Review

Tomas Leon[1,2]
María-Jose Garcia[2,3]
Ingrid Danke[2,4]
Pablo Toro[2,5]

Resting State in Obsessive-Compulsive Disorder. A review of the literature

[1]Psiquiatra
[2]Departamento de Psiquiatría, Facultad de Medicina Pontificia Universidad Católica de Chile
[3]Psicóloga
[4]Interna de Medicina
[5]Profesor Adjunto

Introduction. Obsessive-compulsive disorder (OCD) is a chronic disease that may have a great impact on functionality.

The neuroimaging study on OCD has been advancing along with the advance in the technique. Functional neuroimages suggest the participation of the prefrontal cortex and basal ganglia, forming a subcortical cortex system.

Study of the resting state is a new radiological technique that makes it possible to see connectivity and activity of the neuronal zones during rest. It has been used in many psychiatric conditions, among them OCD.

Objective. To review the studies on resting state in OCD.

Method. A systematic search was made in PubMed, Scielo and Liliacs, and 11 works for found for review.

Results. OCD would be caused by variations in different brain circuits. The constant perception of error and checking need could be due to an internal hyperconnection in the cingulate cortex. Difficulty to control compulsions could be caused by alterations on the prefrontal cortex level. No alterations per se of the OCD and absences in controls have been found. The differences would be more qualitative than quantitative, the OCD being a deregulation of normal processes.

Keywords: OCD, Resting state, Default network

Actas Esp Psiquiatr 2014;42(5):250-8

Estado de Reposo (Resting State) en Trastorno Obsesivo Compulsivo. Una revisión de la literatura

Introducción. El trastorno obsesivo compulsivo (TOC) es una enfermedad crónica que puede causar gran impacto en la funcionalidad.

El estudio de las neuroimágenes en TOC ha ido avanzando de la mano con el avance de la técnica. Las neuroimágenes funcionales sugieren la participación de la corteza prefrontal y los ganglios basales, formando un sistema córtico subcortical.

El estudio del estado de reposo es una nueva técnica radiológica que permite ver la conectividad y actividad de zonas neuronales durante el reposo. Se ha usado en múltiples patologías psiquiátricas, entre ellas TOC.

Objetivo. Revisar los estudios de estado de reposo en TOC.

Método. Se realizó una búsqueda sistemática en PubMed, Scielo y Liliacs, encontrándose 11 trabajos para la revisión.

Resultados. TOC sería causado por variaciones en distintos circuitos cerebrales. La percepción constante de error y necesidad de chequeo podría deberse a una hiperconexión interna en la corteza cingulada. La dificultad para el control de las compulsiones podría ser causada por alteraciones a nivel de la corteza prefrontal. No se han encontrado alteraciones propias del TOC y ausentes en controles, las diferencias serían más cualitativas que cuantitativas, siendo el TOC una desregulación de procesos normales.

Palabras clave: TOC, Estado de reposo, Red por defecto

Correspondencie:
Pablo Toro E.
Tel 27548870
Camino El Alba 12351
Chile
E-mail: ptoro@uc.cl

INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by the presence of recurrent ideas, images or thoughts, called obsessions. These may be accompanied by acts, ideas or rituals whose function is to calm the anguish generated by the obsession, the compulsions. Furthermore, these symptoms should not be caused by any medical disease or substance and may be due to a significant alteration in the functioning of the subject.[1]

OCD is a chronic disease that may become disabling from a social and work point of view. In 1996, the WHO considered it to be one of the 10 conditions with the greatest amount of years lost.[2-4]

It has a prevalence of 2-3% in the population.[5-7] OCD has been characterized by having a heterogeneous presentation, where biological (genetic, neurophysiological, hormonal, etc.), social and environmental aspects play a role in its manifestation.[8]

In regards to the biological aspects, there is evidence of a genetic component, given its high inheritability. There is agreement between monocygotes of 63-87%. Furthermore, the risk of having OCD in first-degree relatives is increased 10 times.[9] However, no causal gene has been found yet, a polygenic inheritance being suspected, with some participation of the serotonin transporter gene.[10]

However, the anatomic and brain function correlates of OCD have not been totally elucidated.

NEUROIMAGES IN OCD

There has been a huge boom in research on OCD images which has been advancing along with improvement of the neuroimaging techniques.

Structural neuroanatomy

First, on the level of structural neuroanatomy, the presence of a circuit that links cortical and subcortical structures in charge of behavioral control and determines the salience of that perceived has been found. This circuit goes from the orbitofrontal cortex (OFC) located in the prefrontal cortex towards the ventral striatum and caudate head to the dorsomedial thalamus to then return to the OFC. Subsequent studies have added the hippocampus, anterior cingulate cortex (ACC) and amygdala to this circuit, which are in charge of providing the emotional component to our decisions.[11,12]

Because of the proven association between alterations in this circuit and behavioral modifications, especially in impulse control and decision-making,[13-15] its participation in OCD has been investigated. A decrease in the OFC size has been found on the MRI, a finding that has often been replicated.[16-19] Furthermore, alterations have been observed in other areas of the circuit, as a reduction in stratial size, [20,21] increase in size of the ACC,[22] thalamus[19] and basal ganglia.[23]

Functional neuroanatomy

The hypothesis on the OFC participation in OCD has been confirmed in several studies with functional images during rest. Hypermetabolism in OFC and in the head of the caudate nucleus has been demonstrated.[24]

In addition, the association of these alterations with the symptom type and intensity of obsessive patients has been investigated. PET studies have shown that patients with a predominance of obsessions and compulsions related with hygiene have a bilateral increase of ACC perfusion, while there is an increase of flow in the striate in those with checking symptoms, on the contrary to those with symmetry obsesions.[30]

Symptomatic stimulation tests have been performed in most of the studies performed with functional magnetic resonance, finding an increase in the activation of OFC, ACC, striate, amygdala and insula in patients versus controls.[25-28] Brain activity in these areas is not only characteristic of patients but also of controls, although it is less in the latter.[29] Furthermore, in patients with cleaning obsessions, activation is greater in the areas involved in perception of emotion and displeasure (visual and insular cortex regions), together with ventrolateral prefrontal cortex, parahippocampal gyrus and amygdala.[31] In those with checking obsessions, there is greater activation of the frontal-striatal and thalamus regions and in patients with hoarding, the glucose metabolism is reduced in the posterior cingulate gyrus (*vs* controls) and dorsal anterior cingulate cortex (*vs* non-hoarding OCD).[32]

Another focus of the study is on the influence of the pharmacological therapy and psychotherapy on the above-described alterations, where it has been found that lower metabolism in the OFC could predict better response to pharmacological and cognitive-behavioral therapy.[33,34]

It stands out that most of these studies were performed with the "region of interest" method in which the investigator examines the brain area specifically to the spot where some alteration may be found. This makes it possible to specifically focus the study, but leaves many areas without analysis.

Voxex Based Morphometry (VBM) is a technique that makes it possible to study the whole brain, without the need for a previous hypothesis. These studies have demonstrated

that there is a decrease in gray matter density in the OFC,[35,36] together with an increase in stratial gray matter,[36] in OCD patients *vs* controls.

BRAIN RESTING STATE

The brain resting state (RS) study is a new functional neuroimaging technique whose principle objective is the analysis of brain activity with the subject in resting state, without a specific mental activity. The neural network that activates when in resting state is called the default network. This technique appears to be the ideal one for the study of psychiatric condition in general, since it is independent of the test application and therefore, more objective.[37] Another benefit is that it is less expensive and less invasive than the PET or SPECT.[38,39]

The capacity of the functional magnetic resonance (fRNM) has been used in order to investigate these connections in order to capture small variations in the brain tissue density, which is modified according to brain oxygenation level dependent (BOLD). Thus, the BOLD effect is a reflection of the brain activity. Previous studies have shown that synchrony of activity between two brain zones shows that they are part of the same neural circuit.[40-45] This means that if synchrony is lower than normal between the two brain zones whose function are normally coordinated, it will be because of a hypocoordination between them, so that the functional connectively between both zones will be decreased.

This technique has already been used in schizophrenia[46] and major depressive disorder,[47] finding alterations in the default mode neural network.

The study of the brain in resting state has started to be used to analyze patients with OCD. However, we are not aware of any publication that has reviewed and systematically summarized the current information on this subject.

OBJECTIVE

This work has aimed to perform a systematic search and to review the literature published on the subject of RS in its OCD application. We have hypothesized that alterations will be found between the cortex and subcortical structures in agreement with that found in structural neuroimages. However, given that little information may be found, a purely descriptive analysis will be made of the results.

METHOD

A systematic search was performed from 1 August 2012 to 30 August 2012 in Pubmed, Scielo and Liliacs, with the MESH terms "*OCD,*" "*Resting State*" and "*Default Network.*" Thirty works were obtained from the search for works in Spanish and English. The "related references" found in Pubmed and the references found in the initial 30 works were then reviewed.

The result was a total of 323 *papers*. Reading the *abstracts,* 40 works were selected that were then read completely by one of the authors. Eleven works were selected that fulfilled the characteristics of analyzing patients with OCD, diagnosed by DSM-IV criteria,[1] using the SCID I structured interview,[48] without considering if they were taking medication or not, and that fMRI with resting state protocol were applied to them.

Exclusion criteria used were that a resting state analysis method other than fMRI, for example EEG, was used. Furthermore, works in which neurocognitive tests or symptom evocation tests and/or that were not analyzed in the resting state.

RESULTS

Up to now, it has been observed in the 11 works selected that the research has lacked systematic organization so that the works are difficult to compare. Therefore, we have preferred to make a brief description of each work and then to analyze the common elements found.

CORTICAL ALTERATIONS

The results corresponding to this section are summarized in table 1.

The work of Yang in 2010[49] compared 22 treatment-naive patients diagnosed of OCD with 22 controls. It was sought to measure regional homogeneity. This is defined as the temporal homogeneity in which two regions have similar BOLDs, which would make it to assume that there would be some degree of neural coordination between these regions.[50]

Using this method, it was found that there is hypercoordination of the left ACC and hypocoordination of the left inferior temporal gyrus in patients with OCD. No correlations were found between the regional homogeneity values and some clinical variables such as the outcome on the Yale scale for OCD or Hamilton Anxiety Scale. The authors interpret these findings as an imbalance in the frontal lobe and ACC function. Hyperactivity of the ACC could be responsible for an exaggerated sensation of error that would cause OCD patient to be continuously restless, with the need to correct. Hyperactivity of the ACC within the context of symptom provocation is associated to greater severity of the OCD.[51]

Table 1 Cortical Alterations

Author	Sample		Study method	Area studied	Results	Conclusions
	OCD	Control				
Yang et al. 2010	22	22	R-MRI/ VBM	Whole brain	Patients with OCD have hypercoordination of the left ACC and hypocoordination of the left inferior temporal gyrus	It is interpreted as an imbalance in the frontal lobe and ACC function
					No correlations were found between regional homogeneity values and some clinical variables	Hyperactivity of the ACC could be the cause of an exaggerated sense of error
Ping Li et al. 2012	20	20	R-MRI / "Region of interest" method"	Anterior prefrontal cortex	Stronger connectivity of the prefrontal cortex with the insula and cingulate cortex	Intrinsic abnormal or spontaneous functional connectivity in the cognitive control system in the resting state can be the basis of OCD physiopathology
					Weaker prefrontal connection with the pre- and post-central gyrus	
Jingming Hou et al. 2012	23	23	R-MRI / VBM	Whole brain	Greater amplitude in OFC and ACC	Besides the abnormality hypothesis in the OFC and ACC zones, there are changes in spontaneous neural activity of the parietal cortex and cerebellum that may play a role in the physiopathology
					Less amplitude in cerebellum and parietal cortex	
Jang et al. 2010	22	22	R-MRI / "Region of interest" method"	Posterior cingulate cortex	Greater activation of medial frontal cortex	The results were associated positively with cleaning symptoms and negatively with checking symptoms

OCD: Obsessive-compulsive disorder; R-MRI: Resting state magnetic resonance; VBM: Voxex Based Morphometry; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex

The hypocoordination observed in this study is considered to be the cause of the alterations in working memory and other executive functions that have been previously described in OCD.[52]

Another work studied the prefrontal cortex.[53] The study compared 20 unmedicated patients with OCD with the same number of controls, using the anterior prefrontal cortex as region of interest. The patients showed stronger connectivity of the prefrontal cortex with the insula and cingulate cortex, areas associated with greater cognitive control.[54] Furthermore, a smaller prefrontal connection was found with the pre- and post-central gyrus, which could be interpreted as lower motor inhibition capacity.[55]

Other studies have analyzed the amplitude of low frequency variations between brain zones. According to some authors, two zones with the same amplitude in the variations would not only have a coordinated activity over time, but would have a connection between them on the neural pathway level.[56] One study applied this technique to OCD,[57] recruiting 23 patients with OCD (18 untreated), after which they compared them with 23 healthy controls by whole brain analysis. In this study, it was found that OCD patients had significantly greater amplitude in OFC and ACC, which was associated to more symptoms. The appearance of less amplitude in the cerebellum and in the parietal cortex, both zones described as being participants in cognitive symptoms of OCD, was somewhat novel.[58-60]

A study by J.H. Jang[61] searched for differences in the RS according to type of symptoms. Using 22 untreated patients versus 22 controls, he described that greater medial frontal cortex activation was positively associated with cleaning symptoms and negatively with checking symptoms.

CORTICAL-SUBCORTICAL CONNECTION ALTERATIONS

The results corresponding to this section are summarized in table 2.

A 2009 Spanish work [62] used the fMRI to compare the connectivity of the stratial cortex circuit in OCD patients *vs* controls. They analyzed 21 OCD patients, with medications versus 21 healthy controls. The connectivity was observed using the ventral and dorsal regions of the basal ganglia (caudate and putamen) as regions of interests. It was found that the four regions were widely connected with cortical regions in both

Table 2 Cortical-Subcortical Connection Alterations

Author	Sample		Study method	Area studied	Results	Conclusions
	OCD	Control				
Harrison et al. 2009	21	21	R-MRI/ VBM and Region of interest	Ventral and dorsal regions of the basal ganglia (caudate and putamen)	OCD patients had stronger connectivity between the ventral striatum (caudate and putamen) and the OFC Force of the connectivity between the striatum and OFC had a correlation with symptom intensity	The hypothesis that OCD is associated with functional alterations of the corticostriatal networks is supported
Sakai et al. 2010	20	23	R-MRI / Regional of Interest Method	Striatum and dorsal caudate. Superior and inferior ventral striatum	Stronger connectivity in patients with superior ventral striatum and several brain regions, among them the OFC and prefrontal cortex There is no significant correlation between force of connectivity and severity of the symptoms	Direct evidence that supports the physiopathological model that includes the basal ganglia in OCD
Zhang et al. 2010	18	16	R-MRI/ VBM and Region of interest	39 regions of interest and then whole brain analysis	Decrease of functional connectivity in posterior temporal regions Stronger connectivity in control regions, as ACC	Intrinsic organizational patterns of brain activity are altered in OCT. This gives us empirical evidence of the aberrant functional connectivity systems of the brain systems in patients with this disorder
Stern et al. 2012	30	32	R-MRI / Regional of Interest Method	Frontoparietal network	Hyperactivated frontoparietal network Larger connections between frontoparietal network and resting state network Larger connections between frontoparietal network and motor areas Small internal connectively in the resting state network	OCD is associated with abnormal intrinsic functional connectivity. The alteration between the resting network and resting frontoparietal network may contribute to aspects of the OCD phenotype

OCD: Obsessive-compulsive disorder; R-MRI: Resting state magnetic resonance; VBM: Voxex Based Morphometry; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex

patients and controls. Connectivity was stronger between the ventral striatum (caudate and putamen) and the OFC in the patients while the connectivity was better in the controls between the ventral caudate and temporal cortex. One important aspect was that the force of the connectivity between the striatum and OFC was correlated with the intensity of the asymptomatology with a Pearson's r^2 of 0.57, even when controlling for anxious and depressive symptoms.

Another work that supports these findings is that of Sakai[63] who studied a sample of 20 untreated OCD patients *versus* 23 controls. This work also found stronger connectivity in patients between the superior ventral striatum and several brain regions, among them the OFC and prefrontal cortex.

Along this line, Zhang[64] took on the evaluation of the connectivity between cortical and subcortical areas, based on Dosenbach who proposed that there would be top-down control circuits and multiple neural regions with precise and interconnected functions on the level of "controlled" regions.[65] In OCD, some alterations have been described on the levels of cortical control as well as prefrontal cortex and ACC.[66] To verify this, he studied 18 patients with OCD (5 untreated) versus 16 healthy controls,

Table 3 Other findings

Author	Sample		Study method	Area studied	Results	Conclusions
	OCD	Control				
Meunier et al. 2011	18	18	R-MRI / VBM	Whole brain	In OCD and in patients with dependency, weaker connection force between the superior and inferior regions of the right OFC was observed Weaker force of connection was correlated with stronger compulsive symptoms in both pictures Weaker connectivity with the posterior cingulate was found in OCD	Orbitofrontal connectivity may serve as a biomarker for compulsivity for diagnostic categories
Fitzgerald et al. 2011	60	60	R-MRI/ Region of interest	Thalamus and striate nucleus	All the patients had stronger connectivity between the prefrontal cortex and dorsal striatum A decreased connectivity between the subcortical regions and the ACC was observed in the pediatric patients. This decrease correlated with the severity of the OCD	Some alterations in OCD are not static but rather evolve with the neurodevelopment

OCD: Obsessive-compulsive disorder; R-MRI: Resting state magnetic resonance; VBM: Voxex Based Morphometry; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex

analyzing 39 regions of interest. After, he performed a rapid whole brain analysis using 45 regions of interest for each hemisphere. An alteration of the architecture of the connections between the prefrontal cortex and other brain areas was found, there being weaker connectivity with the temporal cortex, which would be associated to less capacity to integrate information, leading to worse response on the neurocognitive tests. In addition, stronger local connectivity was observed in the AAC, which is along the line of that previously described.

Based on the previously works, an American work[67] evaluated the existence of two altered circuits in OCD, on the one hand the "frontoparietal network" proposed by Zhang[63] that would be hyperactivated when attention in placed on a stimulus and the "default network" which is that which would turn off when there is a stimulus on the attention. A sample of 30 patients with OCD (17 unmedicated) and 32 controls showed that the patients had more connections between both networks and also better connection between zones of the frontoparietal zones and motor areas. Furthermore, the OCD patients showed less internal connectivity in the default network. For the authors, this can be interpreted that, there would be a natural tendency to activate the frontotemporal network (or directed attention) with difficulty to activate the resting network in the OCD condition.

OTHER FINDINGS

The results corresponding to this section are summarized in table 3.

In a recent article,[68] patients with OCD were compared with substance abuse subjects because alterations were found in the OFC in OCD[69] and addiction.[70]

They compared 18 healthy controls, 18 OCD patients and 18 patients with stimulant-dependence, performing a whole-brain analysis. Both the OCDs and patients with dependency had lower connection force between the superior and inferior regions of the right OFC. This lower force was correlated with compulsive symptoms in both pictures with a Spearman Rho of 0.54. Furthermore, a weaker connectivity with the posterior cingulate was found in OCD patients, confirming the alteration of the OFC in compulsive patients.

Pediatric OCD was analyzed in the work of Fitzgerald[71] who studied 60 ICD patients, aged 8 to 50, and compared them with 61 healthy controls, using the thalamus and stratum as regions of interest. The study showed that some of the OCD alterations were not static but rather were evolving with the neurodevelopment. All the patients had stronger connectivity between the prefrontal cortex and dorsal striatum. There was only a weaker connectivity between the subcortical and ACC regions in children between 8 and 12 years. Decrease of this connection was associated to greater symptom intensity. This alteration could condition the difficulty to control compulsive behaviors.[72]

LIMITATIONS

Because of the heterogeneity of the methodology of the studies reviewed, it was not possible to reach finished conclusions or to carry out meta-analysis techniques that could help perform an integrating analysis of the evidence.

CONCLUSIONS

As was already mentioned, the results from the articles are unequal. However, there appear to be some points that are repeated and that make it possible to reach some conclusions.

OCD is not caused by a single alteration in the brain circuits, but by multiple variations in different circuits, which are correlated with the variety of anxious and cognitive symptoms found in the disorder. From this point of view, the constant perception of error and checking need could be due to an internal hyperconnection in the ACC. The difficulty to control compulsions could be caused by alterations in the OFC.

Alterations appear in regions that are not classically associated to OCD, as the temporal cortex and cerebellum, although their participation in the etiopathogeny of the disorders is still being studied.

No alterations per se of OCD absent in controls have been found. There is stronger or weaker comparative connectivity, but all of the works stress that those connections are present in patients and controls. The differences would be more qualitative than quantitative, so that OCD could be the pathological expression due to deregulation of normal processes.

There are still many areas that have not been fully studied, such as pediatric OCD, where, nonetheless, important advances have been found in the measurement scales and knowledge we have in pharmacotherapy.[73,74]

The association of brain functional alterations with symptom type and intensity has also not been evaluated.

The possibility that OCD would consist in inability to inactivate the "action" frontotemporal network and to go onto the "resting" default network has been proposed in the studies. This hypothesis seems to be integrating and interesting, but must be verified in new studies.

The study of OCD neurobiology is far from finished. However, the resting state study has taken a step forward, allowing for the analysis of a new variable in the basal brain circuitry.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed., Text Revision. American Psychiatric Publishing, 2000.
2. Leon AC, Portera L, Weissman MM. The social costs of anxiety disorders. British Journal of Psychiatry. 1995;Supplement:19–22.
3. Koran LM, Thienemann ML, Davenport R. Quality of life for patients with obsessive-compulsive disorder. American Journal of Psychiatry. 1996;153:783–8.
4. Murray C, Lopez A. The Global Burden of Disease. A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. USA: World Health Organisation, 1996.
5. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD, et al. Lifetime prevalence of specific psychiatric disorders in three sites. Archives of General Psychiatry. 1984;41:949–58.
6. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. Archives of General Psychiatry. 1988;45:1094–9.
7. Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, Lee CK, et al. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. Journal of Clinical Psychiatry. 1994;55(Suppl.):5–10.
8. Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of obsessive- compulsive disorder. Am J Psychiatry. 2005;162(2):228-38.
9. Hanna GL, Himle JA, Curtis GC, Gillespie BW. A family study of obsessive-compulsive disorder with pediatric probands. American Journal of Medical Genetics: Part B Neuropsychiatric Genetics. 2005;134:13–9.
10. Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Taubman J, Greenberg BD, et al. Serotonin transporter promoter gain-of-function genotypes are linked to obsessivecompulsive disorder. American Journal of Human Genetics. 2006;78:815–26.
11. Lawrence AD, Sahakian BJ, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends in Cognitive Sciences. 1998;2:379–88.
12. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biological Psychiatry. 2003;54:504–14.
13. Eslinger PJ, Damasio AR. Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology. 1985;35:1731–41.
14. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994;50:7–15.

15. Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. Science. 1994;264:1102–5.
16. Choi JS, Kang DH, Kim JJ, Ha TH, Lee JM, Youn T, et al. Left anterior subregion of orbitofrontal cortex volume reduction and impaired organizational strategies in obsessivecompulsive disorder. Journal of Psychiatric Research. 2004;38:193–9.
17. Kang DH, Kim JJ, Choi JS, Kim YI, Kim CW, Youn T, et al. Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive-compulsive disorder. Journal of Neuropsychiatry and Clinical Neurosciences. 2004;16:342–9.
18. Atmaca M, Yildirim BH, Ozdemir BH, Aydin BA, Tezcan AE, Ozler AS. Volumetric MRI assessment of brain regions in patients with refractory obsessive-compulsive disorder. Progress in Neuropsychopharmacology and Biological Psychiatry. 2006;30:1051–7.
19. Atmaca M, Yildirim H, Ozdemir H, Tezcan E, Poyraz AK. Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. Progress in Neuropsychopharmacology and Biological Psychiatry. 2007;31:46–52.
20. Rosenberg DR, Keshavan MS, O'Hearn KM, Dick EL, Bagwell WW, Seymour AB, et al. Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. Archives of General Psychiatry. 1997;54:824–30.
21. Szeszko PR, MacMillan S, McMeniman M, Chen S, Baribault K, Lim KO, et al. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. American Journal of Psychiatry. 2004;161:1049–56.
22. Szeszko PR, MacMillan S, McMeniman M, Lorch E, Madden R, Ivey J, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology. 2004;29:826–32.
23. Scarone S, Colombo C, Livian S, Abbruzzese M, Ronchi P, Locatelli M, et al. Increased right caudate nucleus size in obsessive-compulsive disorder: detection with magnetic resonance imaging. Psychiatry Research. 1992;45:115–21.
24. Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessivecompulsive disorder. Psychiatry Research. 2004;132:69–79.
25. Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. American Journal of Psychiatry. 2003;160:522–32
26. Friedlander L, Desrocher M. Neuroimaging studies of obsessive-compulsive disorder in adults and children. Clinical Psychology Review. 2006;26:32–49.
27. Saxena S, Bota RG, Brody AL. Brain–behavior relationships in obsessive-compulsive disorder. Seminars in Clinical Neuropsychiatry. 2001;6:82–101.
28. Remijnse PL, van den Heuvel OA, Veltman DJ. Neuroimaging in obsessive-compulsive disorder. Current Medical Imaging Reviews. 2005;1:331-51.
29. Mataix-Cols D, Cullen S, Lange K, et al. Neural correlates of anxiety associated with obsessive-compulsive symptom dimensions in normal volunteers. Biol Psychiatry. 2003;53:482-93.
30. Shapira NA, Liu Y, He AG, Bradley MM, Lessig MC, James GA, et al. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. Biol Psychiatry. 2003;54:751–6.
31. van den Heuvel OA, Veltman DJ, Groenewegen HJ, Dolan RJ, Cath DC, Boellaard R, et al. Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. Psychiatry Res. 2004;132:225–37.
32. Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. Am J Psychiatry. 2004;161:1038-48.
33. Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch Gen Psychiatry. 1992;49:690–4.
34. Rauch SL, Shin LM, Dougherty DD, Alpert NM, Fischman AJ, Jenike MA. Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. Neuropsychopharmacology. 2002;27:782-91.
35. Valente AA Jr, Miguel EC, Castro CC, Amaro E Jr, Duran FL, Buchpiguel CA, et al. Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. Biological Psychiatry. 2005;58:479–87.
36. Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, et al. Mapping structural brain alterations in obsessive-compulsive disorder. Archives of General Psychiatry. 2004;61:720–30.
37. Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. TheAmerican Journal of Psychiatry. 2003;160:2209–15.
38. Lui S, Ouyang L, Chen Q, Huang X, Tang H, Chen H, et al. Differential interictal activity of the precuneus/posterior cingulate cortex revealed by resting state functional MRI at 3T in generalized vs. partial seizure. Journal of Magnetic Resonance maging. 2008;27:1214–20.
39. Lui S, Huang X, Chen L, Tang H, Zhang T, Li X, et al. High-field RI reveals an acute impact on brain function in survivors of the magnitude 8.0earthquake in China. Proceedings of the National Academy of Sciences of the United States of America. 2009;106:15412–7.
40. Goncalves SI, de Munck JC, Pouwels PJW, Schoonhoven R, Kuijer JPA, Maurits NM, et al. Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: inter-subject variability. Neuroimage. 2006;30:203–13.
41. Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, et al. Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. Proceedings of the National Academy of Sciences of the United States of America. 2003;100:11053–8.
42. Leopold DA, Murayama Y, Logothetis NK. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cerebral Cortex. 2003;13:422-33.
43. Shmuel A, Leopold DA. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: implications for functional connectivity at rest. Human Brain Mapping. 2008;29:751–61.
44. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8:700-11.
45. Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, et al. Functional connectivity of human striatum: a resting state fMRI study. Cereb Cortex. 2008;18:2735-47.
46. Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. Aberrant "default mode" functional connectivity in schizophrenia. Am J Psychiatry. 2007;164:450–7.
47. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus, Biol Psychiatry. 2007;62:429–37.

48. First MB, Spizer RL, Gibbon M, Williams JBW. Structures Clinical Interview for Axis I DSM-IV Disorders-Patient Edition (CID-I/P). New York: Biometrics Research Department, New York State Psychiatric Institute, 1994.
49. Yang T, Cheng Y, Li H, Jiang H, Luo C, Shan B, et al. Abnormal regional homogeneity of drug-naive obsessive–compulsive patients. NeuroReport. 2010;21:786–90.
50. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. Neuroimage. 2004;22:394–400.
51. Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. Psychol Sci. 2003;14:347–53.
52. Nakao T, Nakagawa A, Nakatani E, Nabeyama M, Sanematsu H, Yoshiura T, et al. Working memory dysfunction in obsessive-compulsive disorder: a neuropsychological and functional MRI study. J Psychiatr Res. 2009;43:784–91.
53. Li P, Li S, Dong Z, Luo J, Han H, Xiong H, et al. Altered resting state functional connectivity patterns of the anterior prefrontal cortex in obsessive-compulsive disorder. Neuroreport. 2012;23:681-6.
54. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA. 2008;105:12569–74.
55. Alexander WH, Brown JW. Medial prefrontal cortex as an action-outcome predictor. Nat Neurosci. 2011;14:1338–44.
56. Kiviniemi V, Jauhiainen J, Tervonen O, Paakko E, Oikarinen J, Vainionpaa V, et al. Slow vasomotor fluctuation in fMRI of anesthetized child brain. Magnetic Resonance in Medicine. 2000;44:373–8.
57. Hou J, Wu W, Lin Y, Wang J, Zhou D, Guo J, et al. Localization of cerebral functional deficits in patients with obsessive-compulsive disorder: A resting-state fMRI study. Journal of Affective Disorders. 2012;138:313-21.
58. van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, et al. The major symptom dimensions of obsessive–compulsive disorder are mediated by partially distinct neural systems. Brain. 2009;132:853–68.
59. Nabeyama M, Nakagawa A, Yoshiura T, Nakao T, Nakatani E, Togao O, et al. Functional MRI study of brain activation alterations in patientswith obsessive–compulsive disorder after symptom improvement. Psychiatry Research. 2008;163:236–47.
60. Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive–compulsive disorderduring neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biological Psychiatry. 2005;57:901–10.
61. Jang JH, Kim JH, Jung WH, Choi JS, Jung MH, Lee JM, et al. Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive–compulsive disorder. Neuroscience Letters. 2010;474:158–62.
62. Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez- Ribas R, et al. Altered corticostriatal functional connectivity in obsessive–compulsive disorder. Archives of General Psychiatry. 2009;66:1189–200.
63. Sakai Y, Narumoto J, Nishida S, Nakamae T, Yamada K, Nishimura T, et al. Corticostriatal functional connectivity in non- medicated patients with obsessive-compulsive disorder. European Psychiatry. 2011;26:463–9.
64. Zhang T, Wang J, Yang Y, Wu Q, Li B, Chen L, et al. Abnormal small-world architecture of top–down control networks in obsessive-compulsive disorder. J Psychiatry Neurosci. 2011;36:23–31.
65. Dosenbach NU, Fair DA, Miezin FM, et al. Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci USA. 2007;104:11073-8.
66. Penades R, Catalan R, Rubia K, et al. Impaired response inhibition in obsessive compulsive disorder. Eur Psychiatry. 2007;22:404-10.
67. Stern ER, Fitzgerald KD, Welsh RC, Abelson JL, Taylor SF. Resting-State Functional Connectivity between Fronto-Parietal and Default Mode Networks in Obsessive-Compulsive Disorder. PLoS ONE. 2012;7:e36356.
68. Meunier D, Ersche KD, Craig KJ, Fornito A, Merlo-Pich E, Fineberg NA, et al. Brain functional connectivity in stimulant drug dependence and obsessive-compulsive disorder. Neuroimage. 2012;59:1461-8.
69. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive– compulsive disorder: the orbitofronto–striatal model revisited. Neurosci Biobehav Rev. 2008;32:525–49.
70. Schoenbaum G, Shaham Y. The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. Biol Psychiatry. 2008;63:256–62.
71. Fitzgerald KD, Welsh RC, Stern ER, Angstadt M, Hanna GL, Abelson JL, et al. Developmental alterations of frontal–striatal–thalamic connectivity in obsessive–compulsive disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2011;50:938–48.
72. Rubia K, Smith AB, Woolley J, et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum Brain Mapp. 2006;27:973-93.
73. Ulloa R, De la Peña F, Higuera F, Ávila J, et al. Estudio de validez y confiabilidad de la versión en español de la escala yale–brown de trastorno obsesivo compulsivo para niños y adolescentes. Actas Esp Psiquiatr. 2004;32:216–21.
74. Rosa-Alcázar AI, Iniesta-Sepúlveda M, Rosa-Alcázar A. Los tratamientos farmacológicos en el Trastorno Obsesivo-Compulsivo en niños y adolescentes: Una revisión cualitativa. Actas Esp Psiquiatr. 2013;41(3):196-203.