Neuroimaging Studies in Obsessive Compulsive Disorder: A Narrative Review

Arpit Parmar, Siddharth Sarkar

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]

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).

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Parmar A, Sarkar S. Neuroimaging studies in obsessive compulsive disorder: A narrative review. Indian J Psychol Med 2016;38:386-94.

Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Arpit Parmar
Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India. E-mail: drarpitparmar@yahoo.in
OBSESSIVE COMPULSIVE DISORDER PATHOPHYSIOLOGY

Although OCD was considered a primarily psychiatric disorder initially, recent evidence suggests that structural and functional changes occur 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.[3] 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 GABAergic 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 rejoin 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. 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. 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. 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).

**FUNCTIONAL NEUROIMAGING STUDIES IN OBSESSIVE COMPELLUSIVE 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. 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. 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.

**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. 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, caudate nucleus, anterior cingulate cortex, lenticular nucleus and thalamus, and parietal cortex. 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, anterior frontal gyrus, and caudate nucleus. 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. 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. 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, medial frontal cortex, decreased uptake in the left basal ganglia, and decreased uptake in the right caudate nucleus. 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. Another study reported that responders to pharmacotherapy showed diffuse reduction of regional cerebral blood flow in prefrontal region from high pretreatment levels. 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. Similar changes have also been reported in caudate and prefrontal cortex after psychotherapy. 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. 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. 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. 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. 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.

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. 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. 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. In a recent study using CBT, it was found that patients of OCD with greater clinical improvement showed more stable activation in palladium. 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, 1H-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.

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

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. 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). 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.

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. Similar changes have also been reported by studies in which psychotherapy was used as a treatment modality. 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.\cite{72} The 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.\cite{73-75} Some of the studies reported increased WM connectivity, in adults and adolescent OCD patients.\cite{76,77} Such alterations are most commonly reported in corpus callosum and cingulate bundle, anterior thalamic radiation, and parietal WM.\cite{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.\cite{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.\cite{80,81} Similar finding has also been reported in pediatric patients.\cite{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.\cite{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.\cite{84} Similarly, another study reported that prestimulus alpha was lower in OCD patients as compared to controls.\cite{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.\cite{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.\cite{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.\cite{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. 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. 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). 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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Valleni-Basile LA, Garrison CZ, Jackson KL, Waller JL, McKeown RE, Addy CL, et al. Frequency of obsessive-compulsive disorder in a community sample of young adolescents. J Am Acad Child Adolesc Psychiatry 1994;33:782-91.
2. Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: Summary results, sensitivity analysis and future directions. Bull World Health Organ 1994;72:485-509.
3. Kroll M, Matschinger H, Angermeyer MC. Subjective quality of life of patients with obsessive-compulsive disorder. Soc Psychiatry Psychiatr Epidemiol 2006;41:662-8.
4. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl 1998;35:26-37.
5. Stein DJ, Goodman WK, Rauch SL. The cognitive-affective neuroscience of obsessive-compulsive disorder. Curr Psychiatry Rep 2000;2:341-6.
6. Evans DW, Lewis MD, Iobst E. The role of the orbitofrontal cortex in normally developing compulsive-like behaviors and obsessive-compulsive disorder. Brain Cogn 2004;55:220-34.
7. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 2000;23:563-86.
8. Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF. Beyond the serotonin hypothesis: A role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry 1990;51:36-43.
9. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment. Pharmacol Ther 2011;132:314-32.
10. Murphy DL, Timpano KR, Wheaton MG, Greenberg RD, Miguel EC. Obsessive-compulsive disorder and its related disorders: A reappraisal of obsessive-compulsive spectrum concepts. Dialogues Clin Neurosci 2010;12:131-48.
11. Bolton D, Gibb W, Lees A, Raven P, Gray JA, Chen E, et al. Neurological soft signs in obsessive compulsive disorder: Standardised assessment and comparison with schizophrenia. Behav Neurol 1998;11:197-204.
12. Guz H, Aygun D. Neurological soft signs in obsessive-compulsive disorder. Neurol India 2004;52:72-5.
13. Mercadante MT, Diniz JB, Hounie AG, Ferrão Y, Alvarenga P, Broto S, et al. Obsessive-compulsive spectrum disorders in rheumatic fever patients. J Neuropsychiatry Clin Neurosci 2005;17:544-7.
14. Ebert D, Speck O, König A, Berger M, Hennig J, Hohagen F. 1H-magnetic resonance spectroscopy in obsessive-compulsive disorder: Evidence for neuronal loss in the cingulate gyrus and the right striatum. Psychiatry Res 1997;74:173-6.
15. Insel TR. Toward a neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49:739-44.
16. Rauch SL, Savage CR. Neuroimaging and neuropsychology of the striatum. Bridging basic science and clinical practice. Psychiatr Clin North Am 1997;20:741-68.
17. Rauch SL. Neuroimaging and neuropsychiatric models pertaining to the neurosurgical treatment of psychiatric disorders. Neurosurg Clin N Am 2003;14:213-23, vii-ix.
18. Lochner C, Stein DJ. Heterogeneity of obsessive-compulsive disorder: A literature review. Harv Rev Psychiatry 2003;11:113-32.
19. Adler CM, McDonough-Ryan P, Sax KW, Holland SK, Arndt S, Strakowski SM. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. J Psychiatr Res 2000;34:317-24.
20. Luxenberg JS, Swedo SE, Flament MF, Friedland RP, Rapoport J, Rapoport SI. Neuroanatomical abnormalities in obsessive-compulsive disorder detected with quantitative X-ray computed tomography. Am J Psychiatry 1988;145:1089-93.
21. Robinson D, Wu H, Munne RA, Ashtari M, Alvir JM,
Reduced caudate nucleus volume in obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52:393-8.

22. Rotge JY, Guehl D, Diharre N, Bignol J, Biculac B, Allard M, et al. Meta-analysis of brain volume changes in obsessive-compulsive disorder. Biol Psychiatry 2009;65:75-83.

23. Ferrari MC, Busatto GF, McGuire PK, Crippa JA. Structural magnetic resonance imaging in anxiety disorders: An update of research findings. Rev Bras Psiquiatr 2008;30:251-64.

24. Valente AA Jr., Miguel EC, Castro CC, Amarino E Jr., Duran FL, Buchpiguel CA, et al. Regional gray matter abnormalities in obsessive-compulsive disorder: A voxel-based morphometry study. Biol Psychiatry 2005;58:479-87.

25. Yoo SY, Roh MS, Choi JS, Kang DH, Ha TH, Lee JM, et al. Voxel-based morphometry study of gray matter abnormalities in obsessive-compulsive disorder. J Korean Med Sci 2008;23:24-30.

26. de Wit SJ, Alonso P, Schweren L, Mataix‑Cols D, Lochner C, Menchon JM, et al. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. Am J Psychiatry 2014;171:340-9.

27. Hoexter MQ, de Souza Duran FL, D’Alcante CC, Dougherty DD, Shavitt RG, Lopes AC, et al. Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: A randomized clinical trial. Neuropsychopharmacology 2012;37:734-45.

28. Lázaro L, Caldu X, Junqué C, Bargalló N, Andrés S, Morer A, et al. Cerebral activation in children and adolescents with obsessive-compulsive disorder before and after treatment: A functional MRI study. J Psychiatric Res 2008;42:1051-9.

29. Milad MR, Rauch SL. Obsessive-compulsive disorder: Beyond segregated cortico-striatal pathways. Trends Cogn Sci 2012;16:43-51.

30. Breiter HC, Rauch SL. Functional MRI and the study of OCD: From symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdala. Neuroimage 1996;4 (3 Pt 3):S127-38.

31. Rapoport JL. Obsessive compulsive disorder and basal ganglia dysfunction. Psychol Med 1990;20:465-9.

32. Kang DH, Kwon JS, Kim JJ, Yoon T, Park HJ, Kim MS, et al. Brain glucose metabolic changes associated with neuropsychological improvements after 4 months of treatment in patients with obsessive-compulsive disorder. Acta Psychiatr Scand 2003;107:291-7.

33. Apostolova I, Block S, Buchert R, Osen B, Conrad M, Tabrizian S, et al. Effects of behavioral therapy or pharmacotherapy on brain glucose metabolism in subjects with obsessive-compulsive disorder as assessed by brain FDG PET. Psychiatry Res 2010;184:105-16.

34. Perani D, Colombo C, Bressi S, Bonfanti A, Grassi F, Scaroni S, et al. [18F] FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. Br J Psychiatry 1995;166:244-50.

35. Nordahl TE, Benkelfat C, Semple WE, Gross M, King AC, Cohen RM. Cerebral glucose metabolic rates in obsessive-compulsive disorder. Neuropsychopharmacology 1989;2:23-8.

36. Benkelfat C, Nordahl TE, Semple WE, King AC, Murphy DL, Cohen RM. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. Patients treated with clomipramine. Arch Gen Psychiatry 1990;47:840-8.

37. Swedo SE, Pietrini P, Leonard HL, Scharpio MB, Retten EC, Goldberger EL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch Gen Psychiatry 1992;49:680-4.

38. Saxena S, Brody AL, Maudsley KM, Dunkin J, Colgan M, Alborzian S, et al. Localized orbital-frontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. Neuropsychopharmacology 1999;21:683-93.

39. Baxter LR Jr., Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazzolotti JC, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49:681-9.

40. Schwartz JM, Stoessell FW, Baxter LR Jr., Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 1996;53:109-13.

41. Hansen ES, Hasselbalch S, Law I, Bolwig TG. The caudate nucleus in obsessive-compulsive disorder. Reduced metabolism following treatment with paroxetine: A PET study. Int J Neuropsychopharmacol 2002;5:1-10.

42. Brody AL, Saxena S, Schwartz JM, Stoessell FW, Maudsley K, Phelps ME, et al. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive-compulsive disorder. Psychiatry Res 1998;84:1-6.

43. Hoehn-Saric R, Schlaepfer TE, Greenberg BD, McLeod DR, Pearlson GD, Wong SH. Cerebral blood flow in obsessive-compulsive patients with major depression: Effect of treatment with sertraline or desipramine on treatment responders and non-responders. Psychiatry Res 2001;108:89-100.

44. Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE. Elevated medial-frontal cerebral blood flow in obsessive-compulsive patients: A SPECT study. Am J Psychiatry 1991;148:1240-2.

45. Adams BL, Warneke LB, McEwan AJ, Fraser BA. Single photon emission computerized tomography in obsessive compulsive disorder: A preliminary study. J Psychiatry Neurosci 1993;18:109-12.

46. Lucey JV, Costa DC, Adshead G, Deahl M, Busatto G, Gacinovic S, et al. Brain blood flow in anxiety disorders. OCD, panic disorder with agoraphobia, and post-traumatic stress disorder on 99mTcHMPAO single photon emission tomography (SPECT). Br J Psychiatry 1997;171:346-50.

47. Ho Pian KL, van Megen HJ, Ramsey NF, Mandl R, van Rijk PP, Wynne HJ, et al. Decreased thalamic blood flow in obsessive-compulsive disorder patients responding to fluvoxamine. Psychiatry Res 2005;138:89-97.

48. Diler RS, Kibar M, Avci A. Pharmacotherapy and regional cerebral blood flow in children with obsessive-compulsive disorder. Yonsei Med J 2004;45:90-9.

49. Nakatani E, Nakgawa A, Ohara Y, Goto S, Uozumi N, Iwakiri M, et al. Effects of behavior therapy on regional cerebral blood flow in obsessive-compulsive disorder. Psychiatry Res 2003;124:113-20.

50. Yamashita T, Nakaaki S, Omori IM, Hashimoto N, Shinagawa Y, Hongo J, et al. Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder. Psychiatry Res 2009;172:242-50.

51. Carey FD, Warwick J, Niehaus DJ, van der Linden G, van Heerden BB, Harvey BH, et al. Single photon emission computed tomography (SPECT) of anxiety disorders before and after treatment with citalopram. BMC Psychiatry 2004;4:30.

52. Kim CH, Cheon KA, Koo MS, Ryu YH, Lee JD, Chang JW,
et al. Dopamine transporter density in the basal ganglia in obsessive-compulsive disorder, measured with [123I] IPT SPECT before and after treatment with serotonin reuptake inhibitors. Neuropsychobiology 2007;55:156-62.

53. Yücel M, Wood SJ, Wellard RM, Harrison BJ, Fornito A, Pujol J, et al. Anterior cingulate glutamate-glutamine levels predict symptom severity in women with obsessive-compulsive disorder. Aust N Z J Psychiatry 2008;42:467-77.

54. Chamberlain SR, Menzies L, Hampshire A, Suckling J, Fineberg NA, del Campo N, et al. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science 2008;321:421-2.

55. den Braber A, Ent DV, Blokland GA, van Grootheest DS, Barclay PB, Hoehn-Saric R. Proton magnetic resonance spectroscopy study of brain N-acetylaspartate in patients with obsessive-compulsive disorder after symptom improvement. Psychiatry Res 2014;202:53-9.

56. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: A functional magnetic resonance imaging study. Biol Psychiatry 2005;57:901-10.

57. Sanematsu H, Nakao T, Yoshiura T, Nabeyama M, Togao O, Tomita M, et al. Predictors of treatment response to fluvoxamine in obsessive-compulsive disorder: An fMRI study. J Psychiatr Res 2010;44:193-200.

58. Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, et al. Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. Psychiatry Res 2008;163:236-47.

59. Freyer T, Klöppel S, Tüscher O, Kordon A, Zuwrowski B, Kuelz AK, et al. Frontostriatal activation in patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. Psychol Med 2011;41:207-16.

60. Baslow MH. N-acetylaspartate in the vertebrate brain: Metabolism and function. Neurochem Res 2003;28:941-53.

61. Mohamed MA, Smith MA, Schlund MW, Nestadt G, Barker PB, Hoehn-Saric R. Proton magnetic resonance spectroscopy in obsessive-compulsive disorder: A pilot investigation comparing treatment responders and non-responders. Psychiatry Res 2007;156:175-9.

62. Starck G, Ljungberg M, Nilsson M, Jönsson L, Lundberg S, Ivarsson T, et al. A 1H magnetic resonance spectroscopy study in adults with obsessive compulsive disorder: Relationship between metabolite concentrations and symptom severity. J Neural Transm (Vienna) 2008;115:1051-62.

63. Atmaca M, Yildirim H, Ozdemir H, Koc M, Ozler S, Tetzcan E. Neurochemistry of the hippocampus in patients with obsessive-compulsive disorder. Psychiatry Clin Neurosci 2009;63:486-90.

64. Smith EA, Russell A, Lorch E, Banerjee SP, Rose M, Ivey J, et al. Increased medial thalamic choline found in pediatric patients with obsessive-compulsive disorder versus major depression or healthy control subjects: A magnetic resonance spectroscopy study. Biol Psychiatry 2003;54:1399-405.

65. Jang JH, Kwon JS, Jang DP, Moon WJ, Lee JM, Ha TH, et al. A proton MRI study of brain N-acetylaspartate level after 12 weeks of citalopram treatment in drug-naive patients with obsessive-compulsive disorder. Am J Psychiatry 2006;163:1202-7.

66. Lázaro L, Bargalló N, Andrés S, Falcón C, Morer A, Junqué C, et al. Proton magnetic resonance spectroscopy in pediatric obsessive-compulsive disorder: Longitudinal study before and after treatment. Psychiatry Res 2012;201:17-24.

67. Whiteside SP, Abramowitz JS, Port JD. Decreased caudate N-acetyl-l-aspartic acid in pediatric obsessive-compulsive disorder and the effects of behavior therapy. Psychiatry Res 2012;202:53-9.

68. Arnold PD, Macmaster FP, Richter MA, Hanna GL, Sicard T, Burroughs E, et al. Glutamate receptor gene (GRIN2B) associated with reduced anterior cingulate glutamatergic concentration in pediatric obsessive-compulsive disorder. Psychiatry Res 2009;172:136-9.

69. Tükel R, Aydin K, Ertekin E, Özüyıldırım SS, Taravari V. Proton magnetic resonance spectroscopy in obsessive-compulsive disorder: Evidence for reduced neuronal integrity in the anterior cingulate. Psychiatry Res 2014;224:275-80.

70. Gnanavel S, Sharan P, Khandelwal S, Sharma U, Jagannathan NR. Neurochemicals measured by 1H-MR spectroscopy: Putative vulnerability biomarkers for obsessive compulsive disorder. MAGMA 2014;27:407-17.

71. Tükel R, Aydin K, Ertekin E, Özüyıldırım SS, Barburuglu M. 1H-magnetic resonance spectroscopy in obsessive-compulsive disorder: Effects of 12 weeks of sertraline treatment on brain metabolites. Eur Arch Psychiatry Clin Neurosci 2015;265:219-26.

72. Koch K, Reess TJ, Rus OG, Zimmer C, Zaudig M. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): A review. J Psychiatr Res 2014;54:26-35.

73. Admon R, Bleich-Cohen M, Weizram R, Poyurovsky M, Faragian S, Hendler T. Functional and structural neural indices of risk aversion in obsessive-compulsive disorder (OCD). Psychiatry Res 2012;203:207-13.

74. Fan Q, Yan X, Wang J, Chen Y, Wang X, Li C, et al. Abnormalities of white matter microstructure in unmedicated obsessive-compulsive disorder and changes after medication. PLoS One 2012;7:e35889.

75. Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Nishimura T, et al. Diffusion tensor imaging and tract-based spatial statistics in obsessive-compulsive disorder. J Psychiatr Res 2011;45:687-90.

76. Li F, Huang X, Yang Y, Li B, Wu Q, Zhang T, et al. Microstructural brain abnormalities in patients with obsessive-compulsive disorder: Diffusion-tensor MR imaging study at 3.0 T. Radiology 2011;260:216-23.

77. Zarei M, Mataix-Cols D, Heyman I, Hough M, Doherty J, Burge L, et al. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. Biol Psychiatry 2011;70:1083-90.

78. Fontenelle LF, Harrison BJ, Yücel M, Pujol J, Fujiwara H, Nishimura T, et al. Diffusion tensor imaging and tract-based spatial statistics in obsessive-compulsive disorder. J Psychiatr Res 2011;45:687-90.

79. Barburuglu M. 1H-magnetic resonance spectroscopy: Putative vulnerability biomarkers for obsessive compulsive disorder (OCD). Psychiatry Res 2012;203:207-13.

80. Fan Q, Yan X, Wang J, Chen Y, Wang X, Li C, et al. Abnormalities of white matter microstructure in unmedicated obsessive-compulsive disorder and changes after medication. PLoS One 2012;7:e35889.

81. Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Nishimura T, et al. Diffusion tensor imaging and tract-based spatial statistics in obsessive-compulsive disorder. J Psychiatr Res 2011;45:687-90.

82. Li F, Huang X, Yang Y, Li B, Wu Q, Zhang T, et al. Microstructural brain abnormalities in patients with obsessive-compulsive disorder: Diffusion-tensor MR imaging study at 3.0 T. Radiology 2011;260:216-23.

83. Zarei M, Mataix-Cols D, Heyman I, Hough M, Doherty J, Burge L, et al. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. Biol Psychiatry 2011;70:1083-90.

84. Fontenelle LF, Harrison BJ, Yücel M, Pujol J, Fujiwara H, Nishimura T, et al. Diffusion tensor imaging and tract-based spatial statistics in obsessive-compulsive disorder. J Psychiatr Res 2011;45:687-90.

85. Barburuglu M. 1H-magnetic resonance spectroscopy: Putative vulnerability biomarkers for obsessive compulsive disorder (OCD). Psychiatry Res 2012;203:207-13.

86. Fan Q, Yan X, Wang J, Chen Y, Wang X, Li C, et al. Abnormalities of white matter microstructure in unmedicated obsessive-compulsive disorder and changes after medication. PLoS One 2012;7:e35889.
Ahlfors SP. Increased MEG activation in OCD reflects a compensatory mechanism specific to the phase of a visual working memory task. Neuroimage 2005;24:1180-91.

84. Maihöfner C, Sperling W, Kaltenhäuser M, Bleich S, de Zwaan M, Wittfång J, et al. Spontaneous magnetoencephalographic activity in patients with obsessive-compulsive disorder. Brain Res 2007;1129:200-5.

85. Ciesielski KT, Hämäläinen MS, Geller DA, Wilhelm S, Goldsmith TE, Ahlfors SP. Dissociation between MEG alpha modulation and performance accuracy on visual working memory task in obsessive compulsive disorder. Hum Brain Mapp 2007;28:1401-14.

86. Mathew SJ, Mao X, Coplan JD, Smith EL, Sackeim HA, Gorman JM, et al. Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: A proton magnetic resonance spectroscopic imaging study. Am J Psychiatry 2004;161:1119-21.

87. Jenike MA, Breiter HC, Baer L, Kennedy DN, Savage CR, Olivares MJ, et al. Cerebral structural abnormalities in obsessive-compulsive disorder: A quantitative morphometric magnetic resonance imaging study. Arch Gen Psychiatry 1996;53:625-32.

88. Rauch SL, Dougherty DD, Shin LM, Alpert NM, Manzo P, Leahy L, et al. Neural correlates of factor-analyzed OCD symptom dimensions: A PET study. CNS Spectr 1998;3:37-43.

89. Szaszko PR, Robinson D, Alvir JM, Bilder RM, Lencz T, Ashtari M, et al. Orbital frontal and amygdala volume reductions in obsessive-compulsive disorder. Arch Gen Psychiatry 1999;56:913-9.

90. Rauch SL. Neuroimaging research and the neurobiology of obsessive-compulsive disorder: Where do we go from here? Biol Psychiatry 2000;47:168-70.