Review

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

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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 absent 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

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
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 monoygotes 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 striatal size,20,21 increase in size of the ACC,22 thalamus23 and basal ganglia.24

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 obsessions.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.

Voxel 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,\textsuperscript{35,36} together with an increase in stratial gray matter,\textsuperscript{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.\textsuperscript{37} Another benefit is that it is less expensive and less invasive than the PET or SPECT.\textsuperscript{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.\textsuperscript{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\textsuperscript{46} and major depressive disorder,\textsuperscript{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,\textsuperscript{1} using the SCID I structured interview,\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{51}
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. Jang61 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 stratal 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>
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<th>Table 1</th>
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<td>Jingming Hou et al. 2012</td>
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OCD: Obsessive-compulsive disorder; R-MRI: Resting state magnetic resonance; VBM: Voxer 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 r² 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>
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<td>Harrison et al. 2009</td>
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<td>OCD patients had stronger connectivity between the ventral striatum (caudate and putamen) and the OFC</td>
<td>The hypothesis that OCD is associated with functional alterations of the corticostriatal networks is supported</td>
</tr>
<tr>
<td>Sakai et al. 2010</td>
<td>20 OCD, 23 Control</td>
<td>R-MRI / Regional of Interest Method</td>
<td>Striatum and dorsal caudate. Superior and inferior ventral striatum</td>
<td>Stronger connectivity in patients with superior ventral striatum and several brain regions, among them the OFC and prefrontal cortex</td>
<td>Direct evidence that supports the physiopathological model that includes the basal ganglia in OCD</td>
</tr>
<tr>
<td>Zhang et al. 2010</td>
<td>18 OCD, 16 Control</td>
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<td>39 regions of interest and then whole brain analysis</td>
<td>Decrease of functional connectivity in posterior temporal regions Stronger connectivity in control regions, as ACC</td>
<td>Intrinsic organizational patterns of brain activity are altered in OCD. This gives us empirical evidence of the aberrant functional connectivity systems of the brain systems in patients with this disorder</td>
</tr>
<tr>
<td>Stern et al. 2012</td>
<td>30 OCD, 32 Control</td>
<td>R-MRI / Regional of Interest Method</td>
<td>Frontoparietal network</td>
<td>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</td>
<td>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</td>
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OCD: Obsessive-compulsive disorder; R-MRI: Resting state magnetic resonance; VBM: Voxel 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 evaluated the existence of two altered circuits in OCD, on the one hand the “frontoparietal network” proposed by Zhang 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, patients with OCD were compared with substance abuse subjects because alterations were found in the OFC in OCD and addiction.

They compared 18 healthy controls, 18 OCD patients and 18 patients with stimulant-dependence, performing a whole-brain analysis. Both the ODCs and patients with dependency had lower connection force between the superior and inferior regions of the right OFC. 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.
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 etiopathology 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**


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