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ARTICLE

Outlining new frontiers for the comprehension of obsessive-compulsive disorder: a review of its relationship with fear and anxiety

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Abstract
Anxiety is an important component of the psychopathology of the obsessive-compulsive disorder (OCD). So far, most interventions that have proven to be effective for treating OCD are similar to those developed for other anxiety disorders. However, neurobiological studies of OCD came to conclusions that are not always compatible with those previously associated with other anxiety disorders. *Objectives:* The aim of this study is to review the degree of overlap between OCD and other anxiety disorders phenomenology and pathophysiology to support the rationale that guides research in this field. *Results:* Clues about the neurocircuits involved in the manifestation of anxiety disorders have been obtained through the study of animal anxiety models, and structural and functional neuroimaging in humans. These investigations suggest that in OCD, in addition to dysfunction in cortico-striatal pathways, the functioning of an alternative neurocircuitry, which involves amygdalo-cortical interactions and participates in fear conditioning and extinction processes, may be impaired. *Conclusion:* It is likely that anxiety is a relevant dimension of OCD that impacts on other features of this disorder. Therefore, future studies may benefit from the investigation of the expression of fear and anxiety by OCD patients according to their type of obsessions and compulsions, age of OCD onset, comorbidities, and patterns of treatment response.

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Introduction

The future of the diagnostic classification systems of psychiatric disorders (DSM and ICD) has been a matter of debate in recent literature.[1] Several authors participating in the DSM-5 task force have built the argument in favor of obsessive-compulsive disorder (OCD) as the core diagnosis of a new group within the anxiety disorders umbrella, known as obsessive-compulsive spectrum disorders.[2,3] More recently, the grouping of disorders for both future DSM-5 and ICD-11 (also known as their meta-structures) has been thoroughly reviewed, and additional questions have been raised regarding not only the relationship between OCD and anxiety disorders, but also its relationship to post-traumatic stress (currently classified as an anxiety disorder) and the until now independent group of dissociative disorders.[4]

It has been pointed previously that the grouping of disorders in the future classifications might have several implications to research, diagnosis, and management of psychiatric disorders. Disorders grouped together presume greater familial aggregation and co-occurrence, similar psychopathology or etiological bases, as well as sharing the main pharmacological or psychotherapeutic treatments.[4] As an effort to contribute to this discussion and to bring it to new audiences, we review the main findings in recent literature regarding several aspects of the relationship between OCD and other anxiety disorders from the field of psychopathology, also including a broad selection of methods encompassing human and animal research that investigated the neurobiology of fear and anxiety. Our goal is to investigate the degree of overlap between OCD and other anxiety disorders phenomenology and pathophysiology to support the rational for future research in the area.

OCD classification as an anxiety disorder

Psychopathology

In the DSM IV-TR criteria for OCD, anxiety is mentioned once in the description of obsessions: "Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and inappropriate, causing anxiety or distress" (transcribed from DSM IV-TR manual). The choice of using the conjunction "or" in that sentence leaves the ground open for interpreting that anxiety may not be a symptom required for the diagnosis of OCD. But is that really the case? Moreover, even if anxiety was proven to be a symptom required for OCD diagnosis, another important question to be answered would be: Is anxiety a core symptom of OCD or irrelevant epiphenomena?

The definition of anxiety itself is complex because it includes physiological responses (such as increased sweating, elevated heart rate, tremor, hyperventilation etc.) and cognitive experiences (such as repetitive thoughts about a fearful situation or imagining catastrophic events that might happen in the future). Some authors differentiate fear from anxiety based on their temporal relation to the fearful situation. While anxiety is the anticipation of a future threat, fear is the response to the present threat. However, fear and anxiety share the same physical and mental symptoms.[5]

Most OCD patients report that they perform repetitive rituals to alleviate the uncomfortable feelings resulting from increased anxiety. Nonetheless, after analyzing the verbal reports of subjective sensations preceding patients' compulsive rituals, some authors[6] reported that other feelings (besides increased anxiety) can be part of the discomfort preceding OCD repetitive behaviors. Such subjective feelings have been named sensory phenomena, a term that encompasses localized tactile and muscle-skeletal sensations; "just-right" perceptions associated to sensory stimuli, such as visual, tactile, or auditory; "just-right" feelings not associated with any triggering stimuli; feelings of incompleteness; energy; and an urge.[6,7]

Sensory phenomena have been associated with the need of perfection[8] and the presence of comorbid tic disorders.[6] Miguel et al.[9] tried to differentiate OCD patients with and without Tourette Syndrome (TS) – a severe variant of tic disorders – based on the presence of obsessions, autonomic anxiety, and sensory phenomena. They found that OCD patients without TS had a higher frequency of cognitive phenomena (obsessions) and autonomic anxiety preceding their repetitive behaviors, while OCD patients with Tourette syndrome had a higher frequency of sensory phenomena. Less studied, the finding of higher autonomic anxiety preceding compulsions in OCD patients without tics was neither replicated nor investigated in other studies. To make this issue more complex, some patients report the cognitive component of anxiety in the absence of autonomic symptoms. Therefore, the relevance of sensory phenomena (in comparison with increased anxiety) as the trigger of compulsions has not yet been established, and the question if anxiety is always present in OCD remains unanswered.

The discomfort alleviated by compulsions may also appear as a feeling of "disgust". This feeling is characteristic of OCD with contamination fears and cleaning rituals, but it is present in other anxiety disorders such as post traumatic stress disorder (PTSD)[10] and specific phobia.[11] Disgust, however, cannot be disentangled from anxiety (the higher the disgust the worse the anxiety).[12] So, once more, it is unclear if compulsions can be maintained without increased anxiety.

The role of anxiety in the maintenance of compulsive behavior will be better explored in the treatment response section of this review. Briefly, for a significant part of OCD patients, the treatment based on anxiety reduction and habituation is reasonably effective in reducing OC symptoms.[13] In summary, for a significant proportion of patients, anxiety plays a major role in OCD psychopathology. It is unclear if there is a subgroup of patients who do not have anxiety as the main cause of the discomfort preceding compulsive behavior. Given the current evidence, the classification of OCD as an anxiety disorder based on psychopathology seems reasonable, as well as the continuing investigation of mechanisms involving fear and anxiety in OCD patients.

Epidemiology

Comorbid disorders are the rule rather than the exception in OCD and it is estimated that OCD is accompanied by at least one additional psychiatric condition in 32-90% of the patients.[14-19] As a group, anxiety disorders are the most frequent comorbid conditions in OCD.[16,18-20]

Social anxiety disorder (SAD) is a frequent condition in OCD patients and some studies describe it as the most prevalent comorbidity among the anxiety disorders.[17,21,22]

Epidemiological studies have described the prevalence of SAD in OCD ranging from 15% to 43.5%,[18,19,21,23] whereas in clinical samples the reported prevalence rates were: 14%,[24] 15.6%,[16] 21.8%,[25] 23.4%,[22,26] 26%,[27,28] 36.2%,[29] and 42%.[30]

Rasmussen et al.[31] studied 44 OCD patients and found high rates of comorbidity with other anxiety disorders. Simple phobia was the most frequent condition (27%), followed by SAD (18%), separation anxiety disorder (18%), panic disorder (14%) and agoraphobia (9%). Eisen et al.[22] found the following rates of comorbidity in a prospective study: simple phobia (20.8%), generalized anxiety disorder (19.5%), and panic disorder (11.7%). Rasmussen et al.[28] studied 100 patients with a primary diagnosis of OCD and observed that 22% of them had comorbid simple phobia and 12% panic disorder. In a British epidemiological survey.[18] the most frequent OCD comorbidity was depressive episode (36.8%), followed by GAD (31.4%), agoraphobia or panic disorder (22.1%), SAD (17.3%), and specific phobia (15.1%).

Although relatively more frequent in OCD patients than in the general population, other anxiety disorders may have an independent clinical course. In addition, at least some OCD patients may not experience an additional anxiety disorder during their life span. Therefore, it is adequate to classify OCD as a disorder and not as a symptom of other anxiety disorders. On the other hand, comorbidity patterns point toward a close association between OCD and other anxiety disorders, specially social phobia and GAD.

Neurobiology

The neurobiology of OCD and other anxiety disorders is not fully understood. Clues about the neurocircuits involved in the manifestation of anxiety symptoms have been obtained through the study of animal models of anxiety and structural and functional neuroimaging in humans. The findings that resulted from the use of such methodologies are described below.

Animal models of anxiety

Because OCD is a heterogeneous and extremely complex disorder, different animal models are used in an attempt to better understand the distinct aspects and subtypes of OCD. Due to the cognitive nature of obsessions, they are not directly accessible in animals, but since the cognitive and motor manifestations of OCD are intimately linked, modeling compulsive behaviors is a common approach for an OCD animal model. However, the manifestation of compulsive behaviors is consistent with the presence of some degree of generalized anxiety and, thereby, it is not easy to distinguish among anxiety, obsession, and other forms of distress. Ethological animal models of OCD include repetitive or stereotyped behaviors and instinctive motor behaviors that occur during periods of conflict or stress.[32-34] On the other hand, in pharmacological animal models of OCD certain drug treatments may induce behavioral alterations that resemble the behavioral aspects of this disorder.[32-34] In this section, we briefly describe some ethological and pharmacological animal models of OCD.

Stereotypy models

In animals, motor stereotypy, represented by a wide range of invariant and repetitive behaviors, can be induced through pharmacological manipulation or may occur spontaneously. Grooming has been considered the most common type of stereotyped behavior recorded in animals in the context of the study of the neurobiology of OCD. The acral-lick dermatitis, a grooming disorder characterized by excessive licking or biting of extremities, is related to cleaning rituals observed in OCD and responds to treatment with serotonin reuptake inhibitors (SRIs).[35,36] Also, the plucking of fur or whiskers from cage mates or the animal itself is a common form of an abnormal, repetitive behavior that has similarity with hair pulling in humans (trichotillomania), which is found in OCD.[37,38] Pharmacologically, investigations have focused on the influence of the serotonergic and dopaminergic systems in the expression of these behaviors.

Pharmacologically-induced attenuation in spontaneous alternation behavior

Spontaneous alternation behavior refers to the natural tendency of rats to sequentially and successively explore novel places. In this model, food deprived rats are allowed to run in a T-maze in which both goal-boxes are baited with flavored milk. The mean number of choices made until an alternation occurs is the critical measure. The reduction of spontaneous alternation has been proposed as a model of the perseverative symptoms and indecisiveness seen in OCD[39,40] and it is prevented by chronic treatment with fluoxetine.[40]

Quinpirole-induced compulsive checking behavior

In the experiment first proposed by Szechtman et al.[41], after about 10 repeated injections (spaced at 3-4 day intervals) of the D_2/D_3 dopaminergic agonist quinpirole, rats became sensitized to the drug, reaching a high level of activity in the open-field. Quinpirole-induced behavior has the form of compulsive checking, one of the most distinctive behaviors in OCD patients.[42,43] Compulsive checking is present if a rat returns to a particular locale excessively often and rapidly with rare visits to other places; in addition, quinpirole-treated rats perform a characteristic set of ritual-like motor acts.[41,44] Clomipramine, which is used in the pharmacotherapy of OCD, attenuates the development of quinpirole-induced compulsive checking behavior.[41]

Hypergrooming induced by administration of oxytocin in the central nucleus of amygdala

A possible relationship between oxytocin and OCD was suggested since high levels of this neuropeptide were found in the cerebrospinal fluid of patients with OCD.[45,46] In rodents, administration of oxytocin in the central nucleus of amygdala (CeA) induces hypergrooming and it has been suggested as a model of OCD.[47] In the oxytocin model, rats receive an injection of oxytocin in the CeA and are placed in an open-field for the quantification of grooming behaviors. As a displacement behavior that occurs in situations in which the animal experiences conflict or indecision,[48,49] grooming must act, probably through oxytocin, as a counter mechanism to overlap increased anxiety.

Food restriction-induced hyperactivity

In the food restriction-induced hyperactivity model, rats fed only once a day and given access to a running wheel begin to run excessively and eat less.[50,51] Although food

restriction-induced hyperactivity has long been considered an animal model of anorexia nervosa,[52,53] it also has features analogous to OCD; for example, fluoxetine attenuates food restriction-induced hyperactivity, whereas imipramine, which is ineffective for treatment of OCD, does not affect the development of the syndrome.[51]

The signal attenuation model

The signal attenuation model has been developed based on the theoretical proposal that compulsions result from a deficit in the signaling associated with the performance of goal-directed responses.[33,34] In this model, the goal-directed behavior is lever-pressing for food. The effects of signal attenuation on lever-pressing responses are assessed under extinction conditions (i.e., pressing the lever results in the presentation of a conditioned stimulus but no reward is delivered). The effects of non-reward are clearly seen in the form of excessive lever-presses, suggested as a measure of compulsive behavior.[54] Excessive lever pressing is attenuated by SRIs, whereas tricyclic antidepressants, anxiolytics and antipsychotics had no effect.[54-56]

Marble burying test

Rodents use bedding material to bury either noxious or harmless objects. In this model, burying of glass marbles by laboratory rodents begins as an appropriate activity but, after frustrated investigation of the nonreactive stimulus object, the behavior persists as a compulsive stereotypy.[57,58] Because the duration and extent of burying were reduced by a variety of anxiolytic drugs, this model was originally suggested as a screening test for anxiolytic activity.[57-60] The finding that burying was reduced by SRIs raised the possibility that this behavior may also be related to OCD.[57-59]

From the knowledge obtained with animal models of obsessive-compulsive behavior, it becomes clear that establishing conditions that would enable the differentiation between the action of anxiolytic and anti-compulsive drugs is a critical issue. Accordingly, it is challenging to find an animal model of OCD that avoids the ambiguity frequently seen in the current animal models of anxiety. To disclose particularities in the different forms of fear based on ethological, pharmacological and genetic parameters would be the best approach for addressing certain questions like the development and/or test of new treatments for OCD.

Functional and Structural Neuroimaging in Humans

The classical dominant neurocircuitry model of OCD points to the involvement of cortico-striatal pathways that mainly interconnect the orbitofrontal and anterior cingulate cortices, striatum and thalamus.[61,62] Functional neuroimaging studies performed in patients with OCD, at rest and during symptom provocation, have demonstrated elevated regional brain activity within these regions that attenuates after successful treatment with both selective SRIs and CBT.[62] Likewise, a growing number of short-term longitudinal structural neuroimaging investigations have documented regional gray matter volume changes within cortico-striatal pathways in OCD patients, especially after medication.[61] However, progresses in the field of neurosciences and brain imaging investigations have now suggested that the cortico-striatal model of OCD is not sufficient to explain such a complex and heterogeneous disorder.[63] As aforementioned in this review, the classification of OCD as an anxiety disorder seems pertinent, as a significant proportion of patients experiences extreme levels of anxiety. In these patients, beyond a dysfunction in cortico-striatal pathways, the functioning of an alternative neurocircuitry, that involves amygdalo-cortical interactions and participates in fear conditioning and extinction processes, may be impaired.[64] Moreover, recent anatomical investigations have shown that the cortico-striatal loops are much more integrated to other brain nodes than it was considered in the past.[65] For example, medial portions of the orbitofrontal cortex, a key cortical node within the cortico-striatal loop and extensively implicated in OCD,[66] have connections to several brain regions that mediate fear and anxiety, such as the amygdale.[67]

Convergent data from animal models and human studies indicate that the amygdala plays a central role in threat appraisal and expression of conditioned fear responses, in which exacerbated amygdala activation leads to inappropriate or excessive fear manifestation.[64] On the other hand, particular cortical regions, such as the ventromedial prefrontal and medial orbitofrontal cortices, by inhibiting amygdala hyperresponsiveness, are implicated in fear extinction.[68] In addition, the hippocampus also modulates amygdala responsiveness by providing contextual information of a given situation.[69] Thus, the neurobiology of anxiety disorders may involve a deficient prefrontal top-down inhibition over exaggerated amygdala responses to emotional salient situations.[70]

Evidences of amygdala hyperactivation leading to increased fear response to specific threat-related stimuli have been reported in patients with PTSD,[71] panic disorder,[72] SAD, specific phobia,[73] GAD,[74] and OCD.[75] However, despite some similarities, OCD may differ from other anxiety disorders. The connectivity between the amygdala and the prefrontal cortex, which is usually diminished in other anxiety disorders, is increased in OCD patients compared to controls.[76] Moreover, when submitted to nonspecific threat-related stimuli, instead of hyperactivation, OCD patients present hyporesponsivity of the amygdala.[77] Lastly, the pattern of elevated regional brain activity within orbitofrontal and anterior cingulate cortices, striatum and thalamus extensively observed in OCD patients[62] is not found in other anxiety disorders. Therefore, although the fear response seems to be increased in OCD patients, the mechanisms responsible for this increase might be different from the ones responsible for the exaggerated fear response observed in other anxiety disorders.

Electrophysiological studies in humans

Electrophysiology encompasses a myriad of techniques aimed at measuring physiological responses (such as palmar sweating, heart rate variability, and muscular activity) that are associated with emotional mechanisms (such as fear and anxiety). In this section, we will review the main findings based on the observation of alteration in the galvanic skin conductance response (related to aforementioned palmar sweating), heart rate, and muscular activity consequential to fear in OCD and other anxiety disorders. The studies included in this review have investigated the magnitude of the muscular reflexes triggered by fear (e.g.

acoustic startle) or one pattern of fear acquisition known as classical conditioning. Although other mechanisms of fear acquisition have been previously postulated (for a more comprehensive review see Hofmann[78]), classical conditioning has provided the best experimental conditions. It is easily translated into findings from animal models (as its effects can be observed irrespectively of the underlying cognitive processes involved), and the fear response is acquired by most individuals regardless of their previous contacts with the stimulus presented or with characteristics of their innate fear responses. It is important to mention that this experimental condition does not account for factors such as predictability and uncontrollability of the aversive events; these factors have been shown to be highly associated with the presentation of the fear response in animal models.[79] The lack of studies that evaluated other types of fear acquisition in OCD and the relative abundance of studies of classical conditioning in anxiety disorders was the main reason that guided this decision.

The acoustic startle (also known as auditory startle) is a reflex elicited by sudden loud tones that is characterized by increases in skin conductance, heart rate and contraction of muscles such as the orbicular muscles that are responsible for the blinking movements. The muscular activity measured by the electromyogram is commonly used to determine the startle magnitude. The magnitude of the fear response (acoustic startle) was greater in patients with panic disorder,[80] PTSD,[81] SAD,[82] and GAD[83] than in healthy subjects. In OCD, results are still inconsistent[84,85] but point toward a trend of larger unconditioned responses when compared to healthy controls. In one study, the fear response presented by OCD patients exposed to loud tones was characterized by larger than expected increases in heart rate while alterations in skin conductance and electromyogram showed similar patterns to controls.[85]

The classical conditioning was first described in animals and corresponds to the effect of presenting an innately aversive stimulus (the unconditioned stimulus, e.g. an electric shock) right after a neutral stimulus (the conditioned stimulus, e.g. a blue square figure or a mild sound). This procedure causes the previously neutral stimulus to elicit the fear response in the absence of the unconditioned stimulus. The fear response can be extinguished after repetitive presentations of the conditioned stimulus not followed by the unconditioned one. However, the fear response can resurge after being extinguished and this process is called failure of extinction recall.[86] The fear response produces a sensible increase in the galvanic skin response (associated with palmar sweating)[87] and in the heart rate.[88] Therefore, variability in skin conductance and heart rate are commonly used as methods to estimate the magnitude of the fear conditioned response. As mentioned earlier, the learning of the conditioned fear response as well as that of extinction is associated with the activation of the amygdala (among other brain regions), whereas the ability to recall extinction involves the activation of the medial prefrontal cortex. The hippocampus also plays a key role in this conditioned fear circuit.[69]

Although classical conditioning probably does not explain most of acquired fears, it has been shown to be involved in the etiology of symptoms in specific phobias,[89] SAD,[90,91] panic disorder[92] and PTSD.[93] In panic disorder, one small study (n = 39 panic disorder patients and 33 healthy subjects) has found a pattern suggestive of resistance to extinction of the conditioned fear in patients compared to controls.[92] In SAD, on the other hand, one study (n = 20 SAD patients and 18 healthy subjects) has found that patients responded with fear to aversive facial expressions and showed conditioned fear to stimulus paired with the aversive facial expressions while in controls, such phenomena were not observed.[91] However, the most consistent finding regarding fear conditioning in anxiety disorders is the failure to recall extinction found to be much more prevalent among PTSD patients than healthy subjects.[93,94] One study (n = 39 patients with OCD and 21 healthy subjects), has explored the effects of fear conditioning in OCD.[95] In that study, however, authors chose to look at the responses promoted by fear conditioning and extinction through their effect on the auditory evoked potentials instead of looking at skin conductance and heart rate variability. The suppression of the auditory evoked potentials is a measure of sensory gating (this concept will be better discussed in the following sections of this review) and has been shown to be altered in a broad range of disorders such as schizophrenia and different anxiety disorders. In the study by Nanbu et al.,[95] the sensory gating of OCD patients was altered in both the conditioning and extinction phases of the experiment, while in healthy subjects the altered sensory gating was evident during conditioning but recovered to baseline levels during extinction. These results suggest that although a dysfunction in the ability to extinguish a conditioned fear may not be present in OCD, the sensory gating alterations produced by conditioning do not go back to normal with extinction, as is the case in healthy subjects.

Future studies are warranted to replicate the findings mentioned above. The preliminary results obtained so far corroborate the hypothesis that fear conditioning may be a valid model to be used in the investigation of mechanisms related to fear acquisition and extinction in OCD, at least for a subgroup of patients. However, more elaborate methodology may be required if traditional methods yield negative results.

Sensorimotor gating

Sensorimotor gating corresponds to the ability of the brain to inhibit an unconditioned motor response in the presence of the stimulus that usually elicits that response. Classically, this gating ability is tested trough the presentation of a weak stimulus (the prepulse) preceding the full stimulus that has been previously shown to elicit the motor response (startle) in the individual being tested. The prepulse inhibition (PPI) effect is not prone to extinction or habituation and remains stable even after multiple testing. Moreover, it is observed in all mammals and therefore it can be studied across species.[96]

Initially, PPI was shown to be altered in patients with schizophrenia (the presentation of the weak stimulus was not able to inhibit the startle response more often than in healthy subjects). However, more recently it was found to be altered in other neuropsychiatric disorders as well, such as panic disorder.[97,98] PTSD,[99] OCD,[100,101] and Tourette's Syndrome (TS) alone[102] or comorbid with attention deficit and hyperactivity disorder (ADHD),[103] among others.[96] In OCD, Ahmari et al.[101] performed an exploratory analysis of their results (n = 22 OCD patients and 22 healthy subjects) and suggested that patients with comorbid tics are the ones

with lower levels of PPI. Negative findings have also been reported for PTSD[81,104] and OCD,[105] but the inconsistencies may be explained by methodological issues.[96]

In animal models, the disruption of PPI has been shown to be the consequence of pharmacological interventions interfering with dopaminergic, serotonergic or glutamatergic pathways.[106] In addition, it has been related to lesions in the limbic cortex, striatum, pallidum or pontine tegmentum.[107] Therefore, the findings of unspecific disruption of PPI in different neuropsychiatric conditions may be actually the effect of completely independent mechanisms that lead to the dysfunction of the cortico-striatum-thalamo-cortical circuit.

Neuropsychological studies in humans

The findings from neuropsychological studies suggest that OCD patients present specific cognitive impairments when compared to healthy subjects. The visuospatial abilities and executive functions (mainly inhibitory control and cognitive flexibility) seem to be the most impaired functions in OCD.[108] Such cognitive alterations can even precede the onset of the disorder[109] and also be present in unaffected relatives of OCD patients.[110] In this section, we will review the findings from neuropsychological studies that compared OCD patients with other anxiety disorders as an attempt to elucidate the specificities of cognitive dysfunction in OCD.

A few studies compared the performance of patients with OCD, panic disorder and healthy controls. Using the Cambridge Neuropsychological Test Automated Battery (CANTAB), Purcell et al.[111] found that while panic disorder patients did not differ from controls regarding executive functions, OCD patients presented significant deficits of executive functions (initiation of tasks) and motor abilities (processing speed). Using a different methodology, Clayton et al.[112] found specific deficits in attentional inhibition of OCD patients on psychometric attention tests (Test of Everyday Attention - TEA), compared with panic disorder patients and controls. Boldrini et al.[113] also reported specific deficits in OCD in verbal fluency using the test Controlled Oral Word Association (COWA), in visual performance tasks such as the Corsi Block Task and the Rey-Osterrieth Complex Figure Test (RCFT), and in set shifting using the Wisconsin Card Sorting Test (WCST) when compared to panic disorder patients. In this later study, both groups presented deficits in spatial learning compared to healthy controls. In the study by Bannon et al.,[114] no differences between groups were evident regarding planning, verbal fluency or working memory, but OCD patients had worse performance in tests measuring cognitive flexibility (WCST) and inhibitory control (assessed by Stroop and Go-Nogo tasks).

Regarding neuropsychological performance, OCD patients have shown deficits that are more evident than the ones shown by panic disorder patients. The comparison with other anxiety disorders (SAD, GAD and PTSD) has not been investigated so far. In general, anxiety disorders do not seem to share any specific patterns of dysfunction except for the one described as attentional bias that will be reviewed below.

Attentional Bias

The preferential allocation of attentional resources toward threatening as compared with neutral stimuli is known as attentional bias,[115] which is significantly increased in anxious individuals compared with healthy subjects.[116] The measurement of attentional bias across disorders varies greatly, as paradigms use different types of stimuli and indirect evaluations of attention. Stimuli can be words, images or faces that are threat specific (related to the main condition being investigated) or not.[116] The reaction time to perform a specific task is the most common indirect measure of attention[116] (as is the case for emotional Stroop test and dot probe paradigms) but other measures based on eye movement[117] have also been used.

Most anxiety disorders have been associated with attentional bias, including: specific phobia,[118,119] SAD,[120,121] GAD,[122] PTSD,[123] and panic disorder.[124] In OCD, both positive[115,125] and negative[126,127] findings have been reported. Contrasting with what has been found in other anxiety disorders, unspecific attentional bias was shown not to be prominent in OCD patients compared with healthy subjects.[127] Specific bias has been associated with OCD in a few studies.[115] In a small study (n = 23 OCD subjects with contamination fears and 5 subjects without OCD or contamination fears), Cisler et al.[115] found that OCD patients had slower reactions after the presentation of pictures representing disgust and unspecific fear compared to controls. The authors interpreted that this was a sign of difficulty in disengaging attention from both specific and unspecific threatening stimuli. In a larger study (n = 48 OCD patients), Sizino da Victoria et al.[128] found that within the OCD population the reaction to specific stimuli was associated with the severity of that symptom dimension in the subject being tested. In addition to this specificity of reaction, if any attentional bias is present in OCD, it might be related to specific subtypes. Therefore, further studies exploring attentional bias toward personally salient stimuli in subgroups of OCD patients are still warranted.

Treatment response

Psychopharmacology

Anxiety disorders, including OCD, share similarities regarding pharmacological treatment, although prognosis and length of treatment may vary for each disorder. Most anxiety disorder patients experience a progressive reduction of their symptoms with the continuous use of SRIs and immediate symptomatic relief with benzodiazepines.[129] Specific phobia is the exception to the indication of SRIs. OCD has a specificity related to the preferential response to antidepressants that are potent SRIs. Antidepressants with other mechanisms of action may be effective for the treatment of other anxiety disorders (such as imipramine for panic disorder[130,131] and GAD[132] and amitriptyline for PTSD[133]), but none has been shown to be effective for OCD treatment when used in monotherapy.[134]

Serotonin neurotransmission has been associated with the regulation of emotion including effects related to the response to stressful situations, sleep-wake cycle, sexual activity, and vulnerability to depressive symptoms.[135,136]

However, it is unknown if the dysfunction of serotonergic neurotransmission is the starting point of the etiological mechanisms that lead to anxiety disorders or the results of the interaction with other neurotransmission systems. Indeed, drugs acting in other neurotransmitters have been shown to be affective in the treatment of anxiety disorders. Alterations in the serotonergic pathways (either as the primary dysfunction or as a secondary consequence of other systems' dysfunction) play a major role in the mechanisms related to the maintenance of anxiety in most anxiety disorders including OCD.[137]

Psychotherapy

Regarding psychotherapy, most evidence based manualized treatments target specific anxiety symptoms. For example, prolonged exposure is specifically directed to the treatment of PTSD,[138] techniques of exposure therapy and cognitive restructuring were developed for specific phobia[139] and SAD,[140] and relaxation and breathing retraining are mainly used in panic disorder.[141] In OCD, exposure with response prevention (alone or in combination with cognitive techniques) is the intervention that was most studied and most frequently proven effective.[142] Nonetheless, many of the behavioral and cognitive techniques used in the treatment of anxiety disorders are based on the same principal of fear habituation through stimulus exposure.[143]

Exposure therapy was designed based on the observation that a conditioned fear response could be extinguished with the repeated presentation of the conditioned stimulus not followed by the innately aversive stimulus (also explained in the Electrophysiology section). Therefore, it was postulated that exposure to the frightening stimulus would lead to habituation (in other words, the extinction of the putatively conditioned fear response).[143] Anxiety disorders differ mostly in the characterization of the frightening stimulus. The stimulus can be: height, closed places, snakes, dogs, spiders etc., in specific phobia; public speaking or any social interaction, in social anxiety; physical alterations such as tachycardia, in panic disorder; places that are hard to escape from, in agoraphobia; and variable according to symptoms content in OCD (e.g. public restrooms in patients with contamination fears). In addition to the different type of stimulus, OCD requires that exposure is followed by response prevention; otherwise, the performance of a ritual will lead to a temporary reduction in anxiety that hampers the habituation process. Despite these peculiarities regarding OCD exposure therapy, as well as other anxiety disorders, OCD may improve with the habituation to the fearful stimulus suggesting that fear condition may participate in the etiology of obsessive fears.[144]

Conclusions and directions for future research

Anxiety is an important aspect of OCD with bases on its psychopathological presentation and, so far, most interventions that have been proved effective for treating OCD are similar to the ones developed for other anxiety disorders, such as SAD, GAD, panic, and PTSD. However, the study of the neurobiology of OCD has led to conclusions that are not always compatible with what has been previously associated with other anxiety disorders. For instance, an animal model of OCD has been developed with the injection of oxytocin (a hormone with anxiolytic properties) in the amygdala. In addition, OCD patients may not show increased response or lack of control over unspecific fear, such as SAD and GAD patients show, or may present with dysfunction of executive functions that are not at all impaired in patients with panic disorder. Moreover, OCD patients show a variety of patterns of activation obtained trough functional neuroimaging that not always resemble the classical amygdala activation described in PTSD, panic, and SAD. On the other hand, the pattern involving the orbital frontal cortex found in OCD may be related to the type of OCD symptoms and may not explain the alterations seen in all OCD patients.

The classical neurobiological model that suggests a dysregulation of the cortico-striatal circuits in OCD may be unsatisfactory to explain such a complex and heterogeneous disorder. Recent evidence that implicate an alternative neurocircuitry, which mediates fear responses and anxiety through the interaction between the ventro-medial prefrontal cortex, the medial orbital-frontal cortex and amygdala in the pathophysiology of OCD, may contribute to the development of new treatment approaches directed at fear habituation and extinction.

The investigation of the role of fear and anxiety in OCD may also elucidate the bases for such disparities. But more importantly, it may elucidate the disparities regarding symptom presentation and treatment response seen among OCD patients. It is likely that anxiety is a relevant dimension of OCD that may impact other patients' characteristics. Therefore, future studies should investigate the manifestation of fear and anxiety in association with heterogeneous characteristics of OCD, such as the type of obsessions and compulsions, the age at onset, comorbid diagnosis, and patterns of treatment response. Likewise, studies should investigate whether abnormalities in the ventro-medial pre-frontal cortex, the medial orbital-frontal cortex, and amygdala circuitry in different subtypes of OCD are warranted.

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