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Theoretical models of Obsessive-Compulsive Disorder (OCD): a perspective on future approaches

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ABSTRACT: Obsessive-Compulsive disorder (OCD) is a common psychiatric condition that leads to significant impairment in everyday life. Advancements in neurobiological investigations contributed to a better understanding of pathophysiological mechanisms behind OCD, leading to the understanding that current models employed to conceptualize OCD are not adequate and might be a significant factor in precluding further advancements in how OCD is treated. In this paper, we will use OCD as a model to discuss the limitations of the current diagnostic systems in Psychiatry and to present the novel perspectives based on neurobiological findings that might lead to considerable advancements in treatments for OCD.

Keywords: Obsessive-compulsive disorder/diagnosis; Obsessive-compulsive disorder/physiopathology; Obsessive-compulsive disorder/therapy; Neurobiology/trends.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterized by recurrent, intrusive thoughts (obsessions) and/or repetitive, ritualized behaviors and/or mental acts (compulsions)[1]. OCD typically starts at a young age; among boys, whereas among girls, the disorder usually onsets during early adulthood. OCD is considered a chronic condition throughout the lifespan[2]; although individuals usually experience periods of improvement and worsening of their symptomatology, hardly ever will an individual be free of their obsessive-compulsive symptoms (OCS)[3]. In that way, OCD can lead to significant impairment in quality of life, disability and indirect financial costs[4].

Selective serotonin reuptake inhibitors (SSRI) and cognitive-behavioral therapy (CBT) are both first-line treatments for OCD[5]. The latter, including a specific technique called exposure and response prevention (ERP), is the psychological treatment of choice for OCD. ERP involves gradual and prolonged exposure to fear-provoking stimuli combined with instructions to abstain from the compulsive behavior. Yet, despite the acute efficacy of SSRIs and ERP in the treatment of OCD, some issues have to be considered: there are few adequately trained therapists able to provide ERP to every individual with OCD, particularly when a vast country such as Brazil is taken into account; SSRIs not rarely are accompanied by important side effects such as sexual dysfunction which might preclude its use, particularly among young individuals[6]. Further research looking for novel, cheaper interventions for OCD are required. In that way, non-invasive neuromodulation techniques involving direct current stimulation - transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation- could provide a circuit-based treatment (i.e. targeting specific neural circuits) with fewer side effects. In fact, a recent clinical trial showed that TMS can be used for the treatment of OCD[7]. tDCS, which is cheaper than TMS, can also be applied at home, which would facilitate its use across a large population. Case reports and case series testing the efficacy of tDCS for OCD have reported promising findings[8]. Two recent controlled trials suggested the efficacy of tDCS for the treatment of OCD. In both studies, the target of

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the intervention was the pre-supplementary motor area (SMA)[9,10]. Further research is required to replicate these initial findings.

Dimensional model of OCD

OCD is a highly heterogeneous psychiatric condition as two individuals with the same diagnosis can present with very distinct, non-overlapping profiles of obsession and/or compulsions. For instance, someone with OCD might wash their hands multiple times a day due to preoccupation with getting sick or spreading an illness; constantly pray or apologize to God due to an excessive concern with "right vs. wrong"; repeat the same sentence over and over again with some neutralizing though to ease the distress caused by intrusive, unwanted violent or sexual images (e.g. "I am not a violent person"). Previous research acknowledged the heterogeneity of OCS by analyzing the different factors (i.e. unobserved variables that might explain the variations of observed variables) of the Yale-Brown Obsessive-Compulsive Scale (YBOCS) through factor analysis studies. A meta-analysis of such studies demonstrated the clinical heterogeneity typically seen in OCS could be explained by four factors, which were labeled the four dimensions of OCS; specifically, the four OCS dimensions reported by the meta-analysis were (1) contamination/washing, (2) symmetry/ordering, (3) forbidden thoughts/ checking and (4) hoarding[11-13].

Given OCD is clinically heterogeneous, researchers got interested into evaluating whether the clinical heterogeneity of OCS could explain the inconsistent findings regarding neurobiological substrates of OCD. Specifically, considering the clinical heterogeneity of OCD, researchers were interested into evaluating whether different OCS dimensions were associated with different neurobiological mechanisms and whether a specific neurobiological substrate could be associated with each OCS dimension. In that way, Mataix-Cols et al.[14] employed functional magnetic resonance imaging (fMRI) to evaluate which brain regions would be most activate in sixteen patients with OCD when visual stimuli from different OCS dimensions were presented. Interestingly, authors reported that different OCS dimensions were related to relatively distinct components of the frontostriatothalamic circuits. For instance, when facing contamination/washing-related stimuli, patients demonstrated a significantly greater activation than controls in bilateral ventromedial prefrontal regions and right caudate nucleus, whereas when facing forbidden thoughts/checking stimuli, patients demonstrated a significantly greater activation than controls in the putamen/globus pallidus, thalamus and dorsal cortical areas. Similar OCS-related differences were reported by van den Heuvel et al.[15] who, instead of looking at activation of brain areas through fMRI, aimed at looking at differences in the volumes of grey matter and white matter of different brain regions and concluded that individuals with symptoms of the symmetry dimension were associated with decreased volume of the right motor cortex. Similarly, Alvarenga et al.[16] reported that while individuals with higher scores on the aggression dimension had greater volumes in the lateral parietal cortex in both hemispheres, individuals who scored higher in the sexual/ religious dimension had a greater volumes in the insula in both hemispheres.

Researchers were also interested into evaluating whether different OCS dimensions were associated with different patterns of response to treatment. For instance, it could be possible that individuals with symptoms of the forbidden thoughts/checking dimension would respond better to usual psychotherapeutic approaches typically employed for OCD. In that way, Mataix-Cols et al.[39] analyzed data from 153 patients with OCD who had participated in a multi-center randomized controlled trial of computer - versus clinician-guided behavioral therapy for OCD and reported that individuals with forbidden thoughts/ checking and contamination/cleaning symptoms responded better to the intervention than individuals who did not present with such symptoms. Ferrao et al.[17] reported that individuals who had higher scores in the forbidden thoughts dimension were more likely to not respond to conventional, first-line treatments of OCD (SSRIs and ERP).

Limitations of the dimensional approach to OCD

The dimensional model of OCD is arguably the most studied model of OCD. Yet, despite its importance, this model clearly has important limitations that should be considered. The dimensional model was constructed through phenotypic data, i.e. reports of symptoms from individuals living with OCD. Although the reported symptomatology is of paramount importance in Psychiatry, classifying individuals according only to their symptoms can be misleading. In Medicine, there are several different examples of syndromes in which, although the symptoms and the clinical presentation are fairly similar, the underlying mechanism between different etiologies as well as their treatment is considerably different. For example, if we consider a sexually active woman in their reproductive years who presents to the Emergency Department with a strong, sharp pain in the right lower abdomen, physicians should suspect of either an Appendicitis or a ruptured tubal ectopic pregnancy; in this case, both diseases are characterized by different mechanisms (gastro-intestinal inflammation vs. embryo attachment in the tube) and require different treatments (appendicectomy vs. salpingectomy). Therefore, it could be possible that, although individuals with OCD might report somewhat similar symptoms if we consider OCS dimensions individually, there are different mechanisms underlying OCS symptomatology. This hypothesis is reinforced by the fact that larger neuroimaging

studies employing mega-analysis techniques failed to demonstrate specific neuroanatomical correlates for each OCS dimension as well as distinct treatment response patterns[18,19].

The RDoC initiative and novel insights on classifying OCD

The relative failure in finding adequate treatment for psychiatric disorders in general, exemplified by the lack of consistent findings regarding the model using OCS dimensions lead to new initiatives focused in understanding the mechanisms underlying OCD with the hope that this approach could lead to significant improvements in how we currently treat this condition. In fact, the National Institute of Mental Health (NIMH) launched in the beginning of this decade the Research Domain Criteria (RDoC) initiative with the intent of fostering research aimed at understanding further the neurobiological processes underlying mental phenomena. Currently, the NIMH does not provide funding to intervention trials that do not test the mechanism of action of the proposed treatment. In other words, to get NIMH funding, researchers in the U.S. carrying out a trial of intranasal ketamine for acute suicidality in adults have necessarily to include in their protocol a plan to collect biomarker data (e.g. neuroimaging, electroencephalographic measures, serum markers, etc.).

The RDoC initiative is not directly related to the American Psychiatric Association (APA) and its Diagnostic and Statistical Manual of Mental Disorders (DSM), currently on its fifth edition; therefore, the RDoC initiative does not consider the existence of mental disorders as they were classified by the DSM. In fact, the overall concept behind RDoC is to delineate different psychological constructs or domains of psychopathology which would be associated with specific neurobiological correlates and that would be important to normal psychological functioning. For instance, the construct *affiliation and attachment* underlies the processes of engagement in positive social interactions with other individuals, the construct *arousal* underlies the continuum of sensitivity of the organism to internal and/or external stimuli which facilitates interaction with the environment in a context-specific manner and the construct *reward anticipation* underlies processes that are associated with the ability to anticipate and/or represent a future incentive.

Although the RDoC initiative does not consider the categories of mental disorders determined by the DSM, researchers specialized in different psychiatric disorders advocate that the constructs from the RDoC initiative might provide a novel and interesting perspective in the understanding of mental disorders. Particularly, researchers are increasingly interested in providing neurobiological explanations to clinical characteristics of diagnostic categories by considering psychiatric symptoms as disturbances in the normal functioning of RDoC constructs. For example, Brotman et al.[20] provides a magnificent example of such approach in which authors conceptualize the behavioral symptom of irritability as dysfunctions in the reward or threat processing systems - both of which are RDoC constructs. Although approaches such as this are yet largely theoretical, researchers view with optimism that our understanding of the neurobiology underlying psychiatric disorders will improve with the RDoC initiative.

RDoC constructs and OCD: sensory phenomena as an example

At the moment, few researchers have looked at what RDoC constructs might be important for our understanding of OCD. The few available reports at the moment have mostly focused on inhibitory control and fear/anxiety. This is mostly because initial theories about OCD considered that individuals would repeat a given behavior due to the inability to suppress engaging in the behavior once faced with fear and/or anxiety provoked by obsessions. Little attention has been given to other possible constructs that could play an important role in OCD, such as the sensorimotor/interoceptive system.

Although the hallmark clinical features of OCD are the obsessions and compulsions, some individuals with OCD also acknowledge experiencing unpleasant, distressing sensory experiences which have been described under the term sensory phenomena[21-23]. Among such distressing experiences, individuals report experimenting urges which can be localized to specific body regions as well as sensations that "something is just not right". Sensory phenomena cut across different psychiatric disorders, as those with Tourette's syndrome (TS), trichotillomania and addictive disorders also report experiencing sensory phenomena.

One of the earliest descriptions of sensory phenomena and possibly the first to systematically assess such symptoms in articles published in scientific journals were made during the 1990s. Leckman et al.[24] showed that about 93% of individuals with Tourette Syndrome (ST) of the Tourette Association of America (Tourette Association of America) who participated in a mail interview reported experiencing tension sensations or urges that were momentarily relieved by the occurrence of tics; 89% of individuals with TS who reported experiencing these sensory experiences, at that time called premonitory urges, considered these sensations as physical characteristics often related to a body segment such as head, neck and shoulders. After a year, Leckman et al.[25] also reported that among those with TS, those with OCD as a comorbidity reported more frequently needing to repeat behavior because they felt a nonspecific feeling of incompleteness or something "not just right"; these "not just right" sensations were considered mental phenomena by about 95% of individuals

who reported experiencing them.

Miguel et al.[22] compared patients with OCD, ST, and OCD with comorbid ST to assess differences in the presence of these subjective sensations antecedent to the occurrence of repeated behaviors; authors reported results showed that patients with OCD also had both "not just right" sensations and physical sensations located in body segments, with both types of sensory experiences being more common in patients with OCD who presented TS as comorbidity[21]. In order to develop an instrument for the evaluation of sensorial phenomena in OCD patients, Rosário et al.[23] developed the Sensory Phenomena Scale of the University of São Paulo (University of São Paulo Sensory Phenomena Scale, USP-SPS); in this instrument, sensations of "not just right" and physical sensations were grouped into a single quantitative measure that provides an estimate of the severity of sensory phenomena as a whole. Much of the research on sensory phenomena in OCD that followed used USP-SPS as a measure of sensory phenomena.

At the moment, there is little data regarding possible neurobiological correlates of sensory phenomena in OCD. Understanding the neurobiological correlates of such subjective experiences might enable the development of site-specific interventions targeting the neural circuits associated specifically with sensory phenomena in individuals who suffer from them. Among individuals with TS, behavioral and neurofunctional studies point to an important role of interoception in the genesis of sensory phenomena. Interoception refers to the ability of individuals to sense internal body states[26] - i.e. the capability of sensing own body signals. Ganos et al.[27] demonstrated that interoceptive perception is an important predictor of the severity of sensory phenomena measured by the Premonitory Urges for Tics Scale (PUTS)[28] in TS patients. Rae et al.[29] demonstrated that the severity of sensory phenomena in their sample of TS patients correlated positively with interoceptive sensitivity, but not with interoceptive perception - which presented a significant positive correlation only with tics severity measured by the global severity scale (Yale Global Tic Severity Scale, YGTSS)[30]. Still, several functional neuroimaging studies show that areas involved in interoceptive processes activate just before the occurrence of tics; for example, conducted the first study to evaluate neurofunctional correlates of tics and reported that, during tic occurrence, there was significant hyperactivation as measured by positron emission tomography, insula, somatosensory cortex, and SMA. Bohlhalter et al.[31], Neuner et al.[32] and Wang et al.[33] reported similar results when analyzing the activation of different brain areas through functional magnetic resonance imaging; particularly, SMA and somatosensory cortex appear to be activated prior to the occurrence of tics, whereas insula and other paralimbic areas (eg ACC) appear to be activated for about 1s prior to the occurrence of tics.

Studies investigating the relationship between interoception and sensory phenomena in OCD are largely lacking. Subira et al.[34] demonstrated that patients with OCD who reported experiencing sensory phenomena had a higher volume of somatosensory cortex than patients with OCD who did not report sensory phenomena. Recently, Brown et al.[35] demonstrated a significant correlation between the severity of sensory phenomena measured by the USP-SPS scale and the hyperactivation of insula measured by functional magnetic resonance versus stimuli considered interoceptive in patients with OCD; however, the authors failed to demonstrate a significant correlation between scores of the multidimensional assessment of interoceptive perception (MAIA)[36], a measure of interoceptive sensitivity, and severity of sensory phenomena. Different factors may explain this negative result. For example, it is possible that the measure of interoceptive sensitivity is not adequate to evaluate interoceptive ability because it does not consider an objective measure of interoception, that is, the actual interoceptive performance of the study participants. Moreover, it is also possible that the negative results arise from the fact that the authors did not consider possible heterogeneity of neurobiological correlates associated with mental sensorial phenomena vs. body sensorial phenomena.

Therefore, future research on OCD could aim at demonstrating the neurobiological correlates of sensory phenomena; particularly, it would be interesting to look at whether brain regions associated with interoceptive processing are also associated with the genesis of sensory phenomena in OCD. In that way, researchers could further develop circuit-specific interventions that could lead to better outcomes than the ones obtained with current treatments available for OCD. Although these developing interventions targeted at specific neural circuits is somewhat novel in Psychiatry, few researchers have already tried to evaluate the efficacy of novel interventions for OCD considering the proposed pathophysiological pathways. For instance, considering the possible relationship between sensory phenomena and interoception, Stern et al.[37] recently demonstrated that high-dose ondansetron is capable of reducing the activation of brain regions involved in interoception, such as the insula; it remains to be seen whether ondansetron can be effective in the treatment of OCD, particularly among those individuals who experience sensory phenomena and are likely to have disturbances in the interoceptive system. A randomized, controlled trial previously employed ondansetron as an augmentation strategy in the treatment of individuals with OCD who did not respond to initial treatments, with promising results reported[38]. Additionally, da Silva et al.* (unpublished) recently carried out a clinical trial evaluating

*Personal comunication - Silva et al.

the effectiveness of brain stimulation through direct current on the supplementary motor area as a treatment for OCD, with promising results found; it remains to be seen whether such circuit-based treatment approach could be effective in individuals with OCD who report sensory phenomena.

In conclusion, Psychiatry, in line with other specialties in Medicine, is a science in continuous transformation. Although diagnostic criteria as established by the ICD and the DSM are key to clinical practice and uniformization of diagnosis, treatment and research, they do not consider neurobiological information. Physiopathological information about mental disorders could be employed to improve treatment of individuals with psychiatric disorders; yet, it is not clear how this could be done. Elucidating the participation of specific brain circuitries involved in transdiagnostic features of mental disorders is potentially of great clinical value to guide neurocircuitry-based treatments based on the RDoC initiative. The RDoC approach is novel and there are few studies evaluating how their domains can translate into clinical practice to generate diagnostic and treatment benefits in comparison to current categorial models. Future workgroups of diagnostic manuals should likely consider establishing experimental diagnostic criteria which considers neurobiological data in addition to common diagnostic criteria to expand further research on Psychiatry. Initiatives aimed at identifying intermediate transdiagnostic phenotypes among different psychiatric disorders are also promising and can lead to significant advancements in the field.

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