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Anxiety, Obsessive Compulsive, and Related Disorders (CB Nemeroff, Section Editor)

Symptom Dimensions in Obsessive-Compulsive Disorder as Predictors of Neurobiology and Treatment Response

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Abstract

Purpose of review Specific symptom dimensions of obsessive-compulsive disorder (OCD) have been suggested as an approach to reduce the heterogeneity of obsessive-compulsive disorder, predict treatment outcome, and relate to brain structure and function. Here, we review studies addressing these issues.

Recent findings The contamination and symmetry/ordering dimensions have not been reliably associated with treatment outcome. Some studies found that greater severity of sexual/aggressive/religious symptoms predicted a worse outcome after cognitive behavioral therapy (CBT) and a better outcome after serotonin reuptake inhibitors (SRIs). Contamination symptoms have been related to increased amygdala and insula activation in a few studies, while sexual/aggressive/religious symptoms have also been related to more pronounced alterations in the function and structure of the amygdala. Increased pre-treatment limbic responsiveness has been related to better outcomes of CBT, but most

imaging studies show that important limitations and replication in large-scale studies is needed. We review possible reasons for the strong limbic involvement of the amygdala in patients with more sexual/aggressive/religious symptoms, in relation to their sensitivity to CBT.

Summary Symptom dimensions may predict treatment outcome, and patients with sexual/religious/aggressive symptoms are at a greater risk of not starting or delaying treatment. This is likely partly due to more shame and perceived immorality which is also related to stronger amygdala response. Competently delivered CBT is likely to help these patients improve to the same degree as patients with other symptoms.

Introduction

Obsessive-compulsive disorder (OCD) is characterized by distressing obsessive thoughts, urges, or images, which patients try to manage or neutralize through compulsive rituals [1]. The disorder has a significant impact on quality of life and impairment in work, social, and family life [2], and ranks among the ten leading causes of disability in the developed world [3]. The current meta-analytic evidence suggests that treatment with cognitive behavioral therapy (CBT) involving exposure and response prevention (ERP) helps an average of approximately 50% of patients recover (95% confidence interval between 44 and 56%), significantly more than those only receiving serotonin reuptake inhibitors (SRIs) alone, the other first-line treatment for OCD [4, 5]. A recently developed concentrated exposure treatment reports considerably higher remission rates of ~ 75% after treatment [6, 7]. The immense personal and societal costs of OCD shows the pressing need to better understand the disorder and possible treatment mechanisms, in order to improve clinical outcomes for those who do not respond to current treatments [8].

OCD is highly heterogeneous in terms of symptom profile, comorbidity, and brain alterations, which presents a challenge for understanding and treating the disorder [8]. Several studies have suggested that symptom dimensions may relate to patterns of comorbidity, where especially aggressive/religious/sexual symptoms may predict a greater risk of comorbid mood and anxiety disorders compared to other dimensions [9–11]. That two patients with OCD may have little to no overlap between what they fear and which compulsions they perform has long been recognized [12], and a number of clinical interviews and questionnaires have been developed to measure specific symptom profiles [13, 14]. A prominent strategy for reducing symptom heterogeneity has been to focus on the content of the patient's obsessions and compulsions and to elucidate specific symptoms dimensions. A common measure for OC symptoms is the Yale-Brown Obsessive Scale Symptom Checklist (Y-BOCS-SC) [15], which contains 15 categories of obsessions and compulsions. Mataix-Cols and colleagues reviewed all factor analytic studies of the Y-BOCS-SC, and proposed a prominent multidimensional model [16], which has also received support from a factor meta-analysis [17]. This model suggests that the four dimensions contamination (washing), symmetry (ordering, counting), sexual/religious/aggressive obsessions, and hoarding may be the best conceptualization of symptom dimensions. The factor meta-analysis further indicated that checking compulsions were most related to aggressive/sexual/religious/obsessions [17], while others propose that checking can be a compulsion to decrease uncertainty present in several dimensions [13]. The multidimensional model does not argue that most OCD patients only have symptoms in a specific dimension, but instead that patients typically have symptoms in multiple dimensions but not necessarily with the same severity [16]. The dimensions appear to be somewhat stable over time, where qualitative shifts are rare, and previously having a symptom is the best predictor of having it in the future [18, 19]. However, it should be noted that most of the relevant factor analytic studies use techniques which assume that there are only a few independent dimensions, which may

obscure the correlation between dimensions. Research into symptom dimensions in OCD has also had clinical implications, and led to hoarding disorder as a separate disorder in the DSM-5 [1], and accordingly this review will not focus on hoarding symptoms.

Symptom dimensions could also be useful in discovering genetic markers of vulnerability for developing OCD. Current genome-wide analysis studies (including 1465 and 5061 patients) have not found a reliable genetic marker, though glutamate and serotonin-related polymorphisms show some promise [20–22]. These mostly negative findings could be affected by low sample sizes and the heterogeneity in OCD, and evidence from a British twin study (including 5022 participants) has suggested that symptom dimensions are all affected by common heritability for OCD, but that washing/contamination symptoms are less affected by specific genetic factors than the other dimensions [23]. However, there is also evidence to the contrary [24], and replication is needed.

The present review aims to briefly describe important findings that relate symptom dimensions of OCD to treatment outcomes and neuroimaging findings, discuss the limitations of current studies, and suggest some future directions.

Symptom dimensions as predictors of treatment outcome

Symptom dimensions have been related to the treatment outcome of both CBT and SRIs in several studies [see 25, 26 for reviews]. Out of a total of nine studies using a variant of CBT for adult OCD patients [27–35], three found that baseline sexual/religious symptoms predicted worse outcome [28, 32, 33•]. This was also found in one study which first provided SRIs followed by CBT [29]. In addition, one study found that contamination symptoms predicted better outcome [35] and one reported null findings [34]. Williams et al. [33•] included 87 patients from 2 randomized controlled trials using standard outpatient ERP, and found that a greater severity of sexual/religious/aggressive obsessions was related to a worse outcome after treatment. Follow-up tests indicated that having religious/moral and somatic obsessions was related to approximately 16.5% less symptom reduction after treatment. This study was strengthened by (1) their sample size, (2) including all dimensions as predictors in the same model, (3) providing well-described treatments, and (4) having independent raters evaluate post-treatment symptom severity.

Out of five studies using SRI treatment [36–40], two found that sexual/religious/aggressive symptoms predicted a better outcome [36, 37], and one found that patients with somatic obsessions were less likely to respond to treatment [40]. One study also found contamination symptoms to be a negative predictor of treatment outcome [37]. Finally, three studies reported no significant association between any symptom dimension and response to SRIs [38, 39, 41].

There are several scenarios in which sexual/religious/aggressive symptoms might not be adequately addressed in CBT [42, 43]: for example, when clinicians fear disrespecting the faith of religious patients during exposure to the thought that the patient will be sent to hell or is sinful, when patients struggle with the shame and stigma of admitting and facing taboo thoughts and images, or when clinicians fail to address how subtle mental compulsions, avoidance, and reassurance maintain the disorder [33•, 44]. However, evidence from a randomized controlled trial indicates that these patients are likely to improve as well as the patients suffering with symptoms from other dimensions when

these symptoms are included in the functional analysis and addressed using CBT [45, 46•, 47]. This shows that sexual/religious symptoms are not universally related to a worse outcome after CBT.

Both studies of CBT and SRIs in the literature often share important limitations: few are randomized trials with well-controlled treatments [e.g., 32, 34]; some are older studies using early models of CBT [30, 31, 35]; few measure treatment credibility, adherence, or compliance; and most are small sampled and use varying measures and definitions for symptom dimensions [e.g., 29, 30]. The studies also differ in whether they model symptoms as co-occurring dimensions (where the effect of each symptom dimension should be controlled for against the influence of the others) or as discrete symptom categories where patients only fall into one category (which ignores how patients often show symptoms in multiple dimensions).

Symptom dimensions, brain structure, and function

OCD has been related to subtle alterations in brain structure and function, with most studies focusing on parallel cortico-striato-thalamo-cortical (CSTC) circuits, which also include (para)limbic brain regions [8, 48]. Briefly, adult OCD has in meta- and mega-analyses been related to decreased gray matter volume in the hippocampus, inferior prefrontal cortex/insula, dorsomedial prefrontal cortex/anterior cingulate cortex (ACC), as well as increased volumes of the pallidum and cerebellum [49, 50]. Our recent meta-analysis of 25 emotion processing studies (including a total sample size of 571 patients and 564 healthy controls) using symptom provocation, cognitive tasks with emotional distractors, or other ways of inducing anxiety during scanning found that OCD patients, compared to healthy controls, showed increased activation in the bilateral amygdala, right putamen, orbitofrontal cortex (OFC) extending into the subgenual anterior cingulate and ventromedial prefrontal cortex, as well as the middle temporal, and left inferior occipital cortices [51]. These meta-analyses suggest that OCD is related to alterations in diverse areas of the brain, with functional and structural connectivity studies suggesting several interacting circuits which also include fronto-parietal and cerebellar regions [48, 52–54]. Factors such as medication, comorbidity, and age often influence how pronounced the differences between patients and healthy controls are [49–51, 55•].

Symptom dimensions and brain structure

Six studies have used voxel-based morphometry (VBM) to assess how symptom dimensions relate to regional gray matter volume [56–61]. Four studies found that increased severity of sexual/religious/aggressive and/or checking obsessions to be related to smaller gray matter volume in the temporal lobes [58], extending into the amygdala [60] and insula, as well as left OFC, putamen [56], and right cerebellum volume [59]. Meanwhile, washing and contamination symptoms have been related to smaller volume of bilateral caudate nucleus and right insula [58, 59], as well as smaller right thalamus volume [57]. Findings for the ordering and symmetry dimension are less clear, including both bigger and smaller volume of OFC, as well as bigger volume of other frontal regions such as

the dorsal ACC and medial frontal cortex [59, 61]. One study also found smaller motor, insular, and parietal volumes and bigger bilateral temporal volumes in relation to symmetry/ordering symptoms [58]. Notably, van den Heuvel and colleagues [58] separately analyzed the relation between brain structure and symptom dimensions using both the Y-BOCS-SC and the Padua Inventory-revised in 55 unmedicated OCD patients and 50 healthy controls, which showed some overlap but did not reveal exactly the same results. This shows how the definition of symptom dimensions may affect findings. Two studies have used diffusion tensor imaging (DTI) for symptom dimensions, but have yielded inconsistent findings [62, 63], highlighting the need for larger studies in the future.

Unfortunately, the results of most single-site structural imaging studies have not been replicated in current multi-site mega-analyses. Indeed, recent mega-analyses of subcortical volume (including 1830 patients and 1759 controls) and cortical thickness and surface area (including 1905 patients and 1760 healthy controls) found no significant association between symptom dimensions and brain structure [50, 55•]. The low rate of reproducible findings casts doubts on if and how symptom dimensions relate to brain morphology. Another open question in the current literature is what alterations in gray and white matter volume really mean. Current studies of gray matter volume or cortical thickness in OCD mostly rely on analysis of T1-weighted images, which makes it difficult to distinguish between underlying mechanisms such as changes in dendrites, synapses, glia, or neurogenesis [64]. Similarly, changes in fractional anisotropy in DTI studies can be driven by several different mechanisms which are not easily separated without additional imaging methods [64]. Finally, studies with a longitudinal design are needed to describe how the pathophysiology of OCD develops over the lifespan, which morphological characteristics relate to the vulnerability of developing OCD early in life, and which morphological characteristics are the consequence of a chronic pattern of pathological behavior or long-term effects of treatment [50, 55•].

Symptom dimensions and brain function

Functional studies of brain activation have found increased activation in subcortical structures such as the amygdala and insula during symptom provocation for contamination/washing symptoms [65–67]. These findings suggest an increased involvement of the fronto-limbic and affective circuits [48]. Sexual/religious/aggressive symptoms have been related to increased striatal activation during continuous performance tasks and conflict processing [68, 69], increased activation in the hippocampus during reward-based spatial learning [70], and increased hippocampus activation during symptom provocation [65]. However, two studies using electroencephalography both reported null findings [71, 72]. Improving upon earlier studies with smaller samples, the largest study to date included 67 OCD patients and 67 matched healthy controls who performed an emotional face matching task [73]. Here, sexual/religious/aggressive symptoms predicted greater amygdala activation during the matching of fearful faces. In addition, these symptoms were associated with greater activation in the ACC and premotor areas, and less activation in extended visual areas. The same group also found that the severity of sexual/religious symptoms were associated

with greater right amygdala, para-limbic, and ventrolateral prefrontal activation during a moral dilemma task, where the participants were asked to choose the lesser evil of two outcomes [74]. Finally, they also assessed resting-state functional connectivity with a seed region in the ventral striatum [75]. Here, they found that the severity of aggressive symptoms correlated negatively with connectivity with the bilateral amygdala, and positively with medial prefrontal connectivity. They also found that sexual/religious obsessions correlated positively with connectivity between the ventral striatum, the right inferior frontal gyrus and insula, as well as with the left superior temporal gyrus [75]. In general, neuroimaging studies of symptom dimensions have suffered from small sample sizes, variation in methodologies that limits generalizability, and replication in multi-site mega-analyses is needed. Another challenge for functional neuroimaging is how to best elicit obsessions and anxiety related to aggressive, sexual, and religious obsessions, as these symptoms can be very specific to situations, physical sensations, or images that are hard to experimentally manipulate. Future studies should develop more ecologically valid paradigms to better shed light on the neural correlates of these symptoms.

The current findings suggest that aggressive/sexual/religious symptoms may be related to the function and structure of the amygdala and other structures in the limbic circuit. The amygdala has also been implicated in studies using pre-treatment fMRI to predict treatment outcome [76], where greater amygdala activation has been found to predict better treatment outcome after CBT [77, 78]. A recent resting-state fMRI study further suggested that decreased amygdala-ventromedial prefrontal cortex connectivity predicted good treatment outcome [79]. It should be noted that several of these studies were limited by a low degree of symptom improvement after treatment, two had only small samples (12–17 patients), and that other regions beside the amygdala also predicted treatment outcome. Taking these limitations into account, these studies seem to suggest that increased amygdala activation and decreased fronto-limbic connectivity could predict a better treatment outcome for OCD patients in general. An important question is therefore why patients with sexual/aggressive/religious symptoms show both increased amygdala activation and worse outcome after CBT? We discuss some possible reasons for this below.

Linking the amygdala and sexual/aggressive/religious symptoms

Sexual/aggressive/religious symptoms have been related to struggling with feelings of being immoral or going against one's religion, and these patients more often appraise their obsessions as signs that they are immoral persons [e.g., 80, 81, 82]. These factors, along with the shame and possible rejection of admitting these symptoms [83], have also been suggested as important factors in delaying seeking treatment [42].

There is evidence from both single studies and meta-analysis in healthy controls that the process of moral reasoning is related to increased activation in a network of structures, including the amygdala and ventromedial prefrontal cortex [e.g., 84, 85, 86]. Recent evidence from intracranial field potential recordings further suggests that amygdala serves as a key hub in the detection of

potential intentional harm [87]. This fits with the results of the only functional neuroimaging study of moral reasoning in OCD, reporting that patients with more severe sexual/aggressive symptoms also showed more amygdala activation during moral reasoning [74]. Though more research is clearly needed, this may suggest that the link between sexual/aggressive/religious symptoms, amygdala activation, and connectivity could be partly explained by greater moral disgust and shame [43].

As reviewed above, patients with sexual/aggressive/religious symptoms may show increased amygdala activity (which has previously been related to a better outcome after CBT), but also have worse outcome after CBT than other symptom dimensions in some studies. One reason for this could be that while these patients show intense distress (and amygdala activation) in response to their obsessions, this distress is not useful if it is inadequately addressed in treatment. Indeed, the current literature suggests that higher initial distress levels during exposure are not a reliable predictor of outcome [88, 89]. Instead, recovery is likely a result of learning new ways of tolerating this distress through several factors, including early reduction of safety behaviors and ritualization, exposing oneself in varied contexts, and with variability in distress [88–91]. Given the greater shame and perceived immorality in these patients [42], it is likely even more important to ensure that both patients and therapists adhere to the treatment principles. When this condition is met, they are also much more likely to improve as much as patients struggling with other symptom dimensions [25, 43, 46•, 47].

As reviewed above, the development of symptom dimensions in OCD was partly meant to reduce the heterogeneity of the disorder [16]. However, early findings of symptom dimensions predicting treatment outcome and neurobiology have often not been replicated in larger samples [43, 46•, 50, 55•]. We propose that several improvements are needed. First, the validity of symptom dimensions as predictors for successful treatment need to be evaluated in larger patient samples receiving well-described behavioral treatment of high quality. Second, we need to understand the mechanism for why some symptoms are harder to treat with CBT or SSRIs, and move beyond correlational studies on symptom dimensions solely, and include the full spectrum of behavioral and cognitive characteristics of the clinical phenotype in relation to reliable and reproducible neuroimaging markers. Third, we should apply recent methodological developments, such as machine learning, to see if symptom dimensions provide an added benefit over other clinical and neuroimaging markers in predicting treatment outcome and phenotypical variation. By combining these sources of information, it could be possible to understand why some patients improve and others do not, and how we can better tailor treatment to the individual [92]. A recent example comes from a study of 118 depressed patients, which used pattern recognition to combine structural T1-weighted images, fMRI from emotional face and Tower of London tasks, as well as clinical characteristics to predict which patients remit and which follow a chronic course after 2 years [93]. This study found that activation in response to emotional faces predicted the course better than all other sources of information.

There are currently only two studies that have used machine learning in OCD, and none of them have applied neuroimaging or biological markers. One investigated who remains remitted in a naturalistic study [including 296 patients; 94], and one investigated who responded to internet-delivered CBT [including 61 adolescent patients; 95]. Only one of these found that having a

contamination/washing subtype was related to ever remitting from OCD [94]. However, given the naturalistic and uncontrolled nature of the study, it should be interpreted with caution. The use of machine learning could also be used to reevaluate the relevance of previous regression-based studies, which look at individual voxels or regions but not how they form patterns and interact to predict outcome [77].

Conclusion

The three symptom dimensions of aggressive/sexual/religious obsessions, contamination, and symmetry/ordering partly describe the heterogeneity in OCD. The severity of contamination and symmetry/ordering symptoms are not reliably related to treatment outcome, while some studies suggests that sexual/religious/aggressive thoughts could be harder to treat than other symptoms in CBT, and that these respond better to SRIs than other dimensions. Neuroimaging studies have related sexual/religious/aggressive symptoms to more pronounced alterations in the function and structure of the amygdala and related limbic regions. However, many of the current studies are suffering from methodological limitations and small sample sizes, and most findings have not yet been replicated in larger samples. This weakens the strength of their conclusions, and shows the need for larger and robust studies in the future. Patients with sexual/religious/aggressive symptoms are at a greater risk of not starting or delaying treatment, partly due to more shame and perceived immorality. Adequate CBT that is sensitive to these issues is likely to help these patients improve to the same degree as other patients.

Compliance with ethical standards

Conflict of interest
Anders Lillevik Thorsen declares that he has no conflict of interest. Gerd Kvale declares that she has no conflict of interest. Bjarne Hansen declares that he has no conflict of interest. Odile A. van den Heuvel declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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