuit. This abnormality is thought of as inherent to the functional neuropathophysiology of OCD.[16,17] This circuitry is composed of two loops: A direct pathway (from cerebral cortex-striatum-globus pallidus-substantia nigra and pars reticularis-thalamus back to cortex) and an indirect pathway (from cerebral cortex - striatum-globus pallidus-subthalamic nucleus-globus pallidus rejoins common pathway-thalamus back to cortex).[7] Caudate is involved in cortical information processing for behavioral response initiation and thus, has an important role in procedural learning (i.e. acquisition of new habits and skills requiring minimal consciousness or awareness). Four cortico-striatal-thalamic-cortico (CSTC) circuits are implicated in OCD pathophysiology: (1) Circuit involving projections from sensorimotor cortex via putamen (2) circuit involving projections from paralimbic cortex via the nucleus accumbens (3) projections from orbitofrontal cortex to ventromedial caudate nucleus (4) projections from dorsolateral prefrontal cortex (DLPFC) via dorsolateral caudate nucleus.[18] Other areas implicated in OCD pathophysiology include amygdala and hippocampus. Structural changes have been reported in all these areas in patients with OCD.[19]

STRUCTURAL NEUROIMAGING STUDIES IN OBSESSIVE COMPULSIVE DISORDER

Computed tomography scan and magnetic resonance imaging

Multiple structural imaging modalities including computer tomography (CT) and magnetic resonance imaging (MRI) have been tried in patients with OCD to identify the regions involved in the pathogenesis of OCD. An X-ray CT scan study reported significantly decreased volume of caudate nucleus in patients with OCD as compared to normal healthy controls. However, other structures such as lenticular nuclei and ventricles were similar in size in both the groups suggesting a possible involvement of caudate nucleus in OCD.[20] Similarly, an early MRI study demonstrated significantly lower caudate nucleus volume in patients with OCD as compared to normal controls, but other areas including prefrontal cortex were normal.[21] Other structural imaging studies of OCD have also suggested the presence of abnormalities, mainly involving fronto-striato-thalamic circuitry.[15,22] A review of structural neuroimaging studies in anxiety disorders including OCD reported alterations in the caudate nucleus, putamen, globus pallidus, and striatal region.[23]

Voxel-based morphometry

Recently, volume-based morphometry studies have been used to explore the entire brain for candidate regions. In a study by Valente *et al*., gray matter volume was found to be increased in the orbitofrontal and

parahippocampal regions in OCD patients as compared to healthy controls.[24] A more recent study found a significant reduction of gray matter volume in inferior and medial frontal gyrus, cingulate gyrus, superior temporal gyrus, and insula, and concluded that parietal cortex has a possible role in OCD pathophysiology.[25] Similarly, a mega-analysis showed that OCD patients have significantly smaller volumes of frontal gray and white matter (WM) bilaterally including dorsomedial prefrontal cortex, anterior cingulate cortex, and inferior frontal gyrus as compared to healthy subjects.[26] Treatment-related changes have also been suggested in these areas. A recent study done on treatment naïve OCD patients reported smaller gray matter volume in the left putamen which was undetectable after treatment with fluoxetine and cognitive behavioral therapy (CBT).[27]

FUNCTIONAL NEUROIMAGING STUDIES IN OBSESSIVE COMPULSIVE DISORDER

Functional imaging techniques indirectly measure the activity levels in specific brain areas and have been used to determine whether the structures thought to be involved in OCD are abnormally active.[28] Four types of studies have been used using functional neuroimaging to know the pathophysiology of OCD: (1) Comparison of OCD patients and healthy controls at baseline (2) studying OCD patients before and after treatment and comparing them to healthy controls to measure changes in cerebral activities which may correspond to treatment (3) scanning patients during symptom provocation task and in control states and (4) scanning patients during a cognitive task and comparison conditions. Functional neuroimaging studies in OCD are consistent as compared to findings in other psychiatric illnesses.[29] Early studies of OCD used single-photon emission CT (SPECT) and positron emission tomography (PET) scans. These studies as well as recent studies using functional MRI have shown increased activation in the areas of basal ganglia (predominantly head of caudate), anterior cingulate, and orbitofrontal cortex in OCD patients as compared to normal healthy controls.[7,30]

Positron emission tomography scan

OCD and its association with disorders involving basal ganglia structures led to the suggestion that OCD patients might have abnormal metabolic activity in basal ganglia and other associated areas.[31] PET scan is an imaging technique which produces a three-dimensional image of functional processes in body using radiotracers such as fludeoxyglucose. The concentration of the tracer images indicate metabolic activity of the brain tissues. Studies using fluorodopa-PET in patients with OCD suggested increased metabolism in the orbitofrontal cortex,[32] caudate nucleus,[33] anterior cingulate cortex, lenticular nucleus and thalamus,[34] and parietal cortex.[35] PET studies have also been applied to access the alteration in local metabolic rates of glucose (LMRGlc) in OCD patients before and after treatment. The most consistently reported findings after treatment are decrease of LMRGlc in the orbito-frontal cortex,[32,36-38] anterior frontal gyrus,[34,37] and caudate nucleus.[33,36,38-41] Thus, OCD therapy is thought to ameliorate OCD symptoms by decreasing functional activity along orbitofrontal-basal ganglia-thalamo-cortical circuits. The change in glucose metabolism, although not consistent, has also been found to correlate with change in symptom severity in OCD.[39] Few studies reported that lower relative glucose metabolism in orbitofrontal cortex might be associated with greater improvement in OCD symptoms in patients treated with pharmacotherapy.[38,42] In summary, PET studies in OCD indicate increased metabolism in various regions of brain including caudate, orbito-frontal cortex, and prefrontal cortex, which are a part of CSTC circuit.

Single-photon emission computed tomography scan

Hexamethylpropyleneamine oxime-SPECT studies have demonstrated increased uptake in prefrontal region,[43] medial frontal cortex,[44] decreased uptake in the left basal ganglia,[45] and decreased uptake in the right caudate nucleus.[46] Treatment-related changes have also been reported in studies using SPECT scan. Ho Pian *et al*. in a SPECT study using fluvoxamine for 12 weeks found that regional cerebral blood flow levels decreased significantly in the left caudate and the left and right putamen in both responders and nonresponders.[47] Another study reported that responders to pharmacotherapy showed diffuse reduction of regional cerebral blood flow in prefrontal region from high pretreatment levels.[43] Diler *et al*. studied 12 children with OCD and found that caudate and prefrontal cingulate showed significant regional cerebral blood flow reduction after treatment with paroxetine for 12 weeks.[48] Similar changes have also been reported in caudate and prefrontal cortex after psychotherapy.[49,50] The findings suggest potential reversibility of the brain abnormalities with treatment seen in patients with OCD.

Some studies also focus on transporter density and receptor availability for binding of drugs in OCD.[51] A SPECT study showed decreased binding of dopamine transporters in OCD patients after treatment with selective serotonin reuptake inhibitors (SSRIs) in basal ganglia as compared to baseline, and changes in binding ratio was correlated with changes in symptom severity on Y-BOCS score.[52] These findings suggest the

potential role of dopaminergic system in basal ganglia in OCD symptom improvement.

Functional-magnetic resonance imaging

Functional-MRI (f-MRI) studies have tried to explore the alterations in brain metabolism in the brain regions of CSTC circuit in patients with OCD using conflict tasking, Stroop interference, multi-source interference tasking, and reversal learning paradigms.[53] A study done by Chamberlain *et al*. reported decreased activation in several cortical and subcortical structures including caudate and orbito-frontal cortex in OCD patients.[54] Similar findings were also reported in the first-degree relatives of OCD as compared to normal healthy controls suggesting a shared familial neurobiology. Similarly, another f-MRI study reported significantly decreased brain activation during planning in DLPFC, thalamus, and parietal cortex not only in OCD patients, but also in their monozygotic twins.[55]

Few studies also looked for possible changes in brain activation patterns before and after treatment with medications as well as psychotherapy. Nakao *et al*. found that after symptom improvement, symptom provocation task-related activation in the orbitofrontal cortex, prefrontal cortex, and anterior cingulate cortices decreased.[56] Conversely, Stroop's task-related activation in the parietal cortex and cerebellum increased. Pretreatment activation in the right cerebellum and left superior temporal gyrus was positively correlated with improvement in the Y-BOCS scale and predicted subsequent treatment response to fluvoxamine.[57] Another study suggested that following improvement with cognitive behavior therapy, the cerebellum and parietal lobe showed increased activation, and the orbitofrontal cortex, middle frontal gyrus, and temporal region showed decreased activation during Stroop task.[58] In a recent study using CBT, it was found that patients of OCD with greater clinical improvement showed more stable activation in palladium.[59] All these studies point toward the role of the various regions of CSTC circuitry being involved in OCD pathophysiology and possible normalization of such changes after effective treatment.

NEWER NEUROIMAGING MODALITIES AND OBSESSIVE COMPULSIVE DISORDER

Magnetic resonance spectroscopy

MRS allows *in vivo* and noninvasive assessment of brain biochemistry. Basic principles underlying MRS are the same as MRI, but add an additional dimension of information by detecting the resonance frequencies of different metabolites. More commonly, ^{1}H-MRS is done as a single voxel in which a spectrum is acquired from the specific area of the brain, while MRS imaging provides metabolic maps. This technique provides data regarding the levels of N-acetyl aspartate (NAA, a marker of neuronal density and integrity), choline (Cho, a marker of cellular density and precursor of neurotransmitter acetyl Choline), creatine (Cr, a marker of cellular energy), myo-inositol (mI, a marker of membrane turnover and myelination), and the complex named Glx formed by Glu and glutamine; both of them are involved in the synthesis of GABA.[60,61]

Various study designs have been used to look into OCD pathophysiology using MRS. This includes comparison of OCD patients and healthy controls,[62,63] comparison of OCD patients with other psychiatric disorders,[64] comparing OCD patients before and after treatment,[65-67] comparison of OCD treatment responders to nonresponders,[66] comparing OCD patients during performance of a cognitive task to a comparison condition,[53] and the use of genetic paradigm along with MRS to determine the association between neurological finding and genetic polymorphism.[68]

Many MRS studies reported reduction in NAA levels in OCD patients in various regions of brain involved in CSTC circuitry including corpus striatum, thalamus, basal ganglia, and anterior cingulate cortex.[69,70] This suggests reduction in neuronal viability in brain regions involved in neurobiology of OCD. Similarly, studies also suggest higher levels of Glx and Glu in patients of OCD in areas such as caudate nucleus and anterior cingulate cortex (hyperglutaminergic state).[66,70] A few studies also report an increase in the levels of mI, indicating a compensatory increase in phospholipid synthesis, membrane turnover, and myelination in the brain regions involved in the pathophysiology of OCD.[70]

Some of the studies also report treatment-related changes in these metabolite levels in patients with OCD. They suggest increase in the levels of NAA and decrease in the levels of Glx and mI after successful treatment with SSRIs.[66,71] Similar changes have also been reported by studies in which psychotherapy was used as a treatment modality.[67] However, such studies are scarce. In summary, these MRS studies suggest reduction in neuronal viability and hyperglutaminergic state in the areas of CSTC circuitry, which are potentially reversible after successful treatment.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is comparatively a younger imaging method as compared to other methods and permits the quantification of the diffusion characteristics of water molecules *in vivo*. Water molecules diffuse more freely along myelinated

tracts than across them within cerebral WM, which is known as anisotropy. Any reduction in anisotropy is indicative of altered tissue integrity and suggests change in underlying WM tracts.[72] The most commonly used parameters include fractional anisotropy, axial diffusivity, and radial diffusivity.

As with all neuroimaging studies, results of DTI studies in OCD are heterogeneous. However, a few findings are commonly reported by many of the studies. Most studies done among adult OCD population report decreased WM connectivity in OCD as compared to normal healthy controls.[73-75] Some of the studies reported increased WM connectivity, in adults and adolescent OCD patients.[76,77] Such alterations are most commonly reported in corpus callosum and cingulate bundle, anterior thalamic radiation, and parietal WM.[78,79] The finding of altered WM structures in cingulate and thalamus concurs with the concept of CSTC circuitry involvement in patients with OCD. However, changes reported in parietal WM constitute a new aspect which needs to be explored further. Such alterations vary as a function of clinical characteristics and may be amenable to pharmacologic treatment.[72]

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a neuroimaging technique well-suited for psychiatric disorders with improved safety, no requirement of larger devices, and lower cost, as compared to other techniques. NIRS has almost 10 times higher spatial resolution and can be used repeatedly over a prolonged period in a normal posture unlike other neuroimaging techniques. Although it has been used widely to assess brain function in psychiatric illnesses such as schizophrenia, depression, and bipolar disorder, only few studies have looked for potential changes seen in patients with OCD using NIRS. Adult patients with OCD showed reduced prefrontal cortical hemodynamic responses as compared to normal controls during verbal fluency and Stroop color-word tasks.[80,81] Similar finding has also been reported in pediatric patients.[82] These studies suggest a notion that the prefrontal cortex plays an important role in the pathophysiology of OCD. However, studies using NIRS in OCD are limited with a small sample size and so the findings need to be replicated using a larger sample.

Magnetoencephalography

Recently, MEG has been used to investigate spontaneous brain activity in patients with OCD. It is a neuroimaging tool with high temporal as well as spatial resolution. It represents brain activity more directly than techniques such as SPECT or PET (which uses intermediates such as cerebral blood flow or glucose metabolism). MEG is a potential localizing tool for neuronal function, especially in psychiatric disorders. An initial study examined the evoked MEG signals in OCD patients during the encoding, retention, and retrieval phases of delayed matching-to-sample working memory task and reported that increased MEG activity was phase-specific in OCD.[83] During encoding, the activation was increased in insula. During retention, the activation was reduced in DLPFC and occipital and parietal sulcus. During retrieval, the activation was increased in insula extending toward the parietal cortex. The results are consistent with a hypothesis of compensatory effortful inhibitory control. Another study done on ten OCD subjects reported clustering of slow MEG activity over the left DLPFC providing further evidence of role of prefrontal cortex in OCD pathophysiology.[84] Similarly, another study reported that prestimulus alpha was lower in OCD patients as compared to controls.[85] Task-phase specific reduction in alpha event-related desynchronization was also seen in thalamocortical network which suggested relation of alpha oscillations and thalamocortical network to the etiology of OCD.

Limitations of neuroimaging studies in obsessive compulsive disorder research

As already described, neuroimaging studies have not produced consistent results. Although, most of these studies suggest a role of CSTC circuitry and other associated areas, many studies fail to do so. These differences can be attributed to a multitude of factors including small sample sizes resulting in insufficient statistical power. Many studies included patients with other comorbid axis-I illnesses or patients already on psychotropics, making it difficult to ascertain specificity of the findings reported.[64,86] Matching the OCD patients with controls, especially gender and age is also a critical factor, which might lead to mixed results. As few studies only include female patients, it is difficult to compare their results with other studies.[87] Heterogeneity also exists in the methodology of these studies in terms of their inclusion and exclusion criteria. Severity of illness, age of onset, and duration of illness may all have a bearing on the findings and so, classifying the patients in one group as OCD (which is a heterogeneous group with a diverse set of symptoms) may lead to difficulties in interpretation. In addition, it is important to study the differential neural correlates of specific OCD symptoms which may have the differences in their neural basis.[88] Various imaging-related issues also lead to difficulties in interpretation. For example, a voxel-based method gives details of specific brain regions and so, it has the potential to miss the abnormalities in other brain areas. The differences such as spatial resolutions also lead to difficulty in interpretation.

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the differences in study methodology of the studies, it is evident that neuroimaging studies point toward a role of CSTC circuitry in the pathophysiology of OCD. Various neuro-imaging studies conducted till date have broadly implicated mainly four regions in the pathophysiology of OCD symptoms. These regions are orbitofrontal cortex, cingulate cortex, thalamus, and the head of caudate nucleus. Several authors have suggested that these regions form a circuit that is hyperactive in OCD. Dysfunction in these circuitry plays an important role in implicit processing deficits and intrusive symptoms.[16] These findings are further supported by neuropsychological and treatment studies. However, there is a need for further studies to explore the role of other brain areas in the pathophysiology of OCD. For example, some studies implicate amygdala in OCD pathophysiology.[89] Models involving amygdala are important to understand the OCD pathophysiology as it has been involved in emotional appraisal of external stimuli and acquiring and consolidating reactions to conditioned fear (factors relevant to OCD symptomatology).[90] Disorder-specific changes in the brain also need to be studied in greater depths. The role of CSTC circuitry and its application in OCD symptomatology is still in its infancy and such explanatory model needs to be studied. More studies to find out the specific functional abnormalities within this circuit are required. Longitudinal studies are still limited and so there is a need to follow the unfolding of changes occurring in brain as OCD symptoms evolve (using a high-risk group such as the first-degree relatives of patients with OCD).This may lead to possible identification of specific brain regions involved in the development of specific symptom (obsession, compulsion, urge intensification, and so on). It would provide a more comprehensive and complete understanding of the disorder and would also help in determining the most appropriate time for treatment induction.

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