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Obsessive Compulsive Disorder as a functional interhemispheric imbalance at the thalamic level

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ABSTRACT

Obsessive Compulsive Disorder (OCD) involves failures in two main inhibitory processes, namely cognitive (obsessions) and behavioral (compulsions). Recent research has supported two cortical–subcortical pathways on OCD pathogenesis: (a) the frontostriatal loop (dorsolateral-caudate–striatum–thalamus) responsible for impairments of behavioral inhibition; (b) the orbitofrontal loop (orbitofrontal, medial prefrontal and cingulate) responsible for impairments with cognitive inhibitory processes. These failures in both cognitive and motor inhibitory systems may mediate several neuropsychological deficits in these patients, namely memory, attention, planning and decision making. But are those deficits related to specific hemispheric effects, namely functional imbalance between hemispheres? In this article we hypothesize that: (1) OCD patients have an inter-hemispheric functional imbalance, probably due to inadequate filtering at the thalamic level; (2) the restoration of inter-hemispheric balance, will be correlative to symptomatic improvement.

Introduction

Obsessive Compulsive Disorder (OCD) is one of the most debilitating psychiatric disorders. It has a cross cultural lifetime prevalence of 2.5% [1,2] being characterized by the presence of obsessions (intrusive, upsetting and unwanted thoughts and/or images) and/or compulsions (repetitive and stereotyped behavior or mental rituals) [3].

Most prevailing evidences indicate that OCD is a biological disease. Functional brain imaging studies have converged in order to produce a model for pathophysiology of OCD which involves hyperactivity in certain cortical and subcortical regions [4]. Parallel and partially antagonistic information-processing pathways seem to be involved in order to appropriately create a balanced control of thought and movement. The initiation and sustainability of the repetitive behavior is thought to be modulated by the direct pathway. The completion of these behavioral routines will then be modulated by the indirect pathway. It is suggested that the OCD symptoms result of an hyperactivity in the direct pathway compare to the indirect one leading to a disinhibited thalamus and the creation of a self-perpetuating circuit between the thalamus and the orbital cortex [5,6]. Also, cortico–striatal projections are predominantly glutamatergic, thus excessive activity may contribute to the pathophysiology of OCD. Successful treatment is associated with a reduction in the CSTC hyperactivity.

Thus, it has been thought that OCD involves failures in two main inhibitory processes, namely cognitive (responsible for the obsessions) and behavioral (responsible for the compulsions) [7]. Recent research has supported two cortical–subcortical pathways in OCD pathogenesis: (a) the frontostriatal loop (dorsolateral-caudate–striatum–thalamus) responsible for impairments of behavioral inhibition; (b) the orbitofrontal loop (orbitofrontal, medial prefrontal and cingulate) responsible for impairments with cognitive inhibitory processes.

These two inhibitory processes reflect a broad network of cortico–basal ganglia–thalamic loops [8,9]. Default mode network (DMN) studies also support this assumption, as OCD patients, when compared to health controls (HC), showed less functional connectivity in anterior cingulate cortex, middle frontal gyrus and putamen [10].

Neurophysiological studies in OCD showed decreased intracortical inhibition (ICI) on paired-pulse TMS (Transcranial Magnetic Stimulation) [11,12] and decreased active and resting motor evoked potential threshold [11] that seems to indicate enhanced cortical excitability and lack of inhibition, when compared to health controls (HC), thus supporting the assumption of failure in inhibition processes.

These failures in both cognitive and motor inhibitory systems [13] may mediate several neuropsychological deficits in these patients, namely memory, attention, planning and decision making

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[7,14,15]. But are those deficits related to specific hemispheric effects, namely a functional imbalance between hemispheres?

Several studies suggested specific inter-hemisphere effects. An EEG study [16] demonstrated that OCD patients when compared to HC show less right hemispheric activation. Additionally the beta 2 frequency was correlated with impairments in visuospatial tasks but not with verbal performance. Some authors reported relative decreased variability in the left temporal region [17], "nonspecific theta activity" [18] and a relative significantly increased power in the theta-2 band in the left temporal and central regions along with a significantly reduced variability in frontal and temporal regions [19].

The first TMS study with OCD patients [12], showed symptom improvement when the inhibitory stimulation was on the right dorsolateral prefrontal cortex (DLPFC) but not on the left one. This laterality effect has been also observed in an opposite correlation between acute symptom provocation (as emotional processes play a major role in OCD) and orbitofrontal perfusion in the right and left hemisphere [20], as well as symptom improvement and disruption of abnormal metabolic activity on the right hemisphere after cognitive behavioral therapy [21]. Additionally, symptomatic improvement was found in neurosurgery after right hemisphere anterior capsulotomy but not on left side [22,23]. Neuroimaging studies also found right hemisphere changes associated with therapeutic improvement after medication [24]. Also, abnormalities in the thalamus, a sensory and motor gateway to the cortex, are believed to be involved in the pathophysiological mechanisms implicated in the development of OCD symptoms [25,26]. Evidences come from neurosurgery where partial thalamotomy was associated with a decrease in OCD symptoms in treatment–refractory [25] and neuroimaging studies that demonstrate metabolic abnormalities within the thalamus that have been correlated with OCD symptom severity and subsequent treatment response [5,27,28].

All of these studies support the idea that there are specific hemispheric effects associated to both OCD symptoms and cognitive processing, as well as with the prediction of recovery. But none of the above studies clearly demonstrates hemispheric asymmetries and, more important, none of them explore the connectivity in the neural circuitry involved in the pathophysiology.

A possible interpretation for inter-hemispheric imbalance is that the cognitive processing impairments found in OCD may be associated with cortico–basal dysfunction where cortico–subcortical loops (will act separately, in parallel and with overflow between them) [29] will lead to compensatory processes, performed elsewhere in the brain.

Following this hypothesis Gonçalves et al. [30] proposed that the frontal subcortical activation found in OCD would be correlative to a deactivation of parietal/occipital areas associated with visual-perceptual processing, thus supporting the compensatory mechanism hypothesis. This seem to consistent with the hypothesis that in OCD there will be a dysfunction of thalamic gating [31] responsible for a defective filtering of cortical input by the basal ganglia, therefore leading to compensatory processes.

Evidence for the hypothesis of a compensatory activation and deactivation, that will be ultimately responsible for a functional hemispheric imbalance has been found on several clinical trials with repetitive TMS (rTMS), demonstrating increased symptom improvement e.g. [32,33] when compared with alternative approaches [34,35]. In a recent study [36], with 21 medication-resistant OCD patients receiving 1-Hz rTMS (inhibitory stimulation), delivered bilaterally to the Supplementary Motor Area (SMA) it was found a symptomatic improvement along with normalized cortical hyperexcitability (tendency to symmetry between hemispheres).

Nonetheless, due to the unspecific nature of the compensatory mechanisms, the heterogeneity of OCD patients, and the particular characteristics of the cortical–basal-ganglia–thalamic loops, the deficits in these patients seem not to be related to a specific lateralized dysfunction of a particular hemisphere, but probably due to a functional inter-hemisphere imbalance [37]. In other words, there are no data consistently showing that one hemisphere is significantly altered in OCD, but there is data that supports the notion that there is a functional imbalance between them, probably due to inadequate filtering at the thalamic level [31,38].

Previous studies in our lab [39] show that it may be possible to modulate cortically the cortical–basal ganglia–thalamic circuits with cortical transcranial direct current stimulation (tDCS), as these circuits seem to be highly engaged. Our studies seem also to provide evidence that despite of site of stimulation, similar neuromodulation effects could be obtained, as long as the target areas of stimulation are involved in such networks. Also there are several studies that show that it is possible to neuromodulate one hemisphere, by stimulating the other e.g. [40,41], bringing additional support to the idea that as long as the areas are engaged in similar networks, there will be effects in the entire network.

The hypothesis

The main assumption underlying this hypothesis is that OCD symptoms and deficits are associated with a functional inter-hemispheric imbalance. The restoration of such imbalance will be correlative of symptomatic improvement. This assumption could be a possible explanation as why non-invasive standardize rTMS treatments have only revealed modest clinical effects.

In sum, based on previous studies one can hypothesize that:

(1) The activation of positive and negative DMN in OCD will reveal a specific functional hemispheric imbalance and the improvements in symptomatology will be correlative with the restoration of balance.
(2) Quantitative EEG (QEEG), Event-Related-Synchronization (ERS) and Event-Related-Desynchronization (ERD) will show asymmetric distributions, as well as direct cortical excitability measures by single and paired pulse TMS. The restoration of functional connectivity will also be correlative of symptoms improvement.
(3) The cortical site of non-invasive brain stimulation will not be determinant but the main factor will be the bilaterally deliverance in a cortical area highly engaged in the frontal–striatal loops thus targeting changes in the thalamic gating, and ultimately restoration of balance.

Implications and further studies

If future research validates these hypotheses, important implications may be derived for the development of new therapeutic approaches. For instances, psychotherapy and neurofeedback techniques could be used, in order to promote functional balance between hemispheres. Psychopharmacological treatments could be developed in order to surpass this interhemispheric imbalance by the balance of glutamate and dopamine at the thalamic level. Finally, more recent methods, such as transcranial magnetic stimulation or transcranial direct current stimulation, can be used to bilaterally activate and deactivate several cortical areas related to frontal–subcortical circuits while the patient is confronted with emotional triggers.

Conflicts of interest statement

There are not any financial, relationship and organizational conflict of interests that may bias any of the authors in the establishment of the hypotheses discussed in this article.

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