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On the relation between affective and obsessive-compulsive symptoms during the course of obsessive-compulsive disorder

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CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Obsessive-compulsive disorder (OCD) has various presentations: One OCD patient doubts if he turned off all electric devices when leaving the house. He fantasizes his home going up in flames due to his irresponsible behavior, experiences growing anxiety, and hence checks everything according to rigid rituals before leaving. Another OCD patient has disturbing vivid images about stabbing her baby with a knife leading to anxiety and feelings of guilt and shame. To neutralize these thoughts, she mentally repeats "I will not harm the baby", but to be sure, she also avoids sharp objects. Yet another OCD patient suffers from the fear of getting contaminated with germs, which is accompanied by significant disgust when touching objects such as doorknobs. It results in excessive hand washing and avoidance of potentially contaminated objects. And then, there is also the OCD patient, who cannot stand uneven numbers and thus always takes two sugar cubes for her coffee, sets the volume of the car radio on an even number and when touching an object, she has to touch it again. She does not report anxiety but rather describes a feeling that "it does not feel right", and thus she repeats touching until it does.

Some aspects of OCD may be recognizable for many people, such as uncertainty about turning off electric devices or having a lucky number, which is by no means pathological. On the opposite side of the scale, there are OCD patients who are not able to leave the house, because they are stuck in complex rituals, which they repeat over and over again. They are constantly engaged in compulsive behavior, often involve their housemates in their rituals, and are severely impaired in their daily and social functioning. In-between the range from non-pathological to extreme obsessive-compulsive symptoms, we can distinguish subclinical OCD with minor impairment and clinical OCD with increasing severity, impairment and agony, as well as differences in its course, varying from full recovery to recurrent episodes to chronic or even deteriorating disease (Sharma et al., 2014; Eisen et al., 2013; Fineberg et al., 2012; Skoog et Skoog, 1999).

While about one quarter of the general population ever in their lives has obsessions or compulsions (Fineberg et al., 2012; Ruscio et al., 2010), most of them are able to adapt and experience little impairment. However, during their lifetime, about 1-3% of the general population faces marked distress and dysfunction as a consequence of the obsessions and compulsions, and thus suffers from clinical OCD (Ruscio et al., 2010; Angst et al., 2004; Bijl et al., 1998).

What is obsessive-compulsive disorder?

Obsessive-compulsive disorder (OCD) is defined by the occurrence of obsessions and/or compulsions (World Health Organization, 2019; APA, 2013). Obsessions are recurrent intrusive thoughts, images or urges, which cause distress. Compulsions are repetitive and often ritualistic behaviors. According to the diagnostic classifications of psychiatric disorders, obsessions and compulsions are the core symptoms of OCD (World Health Organization, 2019; APA, 2013) and a shared characteristic of all OCD patients. However, there is much variation in the individual presentation of OCD, e.g., regarding the content of the obsessions and compulsions, accompanying emotions, and cognitive appraisals. Based on these variations, subgroups of OCD patients can be defined. Factor-analytic studies distinguish four OCD-symptom dimensions: obsessions/checking, contamination/washing, symmetry/ordering and hoarding (Mortier et al., 2019; Bloch et al., 2008; Mataix-Cols et al., 2005; Leckman et al., 1997). According to some studies, the obsessions/checking dimension can be further split into the subgroups of responsibility for harm/checking and ”taboo” thoughts (Wheaton et al., 2010; Sulkowski et al., 2008; Rosario-Campos et al., 2006). Due to recent insights, the hoarding dimension currently forms a distinct disorder within the group of obsessive-compulsive and related disorders (World Health Organization, 2019; APA, 2013; Pertusa et al., 2010).

Symptom dimensions are quite stable during the course of OCD with fluctuating severity within the symptom dimension but less often shifts between them (Mataix-Cols et al., 2002). However, they form no independent entities but are highly entangled (Olatunji et al., 2017), which is supported by the observation that most OCD patients have symptoms of more than one symptom dimension. The symptom dimensions have general as well as specific genetic predispositions (Alemany-Navarro et al., 2020; Iervolino et al., 2011; Katerberg et al., 2010; van Grootheest et al., 2008), shared as well as non-shared environmental vulnerabilities (Iervolino et al., 2011; van Grootheest et al., 2008), and common as well as distinct neural correlates (van den Heuvel et al., 2009; Mataix-Cols et al., 2004).

Neuroimaging studies agree on the importance of the cortico-striatal-thalamo-cortical (CSTC) circuits in the etiology of OCD (Shephard et al., 2021; Stein et al., 2019; van den Heuvel et al., 2016). The CSTC circuits are parallel and partly segregated loops from specific cortical to specific subcortical structures with re-projections to the cortex. Distinct CSTC circuits are involved in distinct cognitive and behavioral aspects of OCD. They form the neural correlates underlying the etiological concepts of OCD, such as emotion regulation, executive functioning or an imbalance between goal-directed and habitual behavior:

- The sensorimotor CSTC circuit (from the supplementary motor area to the posterior part of the putamen to the thalamus and back) has a significant role in habitual behavior.
- The dorsal cognitive CSTC circuit (from the pre-supplementary motor area, dorsolateral and dorsomedial prefrontal cortex to the dorsal caudate nucleus to the thalamus and back) is related to working memory, planning and emotion regulation.
- The ventral cognitive CSTC circuit (from the inferior frontal gyrus and ventrolateral prefrontal cortex to the ventral caudate nucleus to the thalamus and back) is associated with response inhibition.
- The ventral motivational CSTC circuit (from the orbitofrontal cortex to the nucleus accumbens to the thalamus and back) is linked to stimulus-outcome-based motivational behavior.

The CSTC circuits are connected to other brain structures, such as the fronto-parietal network, which has a role in the coordination of cognitive control, and the fronto-limbic circuit (from the ventromedial prefrontal cortex to the amygdala to the thalamus), which is important in fear extinction and the processing of emotionally salient stimuli (Shephard et al., 2021; Stein et al., 2019; van den Heuvel et al., 2016).

The extent of involvement of the different circuits varies between individuals with OCD and may also shift during the course of the disease (Stein et al., 2019; van den Heuvel et al., 2016). Depending on alterations in the specific neural circuits, individual symptom patterns emerge, resulting in the heterogeneous presentation of OCD.

What are affective symptoms of OCD?

This thesis uses a rather practical than sophisticated approach to ”affect” and ”affective symptoms”. The term ”affect” is often used synonymously with ”emotion” or ”feeling”, and even experts on this field do not consent on a final definition (e.g., Fox, 2018; LeDoux, 2012). In this thesis, affect is defined as the emotional reaction to external events and internal perceptions. Affective symptoms describe symptoms which express this emotional response.

In OCD, affective symptoms occur

1. during the acute distress response which accompanies obsessions and compulsions and
2. beyond the acute distress response.

According to the learning theory, obsessions provoke distress, which often presents with affective symptoms such as fear, anxiety, disgust or ”not just right experiences”. Subsequently, compulsions are performed, which quickly leads to a reduction of the distress (Salkovskis, 1985; Rachman et Hodgson, 1980).

In OCD, fear and anxiety are not explicitly distinguished. The distress response may present with fear, especially when confronted with a concrete “threat” but may also be accompanied by anxiety, e.g., when related to risk assessment and cognitive appraisals (RDoC matrix, NIMH; Nutt et Malizia, 2006).

Another affective state during the distress response are feelings of disgust. Although the tendency to react with disgust is increased in OCD patients in general (Berle et al., 2012; Olatunji et al., 2011), a distinct association with contamination/washing symptoms has been suggested (Fink-Lamotte et al., 2021; Olatunji et al., 2019; Athey et al., 2015; Brady et al., 2010).

The distress response may also be accompanied by a feeling described as ”not just right experiences” (NJRE‘s) (Melli et al., 2019; Coles et Ravid, 2016; Sica et al., 2015). Some authors regard NJRE‘s as sensory phenomena which elicit a distress response (Fradkin et al., 2020; Fornés et Belloch, 2017). However, although they may present as a physical sensation (Brown et al., 2019), most NJRE’s are experienced mentally (Coles et al., 2003). Studies investigating NJRE‘s often refer to it as a ”feeling” (Coles et al., 2003) or ”sensory-affective disturbance” (Summerfeldt et al., 2014). Thus, NJRE‘s may be regarded as an affective state, which can provoke compulsive behavior (Starcevic et al., 2011). NJRE‘s are reported in all OCD symptom dimensions (Sica et al., 2019) but seem to be particularly related to the symmetry/ordering dimension (Belloch et al., 2016; Coles et Ravid, 2016) and checking behavior (Belloch et al., 2016; van Dis et van den Hout, 2016).

In addition to affective symptoms in response to obsessions, affective symptoms also occur beyond the distress response often presenting as anxiety or depressive symptoms. They may be part of the symptomatology of OCD itself or a consequence of obsessive-compulsive symptoms. They may also result from conditions unrelated to OCD. Depending on the severity and accompanying other symptoms, they can emerge as a comorbid mental disorder.

Anxiety disorders are the most frequent comorbidity of OCD (Visnawath et al., 2012; Ruscio et al., 2010; Torres et al., 2006; Pinto et al., 2006). Until DSM-5, OCD itself has

been categorized within the group of anxiety disorders (APA, 2000). However, research addressing anxiety in OCD in general is very limited. Anxiety has been observed in all OCD symptom dimensions (Starcevic et al., 2011). The few studies explicitly investigating the relation between anxiety and distinct symptom dimensions found a significant association with the obsessions/checking dimension in OCD (Cervin et al., 2021; Hartmann et al., 2019; Sulkowski et al., 2008).

About one third of the OCD patients is diagnosed with a mood disorder, mainly major depressive disorder (Sharma et al., 2021; Viswanath et al., 2012; Quarantini et al., 2011; Ruscio et al., 2010; Kalra et al., 2008), but the group of OCD patients suffering from depressive symptoms is presumably larger (Klein Breteler et al., 2021). The prevalence and severity of depressive symptoms may differ between symptom dimensions, although studies are inconclusive. While some studies found a relation between depression and the symptom dimension obsessions/checking (Torresan et al., 2013; Besiroglu et al., 2007; Hasler et al., 2005), others describe no specific association (Quarantini et al., 2011).

In summary, affective symptoms occur in OCD in relation to obsessions and compulsions and during the course of OCD. They may present as anxiety, fear, disgust, NJRE's or depressive symptoms. Although all presentations of affective symptoms can occur in all symptom dimensions, an association between specific affective symptoms with distinct symptom dimensions is reported.

What is the role of affective symptoms in OCD?

The relation between obsessions and compulsions has traditionally been defined as a causal relationship with distress or anxiety as the "linking pin" which drives the compulsions: Compulsions are performed in response to obsessions with the aim to reduce the distress or anxiety caused by the obsessions or to prevent the dreaded content of the obsessions (Salkovskis, 1985; Rachman et Hodgson, 1980). Several theoretical considerations, but unfortunately only few experimental and observational studies in OCD patients have contributed to this model. The learning theory is based on this assumption, and states that the quick reduction of fear or anxiety after the performance of the compulsions reinforces the compulsive behavior. It resulted in the therapeutic approach of exposure in vivo with response prevention, which is an effective and evidence-based treatment for OCD (Reid et al., 2021).

However, the learning theory cannot explain all aspects of OCD. OCD patients frequently report that reducing anxiety, disgust or discomfort is the reason they perform compulsions, but about the same proportion of compulsions is seemingly performed automatically, indi-

cating this behavior as rather habitual than goal-directed. Both, goal-directed and habitual compulsions can be present at the same time, and most OCD patients report that they perform compulsions for more than one reason. Also, more than one affective expression can emerge due to the same obsession (Starcevic et al., 2011). In addition, some OCD patients do not experience relief after performing compulsive behavior. Others report that the relieving effect of the compulsions diminishes over the time while the performance of the compulsions continues (van Schalkwyk et al., 2016).

The functional relation between obsessions, distress/anxiety and compulsions as the "driver" of OCD currently is challenged by the growing attention for compulsive behavior as the predominant feature of OCD (Fineberg et al., 2018; Gillan et Sahakian, 2015; Craig et Fineberg, 2008). Some authors point to the lack of neural correlates of obsessions and the inconclusive results on the involvement of affective circuits in OCD and regard obsessions and distress as co-occurring phenomena or even consequence of the compulsions (Gillan et Robbins, 2014). They conclude that OCD is in the first place an imbalance between goal-directed behavior and habit forming in favor of the latter, and reduce the role of obsessions to a post-hoc rationalization, while considering distress and anxiety as modulating factors of habit (Gillan et al., 2016).

The categorization of OCD within the group of obsessive-compulsive and related disorders in DSM-5 and ICD-11 seems to change the focus from the affective distress response to executive functioning and compulsivity. This may ask for an evaluation of the role of affect in OCD.

Symptom provocation studies in OCD patients demonstrate that brain structures involved in emotional processing and emotion regulation are activated during the experience of obsessive-compulsive symptoms. Meta-analyses of functional neuroimaging studies confirm that neural networks, which are associated with affective symptoms, are activated during the experience of distress in response to obsessive-compulsive stimuli. Besides activation of structures linked to habit forming, a limbic hyper-responsiveness, including the amygdala, has been observed, which is a result from deficient cortical top-down-control. A reduced connectivity between the dorsal prefrontal cortex and subcortical structures leads to fronto-limbic hyperactivation (Thorsen et al., 2018) which results in an exaggerated emotional distress response (e.g., anxiety) to OCD-related stimuli due to impaired cognitive control (de Wit et al., 2015). The meta-analyses also found a hyperactivity of regions linked to the processing and regulation of affectively salient stimuli and autonomic stimuli, such as the anterior cingulate cortex, the insula and the precuneus (Thorsen et al., 2018; Rasgon et al., 2017).

The involvement of the distinct circuits in OCD may vary depending on the individual OCD symptoms and symptom dimensions (Shephard et al., 2021; Okada et al., 2015; van den Heuvel et al., 2009; Mataix-Cols et al., 2004). As a consequence, also the role of affective symptoms may vary between the symptom dimensions. Differences of neural correlates between symptom dimensions may lead to differences in the role of affective symptoms between OCD patients. While distress expressed by anxiety, disgust or NJRE's drive compulsions in a large group of OCD patients, another group of OCD patients report no distress at all but performs the compulsions rather habitually (Starcevic et al., 2011).

The role and involvement of the distinct neural circuits also varies during the course of OCD. Some authors suggest that during the earlier phases of OCD, structures associated with anxiety, uncertainty and goal-directed behaviors have an important role, such as the fronto-limbic circuit, and the dorsal cognitive, ventral cognitive and ventral reward CSTC. In chronic OCD, an increasing involvement of habit-related structures, such as the sensorimotor, dorsal cognitive and ventral cognitive CSTC circuit, is hypothesized (Stein et al., 2019). Thus, the early phase of OCD may be characterized by the experience of anxiety or other affective distress elicited by the obsessions, as well as fear conditioning and goal-directed behavior to reduce the affective distress, while patients suffering from chronic OCD for a long time may experience a low level of affective distress and may perform the compulsions more habitually. Therefore, the role of affect may change during the course of OCD. Compulsive behavior may automatize during a chronic course, changing from anxiety-driven to habit-driven behavior and thus weakening the functional relationship between obsessions, negative affect and compulsions over the time. This is congruent with the clinical observation that anxiety seems to be more prominent in the early phases of OCD, and that it is experienced to a lesser extend in chronic OCD. However, studies which confirm this hypothesis are lacking.

In summary, affect plays a role in OCD and can be related to neural correlates which are involved in OCD. However, the significance and role in the etiology and maintenance of OCD may vary across symptom dimensions and during the course of OCD.

What is the relation between affective and obsessive-compulsive symptoms?

Obsessive-compulsive and affective symptoms interact and affect each other. Several cross-sectional and longitudinal studies address the relation between affective and obsessive-compulsive symptoms. However, the majority of these studies focus on depressive symptoms in OCD while studies on anxiety or other affective symptoms are rare.

Studies confirm a cross-sectional positive correlation between the severity of OCD symptoms and the severity of depressive symptoms (Klein Breteler et al., 2021; Altintaş et Taşkintuna, 2018; Demal et al., 1996), as well as a positive correlation between the severity of obsessive-compulsive symptoms and anxiety (Klein Breteler et al., 2021; Sulkowski et al., 2008). However, to investigate the direction of the relation symptoms must be examined longitudinally.

Only few longitudinal studies examine the relationship between affective symptoms and OCD and are limited to depressive symptoms. They conclude that changes in obsessive-compulsive symptoms predict changes in depressive symptoms but not vice versa (Tibi et al., 2017; Zandberg et al., 2015; Anholt et al., 2011). Depressive symptoms often are regarded as a consequence of the OCD-symptoms (McNally et al., 2017) and OCD-related impairment (Abramowitz et al., 2007). Other mediating factors leading from obsessive-compulsive symptoms to depressive symptoms may be negative appraisals (Tibi et al., 2018; Abramowitz et al., 2007), specific cognitive styles such as rumination and worry (Shaw et al., 2017; Buchholz et al., 2019), self-esteem (Toledo et al., 2020) or demoralization as a result of chronicity and disability (Tecuta et al., 2015; Milanfranchi et al., 1995). Depressive symptoms also may be triggered by life events or other external or internal circumstances not directly related to OCD (Imthon et al., 2020; Altintaş et Taşkintuna, 2018).

The reverse is also possible: affective symptoms may lead to obsessive-compulsive symptoms. Anxiety may increase the occurrence of harm-related cognitions and obsessions. Some OCD patients report an increase in compulsive behavior in response to general anxiety and distress, suggesting that compulsions also can be a coping mechanism which can be triggered by emotional stress (van Schalkwyk et al., 2016).

Obsessive-compulsive and affective symptoms may not only lead from one to another, but they may both result from a shared underlying factor, e.g., a shared etiological factor or vulnerability (Bolhuis et al., 2014). Instead of regarding obsessive-compulsive and affective symptoms as manifestation of different disorders, they may form symptoms of a common latent factor or generalized vulnerability. Negative affectivity has been proposed as a higher order factor which accounts for the overlap between depression, anxiety and obsessive-compulsive symptoms. In addition to the shared characteristics, specific etiological processes are involved leading to disorder-specific characteristics (Barlow, 2000).

Irrespective of a possible causal relationship between affective and obsessive-compulsive symptoms, affective symptoms may modulate or influence the occurrence and presentation

of obsessive-compulsive symptoms. They also may affect the course, treatment outcome, prognosis and secondary adversities. In OCD patients, depressive symptoms as well as anxiety contribute to a poor quality of life (Remmerswaal et al., 2018; Velloso et al., 2018; Subramaniam et al., 2013), increased functional impairment (Velloso et al., 2018; Storch et al., 2014) and a higher suicidal risk (Pellegrini et al., 2020).

Studies on the effect of depressive symptoms and anxiety on the prognosis of OCD are inconsistent. Some authors relate depressive symptoms (Sharma et al., 2021; Nakajima et al., 2018; Visser et al., 2014; Jacubovski et al., 2013) and anxiety (Nakajima et al., 2018; van Oudheusden et al., 2018; Ferrão et al., 2006) to an unfavorable course. Also the conclusions of studies on the effect of anxiety and depressive symptoms on treatment outcome vary due to differences in treatment modality and methodology (Hazari et al., 2016: Knopp et al., 2013; Keeley et al., 2008). In summary, treatment with serotonergic antidepressants and cognitive behavioral therapy addressing cognitive appraisals seem not to be affected by the presence or absence of depressive symptoms (Klein Breteler et al., 2021; Bloch et al., 2013; Farrell et Boschen, 2011) or anxiety (Kathmann et al., 2022; Farrell et Boschen, 2011). This may be due to the fact that antidepressants as well as cognitive interventions, including the identification and challenge of maladaptive beliefs, are effective in both depressive and anxiety disorders as well as in OCD, and thus address all symptoms. In contrast, treatment outcome of exposure with response prevention (ERP) is negatively affected by co-occuring depressive symptoms but not by anxiety (Steketee et al., 2019). During ERP, OCD patients are exposed to obsessions-provoking stimuli and encouraged to experience the emotional distress without performing compulsions, which finally leads to a decrease and extinction of the emotional distress, and to the correcting experience that compulsions are not necessary to prevent the content of the obsessions or the emotional distress. Exposure in vivo also is an effective treatment in anxiety disorders and addresses anxiety-related cognitions, emotions and behavior. However, OCD patients with severe depressive symptoms may lack the energy and motivation to participate in the ERP exercises (Berman et al., 2020). In addition, ERP may not address core aspects of depression.

In summary, obsessive-compulsive and affective symptoms interact in several ways. These interactions have consequences on the presentation, impairment and treatment of OCD.

Outline of the thesis

The aim of this thesis is to investigate the role of affect in OCD from different perspectives: during an experimentally provoked distress response as well as during the course of OCD, in relation to the obsessive-compulsive symptoms and as a predictor for the course of OCD.

In **chapter 2** we investigate the neural correlates of the emotional distress response during symptom provocation and its relation to disgust sensitivity. The affective distress response may differ between OCD patients experiencing disgust (i.e. OCD patients with contamination/washing symptoms) and those experiencing anxiety, regarding its subjective experience as well as the activation in the brain. Information on distinct and shared neural mechanisms during symptom provocation between different groups of OCD patients may help to understand the heterogeneity of OCD by elucidating which aspects are more general for OCD and which aspects are quite specific for certain symptoms or symptom dimensions. To that aim, we compare the emotional and neural distress response of OCD patients with contamination/washing symptoms to those without. Subsequently, we examine the association of disgust sensitivity with the subjective distress as well as the neural distress response in both groups of OCD patients.

In **chapter 3** and **chapter 4**, we investigate the interaction between affective and obsessive-compulsive symptoms during the long-term course of OCD. For these studies, we use data from the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study, a longitudinal, naturalistic multi-center study which followed 419 OCD patients for six years.

In **chapter 3**, we report the results on the relation between obsessive-compulsive and depressive symptoms. Depressive symptoms are common in OCD, but recommendations how to treat OCD with depressive symptoms are inconclusive. Can we expect the depressive symptoms to improve when the obsessive-compulsive symptoms improve? Or should we also address the depressive symptoms because they may complicate the OCD treatment, maintain the obsessive-compulsive symptoms or affect them negatively? Information about the direction of the relation and the interaction between obsessive-compulsive and depressive symptoms may help to answer these questions. To that aim, we first investigate the effect of comorbid major depressive disorder (MDD) on the severity of OCD. Second, we examine the reciprocal relation between depressive and obsessive-compulsive symptoms longitudinally for one year, and also compare this relation between OCD patients with and without comorbid MDD. In addition, we retrospectively analyze the sequence of the lifetime onset of both OCD and MDD and examine the reciprocal relation depending on the first onset of OCD respectively MDD.

In **Chapter 4,** we investigate the long-term relation between anxiety and obsessive-compulsive symptoms. Are obsessive-compulsive symptoms and anxiety different presentations of a common underlying factor or should we rather understand them as distinct symptom groups? And how do they affect each other during the long-term course? To address these

questions, we compare three different models of the relation between obsessive-compulsive symptoms and anxiety: 1) the cross-lagged model, which regards both groups of symptoms as distinct factors, which affect each other directly during the course of OCD, 2) the stable traits model, which states that both are distinct groups of symptoms, which interact by respective latent traits, and 3) the common factor model, which suggests that obsessive-compulsive symptoms and anxiety share a common factor. In addition, we study whether anxiety is particularly related to a specific symptom dimension. We also examine the strength of the correlation between obsessive-compulsive symptoms and anxiety during the follow-up period.

In **chapter 5**, we take the step from population-based predictions to individual predictions of the course of OCD. Population-based research on predictors of the course of OCD, as described in chapter 3 and 4, has largely contributed to our knowledge on factors influencing the course and severity of OCD. However, results often are inconclusive (Sharma et Math, 2019) and do not lead to reliable predictions on the individual level. In addition, OCD is a multifactorial disorder, and most studies on this topic include single or a limited number of predictive factors and thus are not able to investigate the different impact and interaction between potential predictors. Algorithms created by machine learning techniques can simultaneously include different factors and may have a better predictability. To that aim, we develop a machine learning algorithm to predict OCD remission after 2 years, using data from the NOCDA study and based on predictors easily accessible in the daily clinical routine. In chapter 5, we also discuss the development and evaluation of this algorithm.

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CHAPTER 2

EMOTIONAL PROCESSING AND DISGUST SENSITIVITY IN OCD PATIENTS WITH AND WITHOUT CONTAMINATION-TYPE OBSESSIVE-COMPULSIVE DISORDER - AN FMRI STUDY

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Rickelt, J., de Wit, S.J., van der Werf, Y.D., Schruers, K.R., Marcelis, M., de Vries, F.E., van den Heuvel, O.A., 2019. Emotional processing and disgust sensitivity in OCD patients with and without contamination-type obsessive-compulsive symptoms – An fMRI study. J. Obsessive Compuls. Relat. Disord. 22, 1-11.

ABSTRACT

Objective: Disgust is described as a relevant emotion in OCD, particularly in contamination-type OCD, and may be involved in emotional processing in this OCD-subtype. The present study aimed to investigate the neural correlates of distress processing in contamination-type compared to non-contamination-type OCD, and the relation to disgust sensitivity.

Methods: Forty-three OCD patients (n= 19 contamination-type OCD) were exposed to OCD-related, fear-related and neutral pictures. Subjective distress per stimulus was assessed by a visual analogue scale (VAS) and disgust sensitivity by the DS-R. BOLD brain activation was compared between stimuli that provoked high versus low distress at individual level.

Results: In contamination- and non-contamination-type OCD, the dorsomedial prefrontal cortex, operculum, visual association cortex and caudate nucleus were activated during high versus low distress. Only in contamination-type OCD, disgust sensitivity correlated positively with the VAS scores and was associated with neural activation in the dorsomedial and visual association cortex but not with the operculum.

Conclusions: Brain activation during distress processing in OCD is similar across the OCD subtypes and related to effortful emotion regulation, processing of aversive internal states and attention. In contamination-type OCD, the distress response is related to disgust sensitivity, which correlates with brain regions associated with attention and emotion regulation.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is regarded as a clinically heterogenous disorder with specific symptomatic dimensions (Mataix-Cols et al., 2005). Factor analyses revealed four symptom dimensions in OCD: symmetry/ordering, forbidden thoughts/checking, contamination/washing and hoarding (Bloch et al., 2009; Mataix-Cols et al., 2005). The symptom dimensions have common and distinct clinical symptoms, as well as common and distinct etiological factors (Katerberg et al., 2010; Mataix-Cols et al., 2005; van Grootheest et al., 2008).

A common characteristic of the OCD subtypes are obsessions, which elicit distress, and the performance of compulsions, which diminishes the distress. The evoked distress most often is described as fear or anxiety, giving anxiety a central role in the etiology, treatment and diagnostic categorization (DSM III (APA 1980); DSM IV (APA 2000)). However, there is growing evidence that the distress response may also have other emotional qualities, and that some of these affective states may even be related to specific OCD symptom dimensions: ”Not just right experiences” often are associated with symmetry obsessions (Coles et al., 2005; Starcevic et al., 2011), while feelings of guilt are more often observed in patients with control compulsions (Melli et al., 2017). Disgust is often associated with the OCD symptom dimension contamination/washing (contamination-type OCD) (Cisler et al., 2009; Olatunji et al., 2007a; Phillips et Mataix-Cols, 2004; Stein et al., 2001). Thus, if disgust is an important emotional quality of the distress response in this OCD subtype, the distress response during symptom provocation may be modulated by disgust sensitivity in this subtype of OCD.

Patients with contamination-type OCD show higher disgust sensitivity (Athey et al., 2015; Bhikram et al., 2017; Olatunji et al., 2011). Disgust sensitivity (DS) describes the individual predisposition to experience disgust in response to a range of aversive stimuli like rotten food, waste products, certain animals, body envelope violation, death or transmission of contagions (Olatunji et al., 2007b). Disgust sensitivity directly affects contamination-related beliefs, distress and obsessive-compulsive symptoms (Moretz et McKay, 2008). In healthy volunteers, the individual variation of disgust sensitivity correlates positively with activation in regions that have been associated with disgust processing, like the anterior insula, ventrolateral prefrontal cortex, temporal pole, putamen/globus pallidus, anterior cingulate and visual cortex, and negatively with activation in regions involved in emotion regulation, like the dorsolateral and rostral prefrontal cortex (Calder et al., 2007; Mataix- Cols et al., 2008; Schäfer et al., 2009). Thus, disgust sensitivity may be a modulating factor of the neural

response to disgust evoking stimuli by for example enhancing the salience of disgusting stimuli, defining the emotional quality of the experienced distress, lowering the threshold for and increasing the intensity of the distress response.

In fMRI symptom provocation studies in patients with contamination-type OCD, neural responses to contamination-related stimuli overlap with neural responses to disgusting stimuli in healthy volunteers (Agarwal et al., 2013; Mataix-Cols et al., 2004; Murayama et al., 2013; Phan et al., 2002; Schienle et al., 2005a; Shapira et al., 2003; Simon et al., 2010; Stark et al., 2007). Thus, in contamination-type OCD, the distress response provoked by OCD-relevant stimuli may be regarded as an exaggerated disgust response related to heightened disgust sensitivity. Further research on the relation between disgust sensitivity and its specificity to contamination-type OCD may not only improve our understanding of common and distinct characteristics of the OCD subtypes but may also lead to adjusted treatment approaches focusing more on the disgust response.

The aim of the present study was to investigate the neural distress response in contamination-type OCD and its relationship to disgust sensitivity. We hypothesized that 1) the neural response during distress processing differs between patients with contamination-type OCD compared to non-contamination-type OCD, related to differential activation in disgust processing brain regions, and 2) that disgust sensitivity is differentially associated with the neural distress response in contamination-type OCD versus non-contamination-type OCD. We expected that emotion processing in contamination-type OCD would be related to higher activation in disgust-related regions (e.g., insula) than in patients without contamination symptoms, and that this activation positively correlates with disgust sensitivity.

METHODS

Patients

In this study we re-analysed the demographic, clinical and neuroimaging data of OCD patients as previously presented (Thorsen et al., 2018; de Wit et al., 2015), now specifically comparing the OCD group patients with and without contamination-type symptoms. In addition, the methods used for the fMRI analyses differ from the previous studies, particularly the definition of the distress provoking stimuli and the fMRI contrasts. Thus, new research questions and hypotheses could be investigated without the need to expose a new sample of patients to the discomfort of assessments and MRI-scans.

Participants were forty-three unmedicated adult patients with the primary diagnosis of OCD. Patients with predominant hoarding symptoms, a present or past diagnosis of a psychotic disorder, major physical illness, a history of neurological illness and MRI-contraindications were excluded. Psychiatric comorbidities other than a psychotic disorder were not a reason for exclusion. All patients were free of psychotropic medication for at least 4 weeks.

Patients were recruited through online advertisements, the specialized outpatient clinics participating in the Netherlands Obsessive Compulsive Disorder Association (Schuurmans et al., 2012) and the Academic Anxiety Center Altrecht (Utrecht, The Netherlands). All patients gave written informed consent. The ethical medical review board of the VU university medical center, Amsterdam, approved the study, and written informed consent included the option for re-using the data for new analyses.

Assessment

OCD and axis-I comorbid disorders were diagnosed using the Structured Clinical Interview for the DSM-IV-TR (SCID-I) (First et al., 1999). The severity of the obsessive-compulsive symptoms was measured with the Yale-Brown Obsessive Compulsive Symptom (Y-BOCS) Severity Scale (Goodman et al., 1989a, 1989b). We assessed the disgust sensitivity using the Disgust Scale Revised (DS-R) (Haidt et al., 1994; Olatunji et al., 2007b; van Overveldt et al., 2011), a self-report questionnaire with 27 items (including 2 non-rating items) scored on a 5-point likert scale (0–4), leading to a total score ranging from 0 to 100. The severity of the depressive symptoms was assessed by the Beck Depression inventory (BDI, Beck et al., 1961) and the severity of the anxiety symtpoms by the Beck Anxiety Inventory (BAI, Beck et al., 1988).

Patients were grouped in OCD with contamination/washing symptoms (contamination-type OCD) and OCD without contamination/washing symptoms (non-contamination-type OCD) using the Yale-Brown Obsessive Compulsive Symptom (Y-BOCS) Checklist (Goodman et al., 1989a; Goodman et al., 1989b). The contamination/washing dimension was considered to be present if at least 1 item of the subscales contamination obsessions or cleaning/washing compulsions was scored as currently present. The severity of the contamination symptoms was assessed by the OCI-R washing subscale. The OCI-R is an 18-item self-report questionnaire assessing the severity of different obsessive-compulsive symptom groups. The washing subscale consists of 3 items scored on a Likert scale from 0 to 4 leading to subtype scores ranging from 0 to 12 (Foa et al., 2002).

Task paradigm

The fMRI task used to provoke distress is described in detail in de Wit et al. (2015). To summarize, patients were visually exposed to a total of 81 pictures with neutral, general fearful or potentially OCD-symptom (checking, contamination, symmetry) provoking content. After each picture, patients rated the distress caused by that picture on a continuous visual analogue scale (VAS) ranging from 0 to 100.

The stimuli were presented in blocks of three different pictures of the same stimulus type. Stimuli were either presented with the instruction to experience the stimulus naturally ('attend' condition) or with the instruction to reappraise or reinterpret the stimulus to diminish the negative affect ('regulate' condition). This design was chosen to examine hypotheses addressed in previous research by de Wit et al. (2015) and Thorsen et al. (2018).

Statistical analyses

1. Clinical and behavioral analyses

Descriptive statistics, group differences and correlations were analyzed using SPSS version 23 (SPSS Inc., USA). Differences between contamination-type and non-contamination-type OCD patients regarding age, age of onset of obsessive-compulsive symptoms and duration of obsessive-compulsive symptoms were analyzed using the Mann-Whitney U test. Group differences regarding the symptom dimensions were analyzed using the Fisher's exact test. Group differences regarding the number of lifetime and current comorbidities, number of symptom dimensions, BDI scores, BAI scores, Y-BOCS scores, DS-R scores and mean VAS scores were analyzed using the independent samples t-test. Correlations between the measures were analyzed using Pearson correlation. Statistical threshold was set at an alpha-level of 0.05.

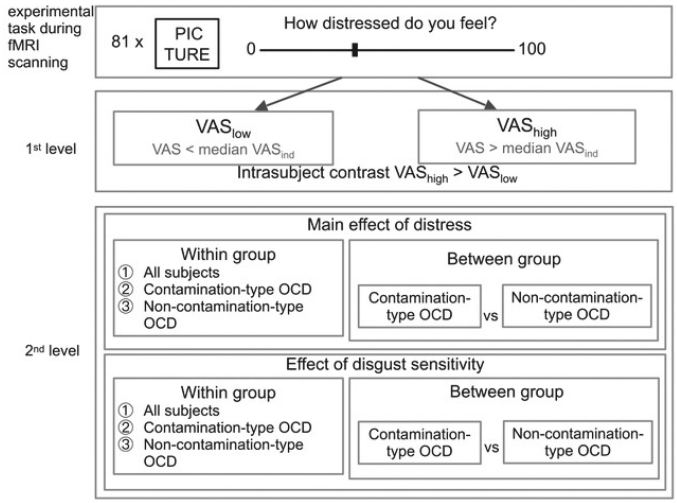
2. fMRI analyses

The experimental task and fMRI analyses are illustrated in Figure 1.

Functional gradient echoplanar and structural T1-weighted imaging was performed on a GE signa HDxt 3.0 T MRI scanner (General Electric USA). Acquisition parameters and preprocessing steps are reported in de Wit et al. (2015). Preprocessing and analysis of the functional images were performed using SPM8 and SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) respectively.

To analyze the blood-oxygen level dependent (BOLD) response related to distress processing and its possible association with contamination-type OCD and disgust sensitivity, different within-group and between-group analyses were performed.

Figure 1. Experimental task to provoke distress using visual stimuli, and 1st (intrasubject) and 2nd level fMRI analyses (main effect of distress, between groups effect and regression of disgust sensitivity). Details are described in the text. VAS visual analogue scale score, median VAS_{ind} individual median VAS score, vs versus.



For the first-level subject-level imaging analysis the visual stimuli were median-split based on individual self-reported distress ratings, resulting in a high distress (VAS_{high}) and low distress (VAS_{low}) condition. Since it is subjective which stimuli are distress-provoking, this was done across all stimuli, regardless of a priori picture categorization (e.g., general fear, neutral or OCD-related) and regardless of initial emotion regulation task instruction (e.g., attend or regulate condition). Thus, two regressors of interest were constructed including the onsets of visual stimuli in the VAS_{high} and VAS_{low} condition (duration of 10 s). Regressors of no interest were the instruction period (modelled as boxcar of 3 s), the presentation of the VAS (modelled as boxcar of 5 s), and the patients' movement parameters. Noise of low-frequency confounds was removed using a high-pass filter with a 128 s cut-off period. At the individual level the BOLD response related to high versus low distress was contrasted [$VAS_{high} > VAS_{low}$] and this contrast was taken up to within and between group-level analyses. Group analyses were performed using a white matter mask to eliminate activated voxels situated in the white matter. Results were considered significant at $p < 0.05$ whole-brain Family Wise Error (FWE) (Worsley et al., 1996) corrected but for exploratory

reasons also reported at $p < 0.001$ uncorrected. Coordinates are reported in Montreal Neurological Institute (MNI) standard space.

2.1. Neural distress processing contamination- and non-contamination- type OCD

The effect of high versus low distress on neural processing was assessed within the whole sample and patients with and without contamination-type OCD separately (one-sample T tests). Further to investigate if the BOLD response to the highly distressing versus less distressing stimuli differs between the contamination-type OCD and the non-contamination-type OCD, a between-group analysis was performed using a two-sample t-test.

2.2. Effect of disgust sensitivity on neural distress processing in contamination- and non-contamination-type OCD

To study the additional effect of disgust sensitivity to the within- and between-group effects of distress, a regression analysis was performed in 1) all subjects, 2) the contamination-type OCD group and 3) the non-contamination-type OCD group by adding the DS-R total score as covariate of interest to the within-group analyses.

2.3. Effect of disgust sensitivity on the group x neural distress response interaction

To investigate if the disgust sensitivity is related to the distress related brain activation between the groups, a between-group analysis of the additional effect of disgust sensitivity was performed by adding the DS-R total score as an interacting covariate to the between-group analysis. Subsequently, these results were masked with the positive regression of the DS-R score within the group of contamination-type OCD patients.

RESULTS

Demographic and clinical characteristics

Forty-three patients were included in the statistical analyses. For the regression analyses, two patients were excluded due to missing DS-R scores. One patient missed the Y-BOCS symptom checklist and was excluded from the comparison of demographic and behavioral data between patients with and without contamination symptoms and the fMRI group and between-group analyses.

Nineteen patients were classified as contamination-type OCD patients and 23 patients as non-contamination-type OCD patients. The majority of the patients had symptoms of more than one OCD symptom dimension (n= 37, 88.1%). Demographic and clinical characteristics are summarized in Table 1. There was a moderate correlation between the scores on

the Y-BOCS Severity Scale and the DS-R (r= 0.308, p= 0.05) in the whole group, but no significant correlation was found when both groups were analyzed separately.

Characteristics of contamination- and non-contamination-type OCD

Patients with contamination-type OCD did not differ from patients with non-contamination-type OCD regarding age, sex, age of onset and duration of the symptoms, and number of current and lifetime co-morbid diagnoses. Both groups did not differ in the severity of depressive symptoms measured by the BDI (p= 0.753) nor in anxiety measured by the BAI (p= 0.162).

Neither the differences on the Y-BOCS severity scale including the obsessions and compulsions subscales (total Y-BOCS scale p= 0.293, Y- BOCS obsessions subscale p= 0.554, Y-BOCS compulsions subscale p= 0.178) nor the mean VAS distress score during task performance (p= 0.976) were significant. Patients with contamination-type OCD scored significantly higher on the DS-R (p= 0.004). Characteristics are shown in Table 1.

Patients with contamination-type OCD had more current OCD symptom dimensions than patients with non-contamination-type OCD. However, in both groups, the number of checking and obsessional symptoms, symmetry symptoms, and hoarding symptoms did not differ significantly (Fisher's exact test p= 0.149, p= 0.504, and p= 0.567 respectively).

Contamination/washing symptoms were only present in the group of contamination-type OCD. The severity of the contamination/washing symptoms measured by the OCI-R showed a large variation from very mild to severe (range 0–12) with a mean of moderate severity (mean 6.3, SD 3.8).

The correlation between mean VAS distress scores and the DS-R was significant in the group of contamination-type OCD (r= 0.516, p= 0.028) but not in non-contamination-type OCD (r= −0.084, p= 0.712).

Table 1. Demographic and clinical characteristics of the study population.

	All subjects (n= 43)	**contamination-type OCD (n= 19)**	**non-contamination-type OCD (n= 23)**
Age (y)	37.6 (19-55)	38.0 (22-55)	38.1 (19-54)
Female/male	22 F (51.2%) / 21 M (48.8%)	9 F / 10 M	12 F / 11 M
Age of onset of OCD symptoms (y)	12.2 (SD 6.4; 4-29)	11.9 (SD 8; 4-29)	12.3 (SD 5.3; 4-26)
Duration of OCD symptoms (y)	26.4 (SD 12; 8-48)	24.6 (SD 12.2; 8-42)	27.7 (SD 12; 9-48)
Number of patients with comorbid diagnoses current	n= 26 (60.5%)	n= 12 (63.2%)	n= 14 (60.8%)
Number of comorbid diagnoses current	1.1 (SD 1.3; 0-5)	1.3 (SD 1.6; 0-5)	1.0 (SD 1.1; 0-4)
Number of comorbid diagnoses lifetime	1.5 (SD 1.5; 0-6)	1.8 (SD 1.7; 0-6)	1.3 (SD 1.3; 0-4)
BDI	14.2 (SD 9.7; 0-38)	15.1 (SD 8.3; 4-38)	14.1 (SD 10.8; 0-35)
BAI	14.9 (SD 9.8; 1-36)	17.2 (SD 10.1; 2-36)	12.9 (SD 9.6; 1-33)
Y-BOCS severity scale	21.6 (SD 6.2; 12-35)	22.9 (SD 6.1; 12-35)	20.9 (SD 6.1; 12-30)
Y-BOCS severity scale - obsessions	10.4 (SD 3.6; 3-18)	10.8 (SD 3.8; 3-18)	10.2 (SD 3.4; 6-18)
Y-BOCS severity scale - compulsions	11.2 (SD 3.2; 5-19)	12 (SD 2.8; 7-17)	10.7 (SD 3.5; 5-19)
DS-R	42.4 (SD 11.3; 20-64)	47.11 (SD 8.7; 29-61)	37.5 (10.9; 20-60)
Mean VAS distress	23.8 (SD 11.95)	23.8 (SD 12.7)	23.7 (SD 11.9)
Number of current symptom dimensions	2.3 (SD 0.95; 1-4)	2.9 (SD 0.91; 1-4)	1.8 (SD 0.65; 1-3)
Symptom dimension			
Contamination/washing	19 (45.2%)	19 (100%)	0 (0%)
Checking/obsessions	31 (73.8%)	16 (84.2%)	15 (65%)
Symmetry/ordering	32 (76.2%)	14 (73.7%)	18 (78.3%)
Hoarding	16 (38.1%)	7 (36.8%)	9 (39.1%)

fMRI results

1. Neural correlates of distress processing in contamination- and non- contamination-type OCD

The whole group showed an increased activation during processing of the highly distressing (VAS_{high}) compared to the less distressing (VAS_{low}) stimuli in the frontal cortex (bilateral supplementary motor area BA 6/BA 8 and dorsomedial prefrontal cortex BA 9), opercular region (bilateral inferior frontal gyrus/anterior insula), occipital cortex (bilateral visual association cortex BA 18 and BA 19) and the right temporopolar region (BA 38) at a

threshold of $p < 0.05$ FWE corrected. In addition, in the uncorrected analysis ($p > 0.001$) the caudate nucleus was activated, among other regions as shown in Table 2.

The opposite contrast ($VAS_{low} > VAS_{high}$) showed activation in the visual association area (right BA 18, $p < 0.05$ FWE corrected), the left operculum ($p < 0.001$ uncorrected), and the primary somatosensory cortex (right BA 1, $p < 0.001$ uncorrected).

Although only significant at an uncorrected threshold ($p < 0.001$), a similar type of activation pattern was observed when we assessed the effect of high versus low distress in the patients with and without contamination-type OCD separately.

Direct comparison of the subgroups did not show significant differences when comparing the VAS high versus low contrast and vice versa. See Table 2 and Figure 2.

Figure 2. Main effect of distress [$VAS_{high} > VAS_{low}$] contrast in participants (N= 43), $p < 0.05$ FWE corrected.

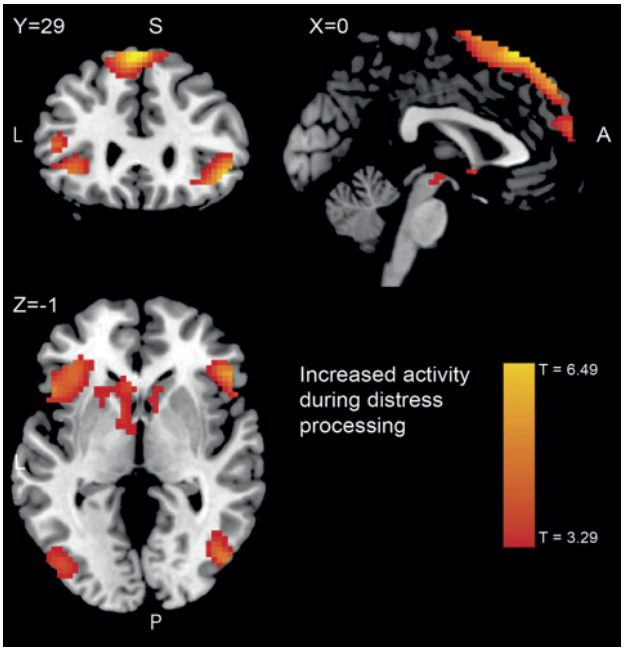


Table 2. Main effect of distress [VAShigh > VASlow] within group and between group analyses (n = 43, 1 participant was excluded from the contamination-type/non-contamination-type group analyses due to missing data). Reported in MNI space. Significant p<0.001 uncorrected.

	Within-group analysis All subjects (n=43)					*Within-group analysis* Contamination-type OCD (n=19)					*Within-group analysis* Non-contamination-type OCD (n=23)					*Between-group analysis* OCD with versus without contamination				
	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T
VAS_{high} > VAS_{low}																				
SMA, dmPFC (BA 6,8, 9) R/L	0	29	61	700	6.49 *	0	11	70	216	5.53	-6	11	70	1	3.51	No suprathreshold clusters found				
SMA (BA 8) L	-36	20	52	19	4.36	-3	50	46	16	4.29	-12	38	52	140	5.24					
											-33	23	49	3	3.94					
Operculum/IFG (BA45/47)/ insula (BA13) R	48	29	-5	105	5.75 *	45	23	-11	34	5.11	45	29	-8	17	4.43					
Operculum/IFG (BA45/47)/ insula (BA13) L	-51	17	1	224	4.96	-51	20	-5	90	4.90										
						-30	26	-14	22	4.85										
Temporopolar cortex (BA 38) R	45	5	-32	17	5.22 *	45	5	-35	2	3.82	42	8	-32	4	4.08					
Temporopolar cortex (BA 38) L	-48	5	-29	3	3.68															
Visual association cortex (BA 19 R)	48	-70	-14	192	6.02 *	48	-70	-17	1	3.75	45	-73	-17	88	4.79					
Visual association cortex (BA 19 L)	-39	-76	-26	163	4.63	-48	-76	1	26	4.73	-42	-76	-20	13	4.08					
Visual association area (BA 18) R	21	-91	-14	19	3.57						21	-88	-14	3	3.74					
Visual association cortex (BA 18) L	-15	-97	-14	4	3.57						-24	-85	-11	1	3.74					
Caudate nucleus R	9	11	-2	9	3.64															
Caudate nucleus L	-6	2	-5	96	4.48	-6	20	-2	14	4.13										
						-18	20	4	1	3.62										
Head of caudate nucleus R	9	-1	-8	4	3.63						3	8	-5	28	4.94					

	Within-group analysis All subjects (n=43)					*Within-group analysis* Contamination-type OCD (n=19)					*Within-group analysis* Non-contamination-type OCD (n=23)					*Between-group analysis* OCD with versus without contamination				
	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T
Amygdala R	30	2	-23	2	3.44															
Angular gyrus (BA 39) L	-57	-58	25	3	3.59															
Medial temporal gyrus (BA 21) R	51	-25	-11	3	3.69															
Cerebellum R	36	-58	-32	2	3.36															
Cerebellum L	-36	-61	-29	1	3.39															
OFC (BA 10) L						-24	56	1	2	3.75										
Fusiform gyrus BA 37 R						45	-67	-20	1	3.69										
Posterior cingulate (BA 31) L											-9	-58	34	17	4.43					
$VAS_{low} > VAS_{high}$																				
Operculum R	63	-22	7	1	3.46											No suprathreshold clusters found				
Operculum L	-36	-34	19	56	4.80	-33	-25	16	2	3.67	-36	-34	19	34	4.22					
Visual association area (BA 18) R	15	-73	22	186	5.13 *	18	-70	19	11	4.59	9	-91	25	27	4.08					
Visual association area (BA 18) L	-12	-88	25	3	3.44						-9	-88	25	6	4.07					
	-12	-79	25	1	3.31															
Primary visual area (BA 17) L	-15	-67	10	12	3.66															
Anterior cingulate cortex (BA 24) R	9	-7	46	4	3.56															
Anterior cingulate cortex (BA 24) L	-9	-4	46	3	3.50															
Posterior cingulate cortex (BA 31) R	9	-34	40	2	3.50															

	Within-group analysis All subjects (n=43)					*Within-group analysis* Contamination-type OCD (n=19)					*Within-group analysis* Non-contamination-type OCD (n=23)					*Between-group analysis* OCD with versus without contamination				
	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T
Primary somatosensory cortex (BA 1) R	45	-25	43	91	3.91															
	60	-10	28	2	3.37															
Primary somatosensory cortex (BA 1) L	-36	-34	43	3	3.44	-63	-16	31	6	4.15										
Primary motor cortex (BA 4) R	24	-25	61	1	3.31	27	-28	58	1	3.74										
Primary motor cortex (BA 4) L	-18	-25	61	3	3.69															
Inferior parietal lobe (BA 40) R						42	-39	52	11	4.05										
						60	-25	37	7	4.03										
Inferior parietal lobe (BA 40) L	-42	-40	49	6	3.47															
Superior parietal lobe (BA 7) R	27	-52	58	1	3.43															
SMA (BA 6) L						-60	-4	34	2	4.20										
Posterior cingulate (BA 23) R						27	-61	10	2	3.89										
Fusiform gyrus (BA 37) L						-30	-46	-11	1	3.74										

* significant p<0.05 FWE corrected. SMA supplementary motor area, dmPFC dorsomedial prefrontal cortex, IFG inferior frontal gyrus.

2. Effect of disgust sensitivity on neural correlates of distress processing in contamination- and non-contamination-type OCD

The regression analysis with the DS-R scores as covariate of interest showed no significant correlation with the activation pattern during distress processing across all participants.

In the group of contamination-type OCD specifically, the DS-R scores correlated positively with distress-related frontal areas (bilateral supplementary motor area and premotor cortex BA 6/BA 8 and dorsomedial prefrontal cortex BA 9, $p < 0.001$ uncorrected), the visual association area/sensory association area (right BA 18/BA 39, $p < 0.001$ uncorrected) and parietal brain activation (bilateral BA 7, $p < 0.001$ uncorrected).

In the group of non-contamination-type OCD, distress-related activation in the right temporal gyrus (BA 20) correlated negatively with the DS-R scores ($p < 0.001$ uncorrected). No other significant correlations were found. Results are presented in Table 3 and Fig. 3.

Figure 3. Effect of disgust sensitivity on distress related activation in the contamination-type OCD patients. Regression analysis between DS-R and BOLD response of distress [$VAS_{high} > VAS_{low}$] in contamination-type OCD patients (N= 18), $p < 0.001$ uncorrected.

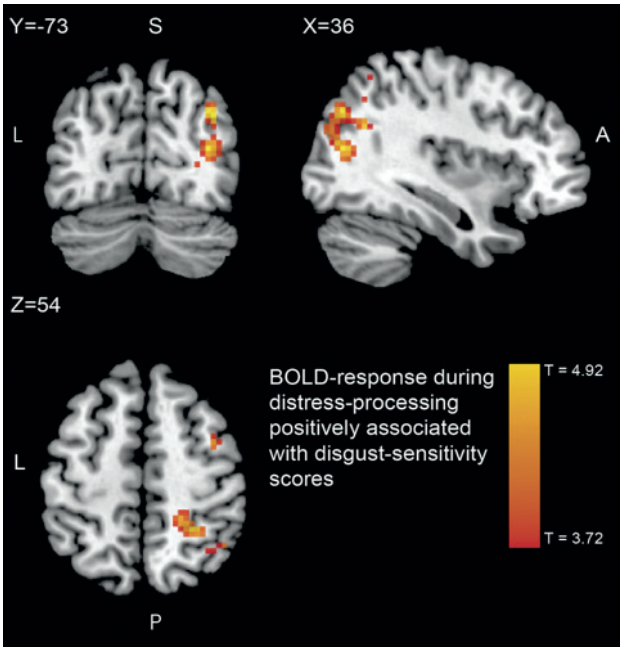


Table 3. Additive effect of disgust sensitivity [regression of DS-R with VAS_{high} > VAS_{low}] within group and between group analyses (n=41, two participants were excluded from the regression analyses, and one additional participant from the contamination-type/non-contamination-type group analyses due to missing data). Reported in MNI space. Significant p<0.001 uncorrected.

	Within-group analysis All subjects (n=41)					*Within-group analysis* Contamination-type OCD (n=18)					*Within-group analysis* Non-contamination-type OCD (n=22)					*Between-group analysis* Contamination-type versus non-contamination-type OCD				
	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T
positive regression DS-R																				
SMA/premotor cortex (BA 6) R	No supratreshold clusters found					39	2	55	4	4.38	No supratreshold clusters found					39	2	58	1	3.47
						15	-16	67	1	3.95										
						18	-13	64	1	3.75						15	-22	64	3	3.34 #
						51	2	49	1	3.74										
SMA/premotor cortex (BA 6) L						-36	-4	61	2	4.36						-54	5	40	1	3.81
						-15	-13	67	3	3.98										
SMA/premotor cortex (BA 8) R						33	23	49	1	3.72										
Dorsomedial PFC (BA 9) R						9	41	22	1	3.85										
Dorsomedial PFC (BA 9) L																-15	50	34	12	3.94
Visual association area (BA 18) R																21	-91	19	12	3.87
Superior occipital gyrus BA 19 L																-24	-88	37	4	3.77
Visual association area/sensory association area (BA 18/BA39) R						39	-73	34	61	4.92						36	-70	10	30	4.57 #
						45	-55	55	4	4.26						39	-79	34	4	3.44
						36	-61	43	1	3.79										
						39	-58	55	2	3.76						39	-79	34	3	3.34 #
Superior parietal gyrus (BA 7) R						30	-46	52	10	4.63										

	Within-group analysis All subjects (n=41)					*Within-group analysis* Contamination-type OCD (n=18)					*Within-group analysis* Non-contamination-type OCD (n=22)					*Between-group analysis* Contamination-type versus non-contamination-type OCD				
	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T	x	y	z	k_E	T
Superior parietal gyrus (BA 7) L						-27	-55	67	4	4.01										
						-15	-40	61	1	3.91										
Superior frontal gyrus (BA 10) R						9	50	-2	1	3.81										
Primary somatosensory cortex (BA 1) L						-18	-34	61	1	3.73										
Cerebellum R						24	-37	-32	1	4.51										
SMA (BA 8) R						33	23	49	1	3.72										
Head of caudate nucleus L																-3	14	7	2	3.61
Superior temporal gyrus (BA 38) L																-39	11	-29	1	3.50
negative regression DS-R																				
Inferior temporal gyrus (BA 20) R	No supratreshold clusters found					No supratreshold clusters found					45	2	-35	3	3.82	No supratreshold clusters found				

[#] between group analysis masked with within group analysis contamination-type OCD. SMA supplementary motor area, PFC prefrontal cortex.

3. Effect of group on the disgust sensitivity x distress state interaction
When assessing whether the relation between disgust sensitivity and BOLD brain activation was moderated by the group (contamination- versus non-contamination type OCD), we indeed found a significantly positive regression between group and DS-R score in the visual and sensory association areas (left BA 19, right BA 18/BA 39, $p < 0.001$ uncorrected). No negative regression was found.

To examine whether the results of the group x DS-R interaction can be explained by the effect of the DS-R within the contamination-type group, these results were masked with the within-group effect of disgust sensitivity in the contamination-type group. The DS-R scores showed a positive correlation with distress-related activation of the supplementary motor area (right BA 6, $p < 0.001$ uncorrected), visual association area (right BA 19, $p < 0.001$ uncorrected) and parieto-occipital (right BA 39/right BA19 $p < 0.001$ uncorrected). Results are shown in Table 3.

DISCUSSION

The present study investigated the neural processing of the distress response in patients with contamination-type and patients with other types of OCD and its relation to disgust sensitivity (DS). In contrast to our hypothesis, we found no difference in the activation patterns during distress processing between both groups, but we did find a difference in its relation to DS. As hypothesized, DS was related to the distress-related behavioral and neural response in contamination-type OCD but not in non-contamination-type OCD. In addition, DS interacted differently with the distress-related brain activation in both groups.

In both contamination-type and non-contamination-type OCD, high versus low distress was associated with activation in the dorsomedial prefrontal cortex (dmPFC) including the supplementary motor area (SMA), the operculum including the anterior insula, the visual association cortex and the caudate nucleus. Low versus high-distress resulted in activation of the operculum, the visual association cortex and the primary somatosensory area. Involvement of these regions during symptom provocation, aversive processing and emotion regulation is reported previously in OCD in general (Banca et al., 2015; Picó-Pérez et al., 2019; Rasgon et al., 2017; Rotge et al., 2008; Sanematsu et al., 2010; Schienle et al., 2005b; Simon et al., 2010) and in contamination-type OCD more specifically (Agarwal et al., 2013; Baoui et al., 2013; Chen et al., 2004; Mataix-Cols et al., 2004; Murayama et al., 2013; Phillips et al., 2000; Shapira et al., 2003). Remarkably, the operculum and the visual association cortex seem to be activated by opposite contrasts. This suggests that these

brain regions are involved in salience processing irrespective of the level of distress. In addition, activation of visual regions in both conditions may also be related to the visual presentation of the stimuli.

The present results do not support the hypothesis that the neural response related to emotion processing differs between contamination-type OCD and other OCD symptom dimensions and is in contrast with previous studies reporting certain variations in structure and function of distinct brain regions correlating with symptoms of distinct OCD symptom dimensions (Mataix-Cols et al., 2004; Gilbert et al., 2008; van den Heuvel et al., 2009; Murayama et al., 2013; Okada et al., 2015). However, these studies used a dimensional approach correlating differences in brain volume or neural activation with symptom subscales of obsessive-compulsive measures. In the present study a categorial approach was chosen, since subscales of instruments defining symptom dimensions in OCD intercorrelate, which makes it difficult to define distinct effects using regressional statistical methods (Pertusa et al., 2012; Rosario-Campos et al., 2009).

Although the observed neural response to distress processing did not differ between contamination- and non-contamination-type OCD, it may be modulated differentially by different factors such as DS. The present study replicated previous findings that patients with contamination-type OCD are more sensitive to disgust compared to patients with other OCD symptoms, since DS scores were higher in the contamination versus non-contamination patients (Athey et al., 2015; Olatunji et al., 2007a; Woody et Tolin, 2002). Further, in the contamination-type OCD group (but not in the non-contamination-type OCD), DS correlated positively with the reported stimuli-induced distress and DS scores in the two groups affected BOLD responses during distress processing differentially in the dmPFC, visual association area and the caudate nucleus. These results seem to indicate that DS is particularly relevant for the emotional response during symptom provocation in contamination-type OCD.

To our knowledge, this is the first study investigating the role of DS in emotion processing in contamination-type OCD compared to non-contamination-type OCD. Schienle et al. (2005b) studied a heterogenous group of OCD patients and found a positive correlation between DS and activation in the thalamus. This difference to our results, however, may be due to methodological differences in the characteristics of the subjects, the lack of categorization of OCD subtypes, the used measure for disgust sensitivity (Questionnaire for the assessment of disgust sensitivity, QADS) and the usage of a region-of-interest (ROI) approach in the fMRI data analysis. Other studies examined the role of DS in neural

correlates of disgust provocation in healthy volunteers and found a positive correlation with regions involved in emotion processing and a negative association with regions involved in appraisal and emotion regulation (Calder et al., 2007; Mataix-Cols et al., 2008; Schäfer et al., 2009; Schienle et al., 2005a; Stark et al., 2005). Although the present study found no negative correlation between disgust sensitivity and neural correlates of distress processing in OCD patients, we also showed a positive correlation between DS and the BOLD response during distress processing in brain regions overlapping with previous findings in healthy volunteers. This argues for the hypothesis of contamination-type OCD being driven by an inappropriate disgust response (Stein et al., 2006). DS may modulate common basic neural mechanisms elicited by disgust and contamination-related symptoms. High DS, like in contamination-type OCD, can be considered a dimensional vulnerability factor decreasing the threshold to respond with disgust, and increasing the distress-related neural response to disgust-provoking stimuli.

In summary, the present results suggest that the distress processing in OCD is similar across the OCD subtypes and mediated by common underlying neural mechanisms related to emotion regulation (SMA and dmPFC in combination with the caudate nucleus (Kohn et al., 2014; Kühn et al., 2011; Morawetz et al., 2017; Picó-Pérez et al., 2018; Thorsen et al., 2018)), processing of an aversive internal state like e.g., disgust (operculum including the insula (Husted et al., 2006; Nagai et al., 2007)), attention and emotional intensity (visual association cortex (Waugh et al., 2010)). In contamination-type OCD, the distress response is at least partially related to DS, that correlates with brain regions associated with attention and emotion regulation suggesting that DS mainly effects the threshold and cognitive regulation of the distress response and to a lesser degree the emotional experience itself.

This study has some limitations. First, besides family-wise corrected results we also reported uncorrected results and therefore cannot rule out type 1 errors due to multiple testing. However, to our knowledge the present exploratory study is the first one investigating DS and its neural correlates in relation to specific OCD symptom clusters, and adds information and hypotheses to existing theories about the heterogeneity, dimensional approach and emotional processing in OCD, which desire further investigation and replication. Second, we used data from a previous study to answer the hypotheses (de Wit et al., 2015; Thorsen et al., 2018). This could have restricted the process of hypothesis generation and led to methodological aspects unrelated to the present study. However, all data relevant to answer the hypotheses were available. Third, a heterogenous OCD sample was included into the study. The group of participants was not free of comorbid psychiatric diagnoses. This, however, is the case for the majority of OCD patients (Klein Hofmeijer-Sevink et al.,

2013). Almost 90% of the patients had symptoms of more than one symptom dimension. Thus, the mere additional effect of contamination-type OCD on the provoked distress-related response may have been too small to be recognized and disappeared in the noise of signals resulting from shared clinical characteristics. We did, however, not choose to exclude patients with more than one symptom cluster, because the vast majority of OCD patients have symptoms of more than one symptom dimension. Both groups only differed in the presence respectively absence of contamination-symptoms and in level of disgust sensitivity. Thus, the influence of other characteristics, such as other obsessive-compulsive symptoms, depressive symptoms or anxiety can be regarded as minimal.

Strengths may be mentioned as well. First, the effect of psychotropic medication was limited since all patients were free of psychotropic medication for at least 4 weeks. Second, the present study used an individual and subjective approach to define the high versus low distress-provoking stimuli, which makes the stimuli individually better fitting and thus more valid (Banca et al., 2015).

In conclusion, the present study demonstrates that the provoked distress-related response is processed by common neural mechanisms in OCD patients irrespective of their specific symptom profile. In the contamination-type OCD group, however, distress-related brain activation is at least partially associated with DS, which is not the case in the non-contamination-type OCD patients. Since DS may have a modulating role in the behavioral and neural response in contamination- type OCD, it may be a therapeutic target in this subtype of OCD. OCD patients with high DS may need adjusted cognitive behavioral therapy that includes interventions on disgust reduction (Fink et al., 2018; Ludvik et al., 2015).

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CHAPTER 3

THE RELATION BETWEEN DEPRESSIVE AND OBSESSIVE-COMPULSIVE SYMPTOMS IN OBSESSIVE-COMPULSIVE DISORDER: RESULTS FROM A LARGE, NATURALISTIC FOLLOW-UP STUDY

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ABSTRACT

Objective: Despite the frequent occurrence of depressive symptoms in obsessive-compulsive disorder (OCD), little is known about the reciprocal influence between depressive and obsessive-compulsive symptoms during the course of the disease. The aim of the present study is to investigate the longitudinal relationship between obsessive-compulsive and depressive symptoms in OCD patients.

Methods: We used the baseline and 1-year follow-up data of the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study. In 276 patients with a lifetime diagnosis of obsessive-compulsive disorder, depressive and obsessive-compulsive symptoms were assessed at baseline and at one-year follow-up with the Beck Depression Inventory (BDI) and the Yale-Brown Obsessive Compulsive Symptom (Y-BOCS) scale. Relations were investigated using a cross-lagged panel design.

Results: The association between the severity of depressive symptoms at baseline and obsessive-compulsive symptoms at follow-up was significant ($\beta = 0.244$, $p < 0.001$), while the association between the severity of obsessive-compulsive symptoms at baseline and depressive symptoms at follow-up was not ($\beta = 0.097$, $p = 0.060$). Replication of the analyses in subgroups with and without current comorbid major depressive disorder (MDD) and subgroups with different sequence of onset (primary versus secondary MDD) revealed the same results.

Limitations: There may be other factors, which affect both depressive and obsessive-compulsive symptoms that were not assessed in the present study.

Conclusions: The present study demonstrates a relation between depressive symptoms and the course of obsessive-compulsive symptoms in OCD patients, irrespective of a current diagnosis of MDD and the sequence of onset of OCD and MDD.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a disabling and often chronic psychiatric disorder which leads to significant impairment in daily life and diminished well-being (Farris et al., 2013; Hollander et al., 2010; Albert et al., 2010; Eisen et al., 2006). About 0.5–3% of the general population develops OCD in their lifetime (Grabe et al., 2001; Kessler et al., 2012; Subramaniam et al., 2012). Comorbidity is the rule rather than the exception, with major depressive disorder (MDD) being one of the most frequent co-morbid diagnoses (Lochner et al., 2014; Klein Hofmeijer-Sevink et al., 2013). Comorbidity rates differ largely due to methodological differences, but overall approximately one third of the patients with OCD suffer from a current comorbid MDD, and about two-third have lifetime comorbidity of MDD (Viswanath et al., 2012; Quarantini et al., 2011; Torres et al., 2006; Pinto et al., 2006; La-Salle et al., 2004). Moreover, many OCD patients suffer from depressive symptoms but do not fulfill the diagnostic criteria for a depressive episode.

Depressive symptoms often are regarded as a consequence of the burden of OCD. OCD is associated with a decreased quality of life and an increased functional impairment in work, family and social life (Huppert et al., 2009). OCD patients spend more time thinking of the obsessions and performing compulsions, accompanied by anxiety, and thus experience less positive activities and emotions, which may lead to depressive symptoms. However, although several studies found a correlation between depressive symptoms and diminished quality of life as well as functional impairment, depressive symptoms appeared to be rather a mediating factor between the severity of the obsessive-compulsive symptoms and these factors than a consequence of them (Kugler et al., 2013; Storch et al., 2014).

Several studies found evidence for common genetic factors of obsessive-compulsive and depressive symptoms. MDD occurs more often in first-degree relatives of OCD patients compared to relatives of healthy controls and vice versa, which demonstrates the familial aggregation of this comorbidity (Carter et al., 2004; Goes et al., 2012). In addition, Bolhuis et al. found that the co-occurrence of obsessive-compulsive and depressive symptoms is mainly explained by shared genetic factors while the contribution of non-shared environmental factors is considerably smaller (Bolhuis et al., 2014).

Despite the frequent occurrence of comorbid obsessive-compulsive and depressive symptoms, the treatment of comorbid depression in OCD is still a matter of debate. Some authors suggest to address also the depressive symptomatology while treating OCD (Olatunji et al., 2013; Abramowitz 2004; Rector et al., 2009), whereas others expect the

depressive symptoms to improve along with the obsessive-compulsive symptoms, and recommend to focus on the treatment of the OCD only, without specific interventions addressing the depression (Anholt et al., 2011; Zandberg et al., 2015; Zitterl et al., 2000).

Further knowledge about the relationship between obsessive-compulsive and depressive symptoms may help to solve this debate. Most cross-sectional studies found a correlation between obsessive-compulsive and depressive symptoms in OCD patients (Besiroglu et al., 2007; Abramowitz and Foa, 2000; Demal et al., 1996), but no conclusions about the direction of this relationship can be drawn from correlational analyses alone. To that end, obsessive-compulsive and depressive symptoms have to be studied over time.

The present study aims to investigate the longitudinal relationship between obsessive-compulsive and depressive symptoms in OCD patients during the disease course. First, we studied the influence of comorbid depression on the severity and the course of OCD. We hypothesized that comorbid depression is associated with more severe obsessive-compulsive symptoms and a worse course. Second, we investigated the direction of the longitudinal relationship between obsessive-compulsive and depressive symptoms, to examine whether obsessive-compulsive symptoms lead to depressive symptoms or vice versa. Based on the literature, we expected a reciprocal influence with a greater impact of obsessive-compulsive symptoms on the depressive symptoms than vice versa. Third, we studied whether the relationship between obsessive-compulsive and depressive symptoms differs between patients with and without a diagnosis of current MDD, and between patients who first had MDD and developed OCD later in life (primary depression) and those who developed MDD during the course of the OCD (secondary depression). We hypothesized a greater influence of depressive symptoms on the obsessive-compulsive symptoms in OCD patients with a comorbid depression and in patients with primary MDD.

METHODS

Participants

Data were obtained from the NOCDA study (Schuurmans et al., 2012). The NOCDA study is an ongoing longitudinal naturalistic multicenter cohort study which examines the course of OCD in 419 OCD patients. Patients were included between September 2005 and November 2009 at one of seven participating mental health care centers in the Netherlands. All referred patients aged 18 years and older with a lifetime diagnosis of OCD were asked for permission to be contacted for research purposes, irrespective of the stage of the disease, the severity of the obsessive-compulsive symptoms and comorbid diagnoses.

The only exclusion criterion was an inadequate understanding of the Dutch language for the completion of the interviews and questionnaires.

Six hundred eighty-seven patients with OCD were invited to participate in the study. Ninety-seven subjects (28.7%) refused tot participate, 32 subjects (4.7%) were not able to participate due to mental or physical health problems and 39 (5.7%) subjects could not be contacted. Subjects who participated in the study and eligible patients who chose not to participate did not differ regarding sex, age or years of education (Schuurmans et al., 2012). At one of the participating centers (Academic Anxiety Center, PsyQ Maastricht) the subjects who participated in the NOCDA study were compared to those who did not participate regarding clinical characteristics, yielding no significant differences (results not published).

All included patients gave written informed consent to participate. The study is approved by the Medical Ethical Committee VUmc (Amsterdam) and the local Medical Ethical Committees of all participating centers.

The present study is based on the data from the semi-structured interviews and the self-administered questionnaires of the baseline measurement and the self-administered questionnaires of the follow-up after one year.

Measures

At baseline, we used the Structured Clinical Interview for the DSM-IV-TR (SCID-I/P) to assess the axis-I morbidity (First et al., 1999). Among others, current and lifetime OCD as well as current and lifetime MDD were diagnosed according to the criteria of the DSM-IV-TR (APA, 2000). We assessed retrospectively the age of onset of the OCD and the MDD using the SCID-I/P. Age of onset was defined by the age of the participant when the DSM-IV-TR criteria of OCD and MDD were first met. If the onset of the lifetime diagnosis of MDD preceded the onset of lifetime diagnosis of OCD, we defined it as primary depression. If the lifetime onset of the MDD succeeded the onset of the OCD, we defined it as secondary depression. If the criteria of OCD and MDD were met at the same age, we considered it as simultaneous onset.

The severity of obsessive-compulsive symptoms was measured at baseline using the clinician rated Yale-Brown Obsessive Compulsive Symptom (Y-BOCS) severity scale (Goodman et al., 1989a, Goodman et al., 1989b) and at one-year follow-up using the self-rate version of the Y-BOCS (Steketee et al., 1996). The severity of depressive symptoms was measured at baseline and at one-year follow-up by the Beck Depression Inventory (BDI, Beck et al., 1961).

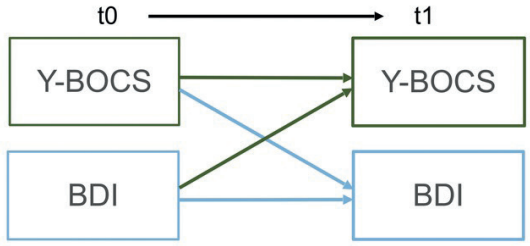
Analysis

Independent samples t-test were used to test for differences between participants with and without comorbid MDD at baseline with respect to their Y-BOCS scores at t0 and t1. Analyses to test for differences in the baseline characteristics of participants who dropped-out versus those who continued their participation were performed using Pearson chi square tests for sex, current/lifetime diagnoses and antidepressants medication, a Mann-Whitney U test for age, and independent samples t-tests for Y-BOCS scores, BDI scores and frequency of contacts with mental health care professionals. The differences between the treatment of participants with and without a comorbid MDD were performed using Pearson chi square tests (antidepressant medication, any contact with mental health care professionals in the last 12 months) and independent samples t-test (frequency of contacts with mental health care professionals in the last 12 months).

To examine the direction of the relation between obsessive-compulsive symptoms and the depressive symptoms, we used a cross-lagged panel (CLP) analysis. After standardizing the Y-BOCS and BDI variables, we fitted the path model shown in Figure 1, where the Y-BOCS and BDI scores at follow-up (t1) are regressed on the scores at baseline (t0) simultaneously. Of particular interest here are the cross-lagged paths (i.e., Y-BOCS t0-BDI t1 and BDI t0-Y- BOCS t1) that provide evidence about the direction of the relationship between two variables (e.g., when one coefficient is large and significant and the other is not). Moreover, we directly tested whether the strength of the cross-lagged coefficients differed by fitting a path model with the cross-lagged paths constrained to be equal and compared this to the unconstrained model using a chi-square test with one degree of freedom. The path models were fitted using maximum likelihood (ML) estimation. To examine whether this relation differs between participants with and without a current MDD at baseline, we repeated these analyses for these subgroups. We also performed a CLP analysis with the subgroups of patients in which the depressive disorder preceded the obsessive-compulsive disorder (primary depression) and those in which the onset of MDD succeeded the onset of OCD (secondary depression) to examine whether the direction of the relation between obsessive-compulsive and depressive symptoms differs between these groups.

If 20% or more of the items were missing for a particular scale for a given subject (i.e., 2 or more items on the Y-BOCS and/or 4 or more items on the BDI), the data were considered unreliable and the subject was excluded from the analysis. If fewer items were missing, we left the scale total as missing and then fitted the path models using full information maximum likelihood (FIML). Analyses were carried out with SPSS (version 20) and R (version 3.2.2), using the lavaan package for the path analyses (Rosseel, 2012).

Figure 1. Cross-lagged panel design. → Regression Y-BOCS t0 – BDI t1 corrected for BDI t0, leading to regression coefficient beta $\beta_{\text{Y-BOCS t0 – BDI t1}}$. → Regression BDI t0 – Y-BOCS t1, corrected for Y-BOCS t0, leading to regression coefficient beta $\beta_{\text{BDI t0 – Y-BOCS t1}}$.



RESULTS

Clinical characteristics

Demographic and clinical characteristics of the sample are shown in Table 1. At baseline, 419 participants were included. At follow-up after one year, 133 participants (31.7%) dropped out, leaving 286 participants. There were no significant differences at baseline between participants who dropped out and participants who continued participation regarding age, sex, current and lifetime diagnosis of OCD, current and lifetime diagnosis of MDD, other comorbidities, severity of obsessive-compulsive symptoms, severity of depressive symptoms, antidepressant medication and previous contacts with mental health care professionals.

At baseline, 72 participants (17.2%) had a current MDD. Within the group that participated in the follow-up, 50 participants (17.5%) had a current MDD at baseline. There was no difference in the use of antidepressant medication, contact with a mental health care professional in the last 12 months and the frequency of contacts with a mental health care professional in the last 12 months between participants with and without a comorbid MDD.

Baseline Y-BOCS and BDI total scores were available for 414 and 398 participants, respectively, and for 283 participants at follow-up. Thirty-four percent of the participants (n= 143) were excluded from the CLP analysis because of missing Y-BOCS and/or BDI scores at baseline or follow-up due to drop out (n= 133) or incomplete questionnaires (n= 10), leaving 276 participants.

Table 1. Characteristics of the sample at baseline and 1-year follow-up.

	Baseline (n=419)	Follow-up (n=286)
Mean age	37 years (18-79)	38 years (19-80)
Male	n= 185 (44.2%)	n= 119 (41.6%)
Female	n= 234 (55.8%)	n= 167 (58.4%)
OCD at baseline current	n= 382 (91.2%)	n= 257 (89.9%)
OCD at baseline lifetime	n= 419 (100%)	n= 286 (100%)
Comorbidity at baseline		
Any current comorbidity	n= 223 (53.2%)	n= 163 (57%)
Any lifetime comorbidity	n= 326 (77.8%)	n= 227 (79.4%)
Major depressive disorder at baseline current	n= 72 (17.2%)	n= 50 (17.5%)
Major depressive disorder at baseline lifetime	n= 237 (56.6%)	n= 168 (58.7%)
Other comorbid diagnoses at baseline (current)		
Dysthymic disorder	n= 22 (5.3%)	n= 12 (4.2%)
Bipolar disorder	n= 4 (1%)	n= 3 (1%)
Social phobia	n= 75 (17.9%)	n= 57 (19.9%)
Panic Disorder with/without agoraphobia	n= 13 (3.1%)	n= 27 (9.4%)
Agoraphobia without panic disorder	n= 7 (1.7%)	n= 4 (1.4%)
Generalized anxiety disorder	n= 38 (9.1%)	n= 30 (10.5%)
Posttraumatic stress disorder	n= 13 (3.1%)	n= 11 (3.8%)
Specific phobia	n= 35 (8.4%)	n= 27 (9.4%)
Anxiety disorder not otherwise specified	n= 2 (0.5%)	n= 2 (0.7%)
Any psychotic disorder (incl. schizophrenia)	n= 10 (2.4%)	n= 5 (1.7%)
Substance related disorders	n= 20 (4.8%)	n= 11 (3.8%)
Somatoform disorders	n= 22 (5.3%)	n= 18 (6.3%)
Eating disorders	n= 19 (4.5%)	n= 17 (5.9%)
Measures		
Y-BOCS mean	20 (0-40, SD 8.1)	15.9 (0-40, SD 8.8)
BDI mean	15.3 (0-51, SD 10.1)	12.6 (0-56, SD 10.6)
Treatment		
Current antidepressant medication	n= 257 (61.3%)	n= 172 (60.1%)
Any contact with mental health care professionals	in the last 6 months n= 348 (83.1%) mean= 9 sessions (0-150, SD 12.1)	in the last 12 months n= 263 (92%) mean= 16.3 sessions (0-260, SD 26)

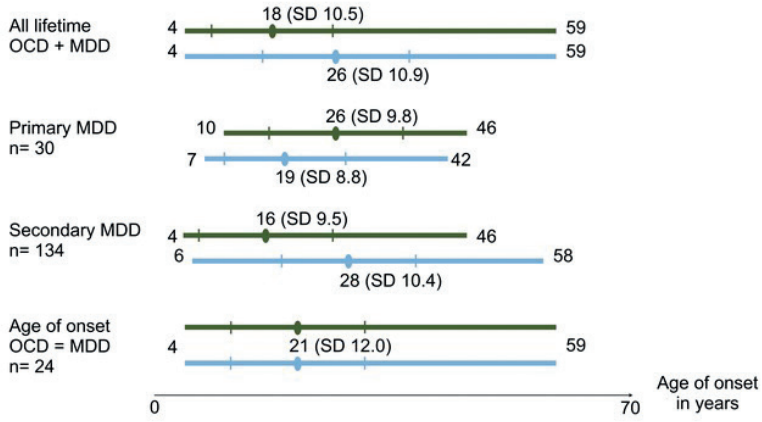
Temporal sequencing

The age of onset of OCD and MDD was available in 377 of the 419 participants with lifetime OCD and in 207 of the 237 participants with lifetime MDD. The mean age of onset of OCD was 18 years (range 4-59 years, SD 9.6), and the mean age of onset of MDD was 26 years (range 4-59, SD 10.9). Of the participants with comorbid lifetime MDD (n= 237), the age of onset of both OCD and MDD was available in 188 participants (79.3%). In 30 participants

(16%) MDD preceded OCD (primary MDD), in 134 participants (71%) OCD preceded MDD (secondary MDD), and in 24 participants (13%) MDD and OCD occurred at the same age. The sequence and age of onset are shown in Figure 2.

For the CLP analyses of the groups of primary and secondary depression, the Y-BOCS and BDI at both baseline and 1-year follow-up were available in 127 participants with known age of onset of OCD and MDD. Eighteen participants (14.2%) had a primary MDD, 94 participants (74%) had a secondary MDD, and in 15 participants (11.8%) OCD and MDD had the onset at the same age.

Figure 2. Sequence of age of onset of OCD and MDD. — Age of onset OCD with mean age of onset. — Age of onset MDD with mean age of onset.



Comorbid major depressive disorder

To examine the relationship between current major depressive disorder (MDD) at baseline and the severity of the obsessive-compulsive symptoms at baseline and follow-up, we compared the mean Y-BOCS score of the depressed participants with the mean Y–BOCS score of the non-depressed participants.

In the group with a current comorbid MDD, the mean Y-BOCS score at baseline was 24.5 (SD 7.6). Non-depressed participants had a mean baseline Y-BOCS score of 18.9 (SD 7.9). This difference was statistically significant ($p< 0.001$). Participants with current MDD at baseline also had a significantly higher mean score on the Y-BOCS severity scale at the one-year follow-up assessment, that is, 18.7 (SD 10.4) versus 15.4 (SD 8.4), respectively ($p= 0.017$).

Relation between obsessive-compulsive and depressive symptoms

To examine the relation between obsessive-compulsive and depressive symptoms, we performed the CLP analysis for the whole group and different subgroups. The results are shown in Table 2.

In all analyses, the relationship between BDI at baseline and Y-BOCS at follow-up was significant, while the association between the Y-BOCS score at baseline and the BDI score at follow-up was not.

When we compared the strength of both regression paths directly, they did not differ significantly, except in the group of primary MDD. In this subgroup, the depressive symptoms had a significantly stronger effect on the obsessive-compulsive symptoms than vice versa.

Table 2. Regression coefficients per subgroup.

	Y-BOCS t0 – BDI t1		BDI t0 – Y-BOCS t1		Test of
	B	p	β	P	$\beta_{\text{Y-BOCS t0-BDI t1}} = \beta_{\text{BDI t0-Y-BOCS t1}}$
All participants (n= 276)	β= 0.097	p= 0.060	β= 0.244	p< 0.001**	p= 0.084
Current MDD (n= 50)	β= 0.127	p= 0.275	β= 0.466	p= 0.001**	p= 0.083
No current MDD (n= 226)	β= 0.099	p= 0.098	β= 0.191	p= 0.003**	p= 0.328
Primary MDD (n= 18)	β= -0.036	p= 0.877	β= 0.719	p< 0.001**	p= 0.034*
Secondary MDD (n= 94)	β= 0.154	p= 0.093	β= 0.261	p= 0.014*	p= 0.504

* significant at p< 0.05, **significant at p< 0.01.

DISCUSSION

In the present longitudinal study we investigated major depressive disorder (MDD) and depressive symptoms in obsessive-compulsive disorder (OCD), using data from the NOCDA study which to our knowledge is the largest longitudinal cohort study in OCD. We found a significant association between the severity of depressive symptoms at baseline and obsessive-compulsive symptoms one year later, while the relation between the severity of obsessive-compulsive symptoms at baseline and depressive symptoms at follow-up was not significant. This effect was observed in all groups, irrespective of a comorbid MDD or whether the MDD preceded or succeeded the OCD.

There are a few prospective longitudinal studies, which address the direction of the relation between obsessive-compulsive and depressive symptoms. A twin study in adolescents with OCD investigated the longitudinal relationship between obsessive-compulsive and

depressive symptoms. They concluded that obsessive-compulsive symptoms predict depressive symptoms two years later to a similar extent to which depressive symptoms predict obsessive-compulsive symptoms. There are several methodological differences that may account for the partially different results. The participants were adolescent twins, the obsessive-compulsive symptoms and depressive symptoms were measured by the Spence Children's Anxiety Scale and the Short Mood and Feelings Questionnaire, and the study period was two years. In addition, the study was designed as a twin study with the primary aim to investigate the influence of genetic versus environmental factors on the comorbidity of OCD and MDD (Bolhuis et al., 2014).

A treatment study which investigated the mediators of change in behavioral versus cognitive therapy in OCD patients found that a reduction in depressed mood mediated changes in OCD symptom severity in both behavioral and cognitive therapy (Olatunji et al., 2013). Other research contradicts this conclusion. Anholt et al. (2011) investigated the relation between obsessive-compulsive and depressive symptoms in patients following different treatment conditions specific for OCD. This study was recently replicated for exposure with response prevention in combination with a serotonergic reuptake inhibitor (Zandberg et al., 2015). Both studies found that obsessive-compulsive symptoms fully mediated changes in depressive symptoms while depressive symptoms only partially mediated OCD symptoms. The studies differ from our study in several aspects. They included patients with clinical symptoms of OCD with a higher mean Y-BOCS severity score for different therapeutic interventions. In contrast, our study used a naturalistic design and included OCD patients irrespective of the state or severity of the OCD leading to a greater range of OCD symptom severity. Both clinical trials had more stringent inclusion criteria and excluded certain comorbidities, while the present study did not.

In the present study, the comorbid diagnosis of MDD was associated with more severe obsessive-compulsive symptoms at the same time as well as one year later. This is in line with several cross-sectional studies that reported more severe obsessive-compulsive symptoms in OCD patients with comorbid MDD (Demal et al., 1996; Viswanath et al., 2012; Quarantini et al., 2011; Karadag et al., 2006; Tükel et al., 2006) although no conclusion regarding the prognostic impact of comorbid MDD can be drawn based on these findings. In a 15-year prospective follow-up study on the course of OCD, Marcks et al. (2011) found that MDD at intake was associated with a decreased likelihood of recovery and remission of OCD.

Because of the reported significant effect of MDD on the severity of the OCD symptoms during the course of the disease, we investigated whether the effect of depressive symptoms on the disease course could be explained by the group of patients with a current comorbid MDD at baseline. Our results show that this was not the case: the depressive symptoms were associated with the course of the obsessive-compulsive symptoms as well in OCD patients with MDD as in OCD patients without MDD.

Some authors suggest that the sequence of onset of OCD and MDD may influence the direction of the relation between both disorders, expecting that obsessive-compulsive symptoms have a greater influence on comorbid depressive symptoms when the depression developed after the onset of OCD (Zandberg et al., 2015; Zitterl et al., 2000; Besiroglu et al., 2007). Several clinical studies found that MDD succeeded the OCD in the majority of cases (Subramaniam et al., 2012; Zitterl et al., 2000; Ruscio et al., 2010; Millet et al., 2004). Also in the present study, seventy-one percent of the patients first suffered from OCD and developed MDD later in life. In the small group with primary MDD, the depressive symptoms had a significant stronger effect on the obsessive-compulsive symptoms than vice versa. But also in the group which developed MDD during the course of OCD, we found a significant relation between depressive symptoms at baseline and obsessive-compulsive symptoms at follow-up while the opposite association was not significant.

These results suggest that the direction of the relation is not influenced by the sequence of onset. However, both OCD and MDD often have a fluctuating course with variations in the severity of symptoms and periods of remission and relapse (Marcks et al., 2011; Eisen et al., 2013; Judd et al., 1998) while temporal sequencing solely assesses the order of the age of onset of the first episode. In addition, a factor that causes a certain disorder may not necessarily be the same as the one that leads to relapse, deterioration or chronicity.

Different underlying mechanisms may explain how depressive symptoms may provoke, maintain, or modulate obsessive-compulsive symptoms in OCD. Depressed patients may have less energy to resist the compulsions which can maintain the obsessive-compulsive symptoms and worsen the prognosis. Depressive cognitions of self-blame, guilt, or catastrophic interpretations may be applied to the occurrence and the content of the obsessions, making them more salient and thus increasing the need to carry out compulsions. Rumination, worries, and doubting are frequent symptoms in depressive patients and may lead to a heightened state of anxiety. In people prone to OCD, attempts to reduce this anxiety may result in an increase in compulsive behavior.

In conclusion, the present study demonstrates a relation between depressive symptoms and the course of obsessive-compulsive symptoms in OCD patients, irrespective of a current diagnosis of MDD and the sequence of onset of OCD and MDD. The effect of the obsessive-compulsive symptoms on the course of the depressive symptoms is less clear. Our results did not demonstrate a significant relation between obsessive-compulsive symptoms and the course of the depressive symptoms but cannot exclude it. When the strengths of both directions of the relation between obsessive-compulsive and depressive symptoms were compared directly, the difference was not significant except in the small group of participants with comorbid MDD preceding the OCD.

The results suggest a causal relationship between the severity of depressive symptoms and the course of obsessive-compulsive symptoms. However, theoretically, there might be other factors affecting both depressive and obsessive-compulsive symptoms, such as comorbidity, antidepressant medication or psychotherapy. No participants were excluded due to comorbidity (in fact more than half of the participants had at least one comorbid diagnosis). This was an explicit choice to ensure the generalizability of our results, as comorbidity is common in OCD. The most frequent comorbid disorders were MDD and diverse anxiety disorders, but overall, the comorbid diagnoses were quite heterogeneous. It therefore seems unlikely that they would explain our results.

More than half of the participants were on antidepressant medication and more than 90% had contacts with a mental health care professional between baseline and follow-up. Antidepressant medication and the contacts with mental health care professionals did not differ between participants with and without MDD. However, we did not assess the therapeutic interventions and the reason for the consultations, which is a clear limitation.

Further limitations are the assessment of the obsessive-compulsive symptoms and the definition of the age of onset. The age of onset was assessed retrospectively and measured in years. For the measurement of the obsessive-compulsive symptoms, we used the clinician-rated version of the Y-BOCS at baseline and the self-report version at follow-up. The follow-up was less extensive than the baseline assessment and contained only self-report questionnaires to limit the patients' study burden. However, the self-report Y-BOCS is a reliable and valid measure, which shows strong convergent validity with the interview Y-BOCS (Steketee et al., 1996).

Another limitation is the possibility of a selection bias. Patients were recruited from outpatient clinics and treatment programs for anxiety and obsessive-compulsive disorders.

Probably, there were also patients with both MDD and OCD who were referred to an outpatient clinic or treatment program for mood disorders, and hence were not included in the present study. This might explain the mild to moderate severity of the depressive symptoms and the prevalence of current MDD being eighteen percent, which is quite low compared to the literature. On the other hand, the lifetime prevalence of MDD in our sample was 57%, which is in line with most of the lifetime prevalence rates reported in the literature (Quarantini et al., 2011; Pinto et al., 2006; Zitterl et al., 2000; Marcks et al., 2011).

Finally, the study had a 31% dropout at follow-up. We dealt with missing data using an estimation method (FIML) that is appropriate when the missing data are missing at random (MAR). Estimation or imputation methods could not be applied reliably to the dropouts for their data is likely not missing at random (non-ignorable missingness). However, we do not expect that the missing data affected our results, because the dropouts and completers did not differ in their clinical characteristics at baseline. In addition, dropouts were taken into account in the design of the study (Schuurmans et al., 2012), and even after dropout the analyses were based on the large sample size of 286 participants.

There are few prospective longitudinal studies that address the relation between obsessive-compulsive and depressive symptoms and to our knowledge the present study is the first one which studied a naturalistic course in adult OCD patients. Replication of the study in other clinical or population-based samples may answer the question whether the results can be generalized to other groups than OCD patients. Future studies should also focus on possible factors that mediate the reciprocal influence of obsessive-compulsive and depressive symptoms, such as shared vulnerabilities or common biological mechanisms.

The findings of the present study have several clinical implications. Considering the high prevalence of lifetime and current MDD in OCD patients and the influence of the depressive symptoms on the course of the obsessive-compulsive symptoms, depressive symptoms should be routinely assessed in OCD patients. Our results do not confirm the assumption that in OCD patients the depressive symptoms improve along with the obsessive-compulsive symptoms. Instead, depressive symptoms may maintain or worsen OCD symptoms. Therefore, we recommend that treatment also needs to address the depression. There are examples of treatment programs that combine interventions from cognitive behavioral therapy for depression and OCD, with positive results (Abramowitz, 2004; Arco, 2015; Rector et al., 2009). Pharmacotherapy with serotonergic antidepressants is another treatment option which addresses both disorders and can be combined with cognitive behavioral therapy for OCD (Romanelli et al., 2014; Soomro et al., 2008).

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CHAPTER 4

ANXIETY DURING THE LONG-TERM COURSE OF OBSESSIVE-COMPULSIVE DISORDER

published as

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ABSTRACT

Objective: Anxiety is common in OCD and plays a significant role in the clinical presentation of this disorder, even beyond the immediate distress response related to obsessions and compulsions. The present study aimed to investigate anxiety and its relation with obsessive-compulsive symptoms during the long-term course of OCD.

Methods: We compared three different models: 1) the cross-lagged model, which assumes that anxiety and obsessive-compulsive symptoms are two distinct groups of symptoms which interact directly on the long-term; 2) the stable traits model, which assumes that anxiety and obsessive-compulsive symptoms result from two distinct latent factors, which are stable over the time and interact with each other; and 3) the common factor model, which assumes that anxiety and obsessive-compulsive symptoms are presentations of the same latent factor. We used data from the Netherlands OCD Association (NOCDA) study, which included 419 participants with a lifetime diagnosis of OCD. The severity of obsessive-compulsive symptoms and anxiety at baseline and after two, four, and six years were entered into the three models, which were analyzed and compared using structural equation modeling.

Results: The cross-lagged model and the stable traits model showed good model fit and similar fit indices, and thus both are valid models. The common factor model had a poor model fit and was rejected.

Conclusions: We conclude that anxiety and obsessive-compulsive symptoms in OCD patients do not result from a shared underlying factor but are distinct, interacting symptom groups, probably resulting from distinct, interacting latent factors.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is defined by recurrent, intrusive thoughts, urges or images (obsessions) and repetitive and often ritualistic behaviors (compulsions) (DSM-5, APA 2013). According to the learning theory obsessions provoke distress, which often presents as anxiety. Subsequently, compulsions are performed to diminish the distress or anxiety. Several studies and theories address the short-term relation between obsessions leading to anxiety leading to compulsions (e.g., Hartmann et al., 2019; Starcevic et al., 2011; Salkovskis, 1985; Rachman et Hodgson, 1980), but anxiety in OCD also occurs unrelated to the immediate distress response (Citkowska-Kisielewska et al., 2019; van Schalkwyk et al., 2016).

OCD is a heterogeneous disorder with common aspects which are present in all OCD patients as well as distinct characteristics which vary between subgroups of patients (Olatunji et al., 2017; Starcevic et al., 2011). Based on the content of the obsessions and compulsions, different OCD symptom dimensions can be distinguished: aggressive obsessions/checking, contamination/washing, symmetry/ordering and hoarding (Bloch et al., 2008; Mataix-Cols et al., 2005; Leckman et al., 1997). Although anxiety is reported in all symptom dimensions (Starcevic et al., 2011), the role of anxiety in OCD may vary between them. Studies point towards a particular relation of anxiety with aggressive obsessions/checking symptoms (Cervin et al., 2021; Hartman et al., 2019; Sulkowski et al., 2008).

Anxiety has a significant role in the clinical picture of OCD (Citkowska-Kisielewska et al., 2019). More severe anxiety is related to chronicity (Nakajima et al., 2018; van Oudheusden et al., 2018; Ferrão et al., 2006), impaired quality of life (Remmerswaal et al., 2018; Velloso et al., 2018; Subramaniam et al., 2013) and more functional impairment (Velloso et al., 2018; Storch et al., 2014). It is also associated with more severe obsessive-compulsive symptoms cross-sectionally (Klein Breteler et al., 2021; Sulkowski et al., 2008). In treatment studies, no effect of anxiety on treatment outcome was observed (Kathmann et al., 2022; Knopp et al., 2013; Farrell et Boschen, 2011; Steketee et al., 2019), possibly because most therapeutic interventions for OCD, such as cognitive behavioral therapy and serotonergic antidepressants, also effectively reduce anxiety (Anand et al., 2011; Blair Simpson et al., 2008). Therefore, natural follow-up studies may be preferred to study the long-term relation between anxiety and obsessive-compulsive symptoms. To our knowledge, these studies are lacking and information on the long-term course of anxiety in OCD is very limited. Insight on the long-term relation between anxiety and obsessive-compulsive symptoms may help to understand the nature of OCD and may clarify aspects of its heterogeneity.

It may also contribute to the discussion on the hypothesis whether the role of anxiety decreases with the duration of OCD (Stein et al., 2019).

Different models of the long-term relation between anxiety and obsessive-compulsive symptoms in OCD are plausible. The severity and course of the distinct symptoms may reflect a dynamic interaction and may result from a specific effect of one symptom towards the other (Klein Hofmeijer-Sevink et al., 2018; McGorry et al., 2018). In that case, anxiety and obsessions/compulsions may be regarded as co-occurring but distinct symptoms which affect each other directly during the course of OCD. The severity of anxiety may be positively associated with the severity of the obsessions and compulsions in the future, or the severity of the obsessive-compulsive symptoms may be related to anxiety in the future. However, a bi-directional interaction is also possible.

Another hypothesis is, that the reciprocal relation between obsessive-compulsive symptoms and anxiety results from distinct underlying latent factors, which interact. Obsessive-compulsive disorder often has a chronic course (Garnaat et al., 2015; Kempe et al., 2007; Skoog and Skoog, 1999) and thus the occurrence and severity of obsessions and compulsions may be associated with a latent underlying obsessive-compulsive factor, e.g., a chronic vulnerability, which is stable over the time and results in a specific expression of obsessive-compulsive symptoms at specific moments during the course of OCD. In the same way, anxiety may result from a latent underlying anxiety factor. The interaction between anxiety and obsessive-compulsive symptoms rather may be an interaction of the underlying stable latent factors, than a direct interaction at the specific moment.

A third hypothesis is the presence of a common latent factor of obsessive-compulsive symptoms and anxiety, which determines the course of both. This is in line with studies suggesting a “higher-order factor” which is shared by different mental disorders including OCD (Caspi et al., 2014; Barlow et al., 2000). In that case, anxiety and obsessions/compulsions are presentations of a common latent factor, i.e. they may form distinct symptoms of shared underlying mechanisms or vulnerabilities. Changes in the common latent factor may subsequently lead to changes in its presentation with anxiety and obsessions/compulsions over time.

The aim of the present study was to investigate the role of anxiety during the long-term course of OCD, and specifically the relation between anxiety and obsessive-compulsive symptoms. We tested three different models to describe this relation. We hypothesized that anxiety and obsessions/compulsions are distinct but related aspects of OCD which affect each other longitudinally. We also expected that the role of anxiety diminishes over the

time and that the strength of the association between anxiety and obsessive-compulsive symptoms decreases during the long-term course of OCD.

METHODS

Participants

The present study used data from the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study, a longitudinal naturalistic cohort study which followed 419 adult OCD patients for six years. The study design and characteristics of the baseline assessment are described in detail elsewhere (Schuurmans et al., 2012). Participants were included at one of the seven participating mental health care centers in the Netherlands. Inclusion criteria were a lifetime diagnosis of OCD, irrespective of the state of the disease, and age of 18 years or older. Insufficient understanding of the Dutch language to complete the interviews and questionnaires was the only exclusion criterion. All participants gave written informed consent. The protocol was approved by the Medical Ethical Committee VU University Medical Center Amsterdam and the local Medical Ethical Committees of all participating centers.

Measures

The present study analyzed information from interviews and questionnaires of the baseline assessment and follow-up after two, four, and six years.

At baseline, current and lifetime diagnoses of OCD were ascertained according to the criteria of the DSM-IV-TR (APA, 2000) using the Structured Clinical Interview for the DSM-IV-TR (SCID-I/P) (First et al., 1999). Symptom dimensions were categorized at baseline using the Yale-Brown Obsessive-Compulsive Symptom Checklist (Y-BOCS SL), an 80-items interview which allows classification of the aggressive obsessions/checking dimension, the symmetry/ordering dimension, the contamination/washing dimension, and the hoarding dimension (Leckman et al., 1997; Summerfeldt et al., 1999). If one or more symptoms of the respective symptom dimension were reported by a participant, the symptom dimension was considered to be present.

At baseline and each follow-up after two, four, and six years, the severity of the obsessive-compulsive symptoms was assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989a; Goodman et al., 1989b). The severity of anxiety symptoms was measured by the Beck Anxiety Inventory (BAI) at baseline and at each follow-up after two, four, and six years (Beck et al., 1988).

Descriptive and cross-sectional statistical analyses

Differences at baseline between participants who completed all assessments and drop-outs were analyzed by Pearson's chi square tests (sex and current symptom dimensions), and independent samples t-test (age, number of symptom dimensions, Y-BOCS and BAI scores at baseline).

To investigate if the strength of the correlation between anxiety and obsessive-compulsive symptoms decreases during the follow-up, we tested: $H_0: \rho_T = 0$ cross-sectionally at baseline and each follow-up, where ρ_T denotes the correlation between anxiety and obsessive-compulsive symptoms at baseline *(t* = 0*)* and at the 2, 4, and 6-year follow-ups (*t* = 2, 4, 6, respectively).

To examine if more anxiety is reported in distinct OCD symptom dimensions, the BAI scores of participants reporting symptoms of a distinct symptom dimension were compared with the BAI scores of participants without symptoms of this distinct symptom dimension. We performed four t-tests to compare the baseline BAI scores 1) between participants reporting symptoms of the aggressive obsessions/checking dimension and participants who did not, 2) between participants with versus without symptoms of the contamination/washing dimension, 3) between participants with versus without symptoms of the symmetry/ordering dimension, and 4) between participants with versus without symptoms of the hoarding dimension.

Structured equation modeling

To investigate the longitudinal relationship between anxiety and obsessive-compulsive symptoms, the BAI and the Y-BOCS were analyzed using three different models: 1) a cross-lagged model, 2) a stable traits model, and 3) a common factor model. The models are illustrated in Figure 1.

The cross-lagged model (Figure 1a) hypothesized that anxiety measured by the BAI and obsessive-compulsive symptoms measured by the Y-BOCS are distinct symptoms, and that anxiety and obsessive-compulsive symptoms are directly related. We analyzed the cross-lagged regression paths to examine the reciprocal relation between each Y-BOCS and the BAI two years later and vice versa. The auto-correlations for the longitudinal effects of the Y-BOCS on the following Y-BOCS and the BAI on the following BAI were included, as well as the cross-sectional covariances between the BAI and Y-BOCS scores. The strength of the respective cross-lagged regression paths subsequently were compared against each other: the path baseline Y-BOCS to 2-years BAI versus the path baseline BAI to 2-years Y-BOCS, the path 2-years Y-BOCS to 4-years BAI versus the path 2-years BAI to 4-years Y-BOCS, and the path 4-years Y-BOCS to 6-years BAI versus the path 4-years BAI to 6-years Y-BOCS.

The stable traits model (Figure 1b) hypothesized that anxiety measured by the BAI and obsessive-compulsive symptoms measured by the Y-BOCS are distinct symptoms, which do not interact directly but by latent traits. The latent trait reflects an underlying unobserved construct, which is stable over the time. For the stable traits model, we used a confirmatory factor analysis with 2 latent factors (the obsessive-compulsive trait and the anxiety trait), which were allowed to correlate. The observed measures of the Y-BOCS and BAI at baseline, and the 2-, 4-, and 6-years follow-up were the respective indicators of the latent traits. The auto-correlations for the Y-BOCS and the BAI were included into the model, as well as the cross-sectional co-variance between the BAI and the Y-BOCS.

The common factor model (Figure 1c) hypothesized that the symptoms measured by the Y-BOCS and the symptoms measured by the BAI originate from a common latent factor. In this model, the baseline Y-BOCS and the baseline BAI are indicators of a latent baseline factor, and each follow-up measure of the Y-BOCS and BAI are the indicators of the respective latent factor during follow-up. Auto-correlations for the Y-BOCS and BAI were included in this model.

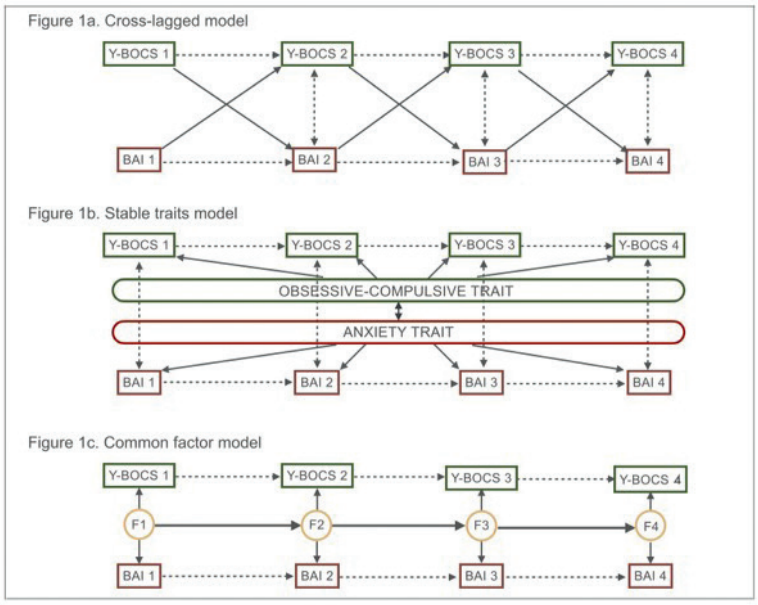
To analyze these three models, structural equation modeling was used, including the Y-BOCS and BAI total scores of the baseline and each follow-up assessment after two, four, and six years. Subsequently, analyses were repeated using the Y-BOCS compulsion subscale (Y-COM) and the BAI total score, because hypotheses over anxiety-driven behavior in OCD often focus on the relation between anxiety and compulsive behavior (Stein et al., 2019; Gillan et al., 2016).

Y-BOCS and BAI scores were rescaled to equal both measures before entering the scores into the structured equation modeling analyses. To account for missing data (that were assumed to be missing at random), the models were fitted using the full information maximum likelihood (FIML) estimation.

Fit indices of the three models were compared using the following indicators for a good fit: a chi-square test p-value > 0.05, a comparative fit index (CFI) value > 0.95, a Tucker Lewis index (TLI) value > 0.90, a root mean square error of approximation (RMSEA) value < 0.08, and a standardized root mean square residual (SRMR) value < 0.05.

Data were analyzed with SPSS (version 23) and R (version 3.6.0) using the lavaan package for the structured equation modeling (Rosseel et al., 2012).

Figure 1. Models of the longitudinal relationships between the Y-BOCS and BAI scores. Regression paths and loadings (continued arrows), auto-regressions and covarinces (dotted arrows), observed variables (squares) and latent variables (circles).



RESULTS

Clinical characteristics

At baseline, 419 participants completed the interviews and questionnaires. Due to drop-out, at follow-up after two years 311 patients (74.2%) still participated, at follow-up after four years 295 patients (70.4%), and at follow-up after six years 268 patients (64%). Complete questionnaires of the baseline and all follow-up assessments of the Y-BOCS and BAI were available for 187 participants (44.6%). At baseline, the group of completers did not differ significantly from the group with missing data regarding age, sex, current diagnosis of OCD, current OCD symptom dimensions, Y-BOCS and BAI scores. Characteristics of all participants at baseline are summarized in Table 1.

The mean Y-BOCS and BAI scores per assessment are shown in Table 2. Mean Y-BOCS and BAI scores both were highest at baseline, declined towards the 2-year follow-up, and remained stable towards the 4-year and 6-year follow-up.

Cross-sectional correlation analyses at baseline and all follow-ups showed a significant correlation between BAI and Y-BOCS total scores, between the BAI and the Y-BOCS obsession subscale, and between the BAI and the Y-BOCS compulsion subscale, as shown in table 2.

Most participants (n= 331, 78.9%) had symptoms of more than one symptom dimension with a mean of 2.3 symptom dimensions. Frequencies of the symptom dimensions are reported in Table 1. Participants with the symptom dimension aggressive obsessions/checking had significantly higher BAI scores compared to participants without symptoms of this dimension (mean 18.1 (SD 12.0) versus 9.7 (SD 8.9), p< 0.001). Also, participants with symptoms of the contamination/washing dimension had significantly higher BAI scores compared to participants without contamination/washing symptoms (mean 18.9 (SD 12.6) versus 14.9 (SD 10.6, p= 0.001). The presence or absence of symptoms of the symmetry/ordering dimension did not lead to a significant difference in BAI scores (mean 17.8 (SD 12.1) versus 16.3 (SD 11.8), p= 0.231), neither did the presence or absence of the hoarding dimension (mean 19.5 (SD 12.9) versus 16.9 (SD 11.8), p= 0.114).

Table 1. Characteristics of all participants (n=419) at baseline.

	n= 419
Age	36.6 yrs (18-79 yrs)
Male/female	n= 185 male (44.2%), n= 234 female (55.8%)
OCD current	n= 382 (91.2%)
OCD lifetime	n= 419 (100%)
Duration OCD	17.9 years (SD 12.2, range 0-64 yrs)
Y-BOCS	
Total score	19.8 (SD 8.1, range 0-40)
Obsessions	9.9 (SD 4.3, range 0-20)
Compulsions	10.0 (SD 4.8, range 0-20)
BAI	17.3 (SD 12.0, range 1-60)
Symptom dimensions	
aggressive obsessions/checking	n= 370 (90.7%),
symmetry/ordering	n= 282 (62.1%)
contamination/washing	n= 251 (61.5%)
hoarding	n= 68 (16.7%)
Number of current OCD symptom dimensions	
n= 0	n= 18 (4.3%)
n= 1	n= 76 (18.1%)
n= 2	n= 123 (29.4%)
n= 3	n= 145 (34.6%)
n= 4	n= 46 (11%)

Table 2. Y-BOCS scores, BAI scores (mean, standard deviation and range) and the correlation of the BAI scores and Y-BOCS total scores (Y-BOCS), Y-BOCS obsession subscale (Y-OBS) and Y-BOCS compulsions subscale (Y-COM) of all participants.

	Baseline	2-yrs FU	4-yrs FU	6-yrs FU
Y-BOCS				
Total score	20.0 (SD 8.1, 0-40)	15.1 (SD 9.0, 0-40)	15.4 (SD 9.2, 0-40)	15.6 (SD 9.4, 0-40)
Obsessions	9.9 (SD 4.3, 0-20)	7.4 (SD 4.8, 0-20)	7.5 (SD 4.7, 0-20)	7.5 (SD 4.8, 0-20)
Compulsions	10.0 (SD 4.8, 0-20)	7.7 (SD 5.0, 0-20)	7.9 (SD 5.2, 0-20)	8.1 (SD 5.1, 0-20)
BAI	17.3 (SD 12.0, 0-60)	13.4 (SD 11.2, 0-52)	13.6 (SD 10.9, 0-55)	13.6 (SD 10.7, 0-54)
Correlation				
Y-BOCS - BAI	r= .41, p< 0.001	r= .50, p< 0.001	r= .46, p< 0.001	r= .49, p< 0.001
Y-OBS - BAI	r= .38, p<0.001	r= .51, p< 0.001	r= .43, p< 0.001	r= .49, p< 0.001
Y-COM - BAI	r= .34, p< 0.001	r= .42, p< 0.001	r= .42, p< 0.001	r= .44, p< 0.001

Long-term relation between anxiety and obsessive-compulsive symptoms

Model fit indices of the models based on the BAI and Y-BOCS total scores (resp. the Y-BOCS compulsion subscale) are shown in Table 3. The cross-lagged model and the stable traits model both had a good model fit and similar fit indices, and thus both are valid models. The common factor model had poor model fit and therefore was rejected as a plausible model.

When the analyses were repeated with the BAI and the Y-BOCS compulsion subscale, the pattern of results did not change.

Table 3. Model fit indices of the cross-lagged model (CLM), stable traits model (STM) and common factor model (CFM) using the BAI and the Y-BOCS total scores (Y-BOCS) and Y-BOCS compulsion subscale (Y-COM), respectively.

	CLM Y-BOCS	CLM Y-COM	STM Y-BOCS	STM Y-COM	CFM Y-BOCS	CFM Y-COM
Chi-square	p= 0.117	p= 0.056	p= 0.095	p= 0.042	p< 0.001	p< 0.001
CFI	0.995	0.994	0.995	0.993	0.872	0.831
TLI	0.985	0.978	0.984	0.977	0.674	0.569
RMSEA	0.038	0.046	0.039	0.047	0.178	0.206
SRMR	0.022	0.022	0.026	0.029	0.096	0.124

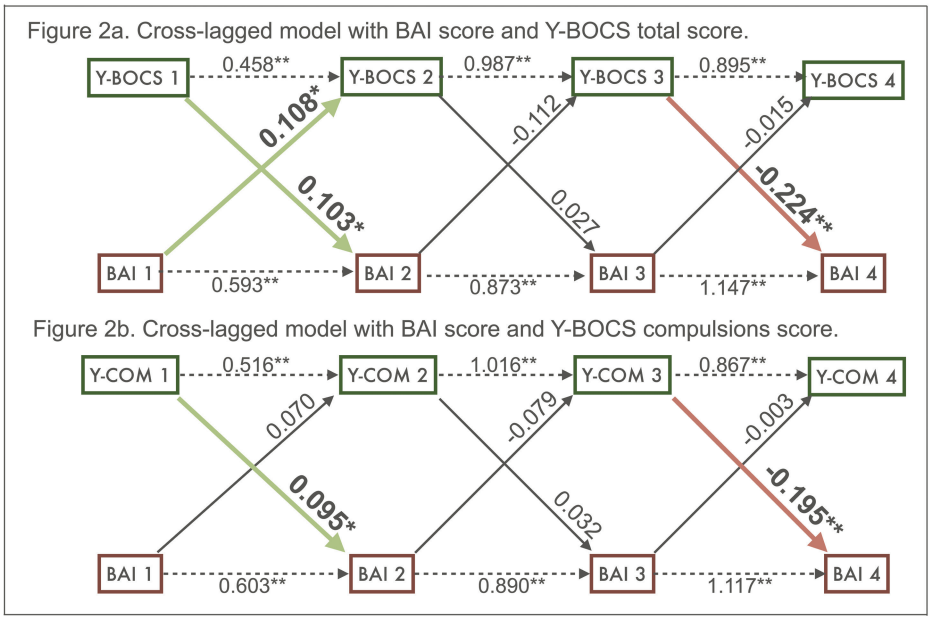
1. The cross-lagged model

The standardized regression coefficients and auto-correlations of the cross-lagged model are illustrated in Figure 2.

The regression paths from the baseline BAI to the 2-years follow-up Y-BOCS and the cross-lagged path from the baseline Y-BOCS to the 2-years BAI showed a significant positive relation (ß= 0.108, p=0.042 and ß= 0.103, p= 0.20, respectively), while the path from the 4-years Y-BOCS to the 6-years BAI showed a significant negative relation (ß= -0.224, p= 0.001). All other regression paths were not statistically significant. When the strengths of the cross-lagged paths were compared against each other, no significant differences emerged (baseline to 2-years follow-up p= 0.643, 2-years follow-up to 4-years follow-up p= 0.115, 4-years follow-up to 6-years follow-up p= 0.146).

When the cross-lagged analyses were repeated using the BAI scores and the Y-BOCS compulsion (Y-COM) scores, a significant positive relation was found between the baseline Y-COM and the 2-years BAI (ß= 0.095, p= 0.028) and a significant negative relation between the 4-years Y-COM and the 6-years BAI (ß= -0.195, p= 0.001). All other regression paths were not significant. When the strengths of the respective cross-lagged paths were compared directly, no significant results were found (baseline to 2-years follow-up p= 0.781, 2-years follow-up to 4-years follow-up p= 0.143, 4-years follow-up to 6-years follow-up p= 0.193).

Figure 2. Cross-lagged model. Y-BOCS Y-BOCS total score, Y-COM Y-BOCS compulsion subscale score. Standardized regression coefficients per path (continued single-arrowed line) and auto-correlations (dotted single-arrowed line).* p< 0.05, ** p< 0.01



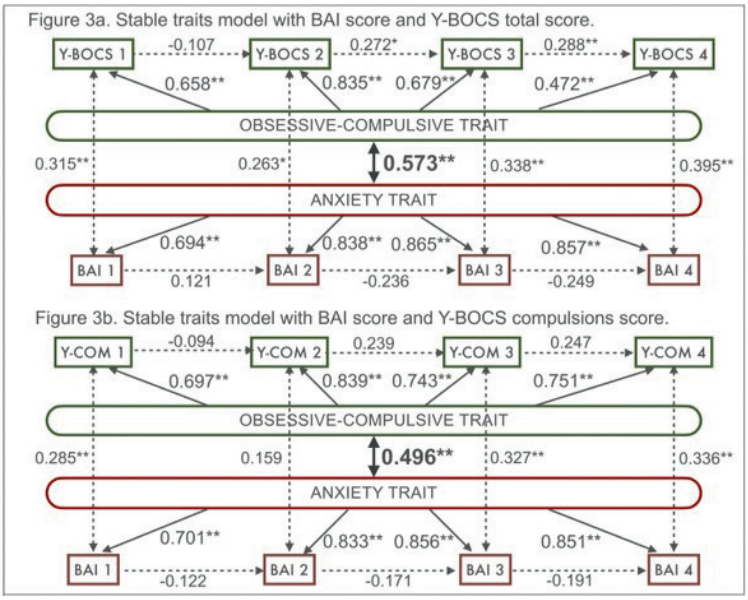
2. The stable traits model

The regression paths and auto-correlations of the stable traits model are illustrated in Figure 3.

The observed measures of the Y-BOCS significantly loaded on the obsessive-compulsive trait, and the observed measures of the BAI on the anxiety trait. The obsessive-compulsive trait and the anxiety trait correlated strongly (r= 0.573, p< 0.001). Covariances at each follow-up were moderate and significant, suggesting that at each distinct follow-up additional factors outside the modelled correlation of both latent traits were related to the Y-BOCS and BAI scores.

When analyses were repeated using the BAI scores and the Y-BOCS compulsion scale scores, the Y-BOCS compulsion subscale at baseline and each follow-up significantly loaded on the compulsivity trait, as did the BAI scores on the anxiety trait. The anxiety and compulsivity trait strongly correlated (r= 0.496, p< 0.001). Cross-sectional error correlations were moderate except that at the follow-up after 2 years it was not significant.

Figure 3. The Stable traits model. Y-BOCS Y-BOCS total score, Y-COM Y-BOCS compulsion subscale score. Partial regression coefficients (continued single-arrowed line), auto-correlations (dotted single-arrowed line), error correlations between the Y-BOCS total score and BAI score (double-arrow dotted line) and correlation between the stable traits (double-arrowed continued line). * p<0.05, ** p< 0.01.



DISCUSSION

In the present study we investigated the long-term relation between anxiety and obsessive-compulsive symptoms during the course of OCD in three different models.

The cross-lagged model as well as the stable traits model showed good model fit and therefore both are valid descriptions of the long-term relation of anxiety and obsessive-compulsive symptoms. The common factor model fitted poorly and was rejected. Based on these results, we concluded that anxiety and obsessive-compulsive symptoms in OCD patients do not result from a shared underlying factor. Instead, anxiety and obsessive-compulsive symptoms are distinct groups of symptoms, which interact on the long-term, probably resulting from two distinct interacting latent traits.

According to the cross-lagged model, obsessive-compulsive symptoms are related to previous anxiety symptoms, while anxiety symptoms are related to previous obsessive-compulsive symptoms. However, in the present study, the reciprocal relation between anxiety and obsessive-compulsive symptoms was only significant in the first two years of follow-up. When the relation between solely compulsions and anxiety was analyzed, compulsions at baseline correlated with anxiety two years later, but anxiety did not correlate with compulsions. Thus, anxiety and obsessive-compulsive symptoms seem to interact especially in the earlier phases during the course of OCD. After four years, this relation changed to the opposite and more severe obsessive-compulsive symptoms, as well as solely compulsions, were subsequently associated with less anxiety. Probably, after years of obsessive-compulsive symptoms, patients may already perform compulsions in anticipation of anxiety prior to the experience of it, and thus prevent its occurrence. In addition, the compulsions may be performed more habitual over the time (Stein et al., 2019; van den Heuvel et al., 2016), which may lead to less anxiety in general. However, although the cross-lagged model was valid according to the measures of model fit, the strengths of the regression paths were rather weak and did not differ when the respective cross-lagged paths were compared directly. Thus, the results of the path analyses should be interpreted with caution.

In the cross-lagged model more severe obsessive-compulsive symptoms were strongly associated with more severe previous obsessive-compulsive symptoms, and more anxiety was strongly associated with more previous anxiety. In other words, the severity of obsessive-compulsive symptoms and anxiety was carried forward during the follow-up, and thus may rather result from an underlying latent factor for obsessions/compulsions

and respectively anxiety, which is stable over the time and determines the severity of obsessions/compulsions and anxiety during the course of OCD, as e.g., a chronic vulnerability. These considerations were modeled in the stable traits model, which included two latent factors, the obsessive-compulsive trait and the anxiety trait. The severity of the obsessive-compulsive symptoms at each assessment was strongly associated with an underlying latent factor, the obsessive-compulsive trait, while the severity of anxiety at each measure was strongly associated with another underlying latent factor, the anxiety trait. Both traits correlated strongly, and the relation between anxiety and obsessive-compulsive symptoms during the follow-up period was primarily defined by the interaction between both traits. Thus, the relation between anxiety and obsessive-compulsive symptoms on the long-term rather results from the interaction of stable underlying factors than from an immediate interaction at each follow-up. However, at each follow-up moment, a residual variance remained, which was not explained by the respective underlying traits or previous anxiety and obsessive-compulsive symptoms. This may point towards other traits or factors not included into this model, which also affect anxiety and obsessive-compulsive symptoms in OCD.

In the present study, anxiety and obsessive-compulsive symptoms correlated strongly at baseline and each follow-up, and the strength of the cross-sectional correlation did not change over the time. In addition, the duration of OCD at baseline varied widely between the participants of the study, which limited the possibility to study the change of symptoms in relation to the illness duration. Thus, we could not confirm our hypothesis, that the role of anxiety diminishes during the course of OCD. However, we can conclude that anxiety in general remains an important symptom during the course of OCD.

The results of the present study provide novel insights into the long-term relation between obsessive-compulsive symptoms and anxiety in OCD patients. Although the present study included only patients with a lifetime diagnosis of OCD, our results are in line with current transdiagnostic theories, which state that the predominant symptoms of OCD result from a complex interaction of different independent transdiagnostic dimensions, as e.g., anxiety and compulsivity (Gillan et al., 2017). According to the results of the stable traits model, the correlation between anxiety and obsessive-compulsive symptoms did not explain all of the variance of the respective symptoms, and thus additional factors may play a role. Besides anxiety and compulsivity, various transdiagnostic symptoms and concepts relevant to OCD have been proposed, such as negative affectivity (Barlow, 2000), depressive symptoms (Chavez-Baldini et al., 2021), obsessive beliefs (Anholt et al., 2014), intolerance of uncertainty (Carelton et al., 2012), or not-just-right experiences (Fergus, 2014). However,

not all of these aspects may be equally relevant in all OCD patients. Results of the present study show, that anxiety is particularly related to the aggressive obsessions/checking and contamination/washing dimensions, which is mostly in line with previous research (Cervin et al., 2021; Hartman et al., 2019; Sulkowski et al., 2008). Thus, the co-occurence of distinct transdiagnostic symptoms and their reciprocal interactions may vary between the symptom dimensions and may contribute to the heterogeneous presentation of OCD.

Some limitations of the present study have to be addressed. Only 60 to 75% of the participants enrolled at baseline participated in the follow-ups, and less than half of the participants completed all assessments during the 6-year follow-up. However, drop-out is not uncommon for longitudinal studies with such a long duration, and the study design and power calculation took this into consideration (Schuurmans et al., 2012). To deal with the missing data, we used full information maximum likelihood estimation (FIML) under the assumption that missing data were missing at random. Given that participants who completed all assessments and participants with missing data did not differ in their demographic or clinical characteristics at baseline, we were willing to tentatively make this assumption.

Another limitation is the heterogeneity of the group of OCD patients regarding the duration of the disease ranging from 0 to 64 years at baseline. OCD patients were included during various stages and the majority experienced OCD symptoms since several years. In this subgroup of chronic OCD, the relation between anxiety and obsessive-compulsive symptoms probably was already diminished, which may have affected the cross-lagged path analyses and the cross-sectional analysis during follow-up due to a floor effect.

We were not able to directly compare the level of anxiety between the distinct symptom dimensions for almost 80% of the participants experienced symptoms of more than one symptom dimension. However, the large overlap of symptom dimensions in OCD patients is rather the rule than the exception (Olatunji et al., 2017) and excluding these participants would have limited the generalizability of the results. Continuous instead of categorical assessment of the symptom dimensions may be recommended for future research.

The present study used the BAI, which is a valid and widely used measure of anxiety in primary as well as specialized mental health care settings (Muntingh et al., 2011; Leyfer et al., 2006; Beck et al., 1988). However, critics remark that it is rather a measure of panic than of anxiety in general (Cox et al., 1996). Although other studies partially contradicted this remark (Muntingh et al., 2011; Leyfer et al., 2006), the BAI emphasizes the somatic

experience of anxiety, while aspects as anticipatory anxiety, avoidance behavior, worry, or cognitive appraisals are not included.

To our knowledge, the present study is the first one, which investigated anxiety during the long-term course of OCD, using a large naturalistic study, which followed participants for several years. We explicitly aimed to investigate the long-term relation between anxiety and obsessive-compulsive symptoms and thus do not pretend to make assumptions about the short-term interactions or the possible functional role of anxiety as a driver of compulsions. This may be subject to further research. Due to methodological limitations we could not answer the question whether the role anxiety changes in relation to the duration of OCD. More evidence on the hypothesized switch from anxiety-driven to habit-driven behavior (Stein et al., 2019; van den Heuvel et al., 2016) is warranting and may be addressed in future studies.

In conclusion, the present study contributes to the discussion on the role of anxiety during the long-term course of OCD. We demonstrated that anxiety and obsessive-compulsive symptoms are distinct but interacting concepts. Symptoms of anxiety are common and relevant during the course of OCD, also after years of disease, but their role differs between groups of OCD patients. Besides anxiety, other factors, such as habit-driven behavior or not-just-rights experiences, may have a role in OCD. Future research should address these factors and their interaction with obsessive-compulsive symptoms within OCD and transdiagnostically.

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CHAPTER 5

PREDICTION OF ILLNESS REMISSION IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER WITH SUPERVISED MACHINE LEARNING

published as

Grassi, M., Rickelt, J., Caldirola, D., Eikelenboom, M., van Oppen, P., Dumontier, M., Perna, G., Schruers, K.R., 2022. Prediction of illness remission in patients with obsessive-compulsive disorder with supervised machine learning. J. Affect. Disord. 296, 117-125.

ABSTRACT

Objective: The course of OCD differs widely among OCD patients, varying from chronic symptoms to full remission. No tools for individual prediction of OCD remission are currently available. This study aimed to develop a machine learning algorithm to predict OCD remission after two years, using solely predictors easily accessible in the daily clinical routine.

Methods: Subjects were recruited in a longitudinal multi-center study (NOCDA). Gradient boosted decision trees were used as supervised machine learning technique. The training of the algorithm was performed with 227 predictors and 213 observations collected in a single clinical center. Hyper-parameter optimization was performed with cross-validation and a Bayesian optimization strategy. The predictive performance of the algorithm was subsequently tested in an independent sample of 215 observations collected in five different centers. Between-center differences were investigated with a bootstrap resampling approach.

Results: The average predictive performance of the algorithm in the test centers resulted in an AUROC of 0.7820, a sensitivity of 73.42%, and a specificity of 71.45%. Results also showed a significant between-center variation in the predictive performance. The most important predictors were related to OCD severity, OCD chronic course, use of psychotropic medications, and better global functioning.

Limitations: All recruiting centers followed the same assessment protocol and are in The Netherlands. Moreover, the sample of the data recruited in some of the test centers was limited in size.

Conclusions: The algorithm demonstrated a moderate average predictive performance, and future studies will focus on increasing the stability of the predictive performance across clinical settings.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a debilitating disorder characterized by intrusive thoughts or images (obsessions) and ritualized stereotypic and often repetitive behavior (compulsions) that are time-consuming and interfere with daily functioning (American Psychiatric Association, 2013). It is listed as the tenth most disabling medical disorder in the World Health Organization (WHO) burden of disease study (Ezzati et al., 2004) and is associated with diminished quality of life (Coluccia et al., 2016; Pozza et al., 2018).

Despite the effectiveness of selective serotonin reuptake inhibitors and cognitive-behavioral therapy, obsessive-compulsive symptoms persist in a large group of patients. Remission rates vary from 50 to 80% depending on treatment modality and definition of treatment outcome (Agne et al., 2020; Fineberg et al., 2012; Ost et al., 2015). OCD tends to run a chronic course in the majority of patients. Long-term treatment follow-up studies found varying remission rates of 50% to 65% (Cherian et al., 2014; Kempe et al., 2007; Nakajima et al., 2018; van Oppen et al., 2005) with relapse during follow-up in more than half of the remitted OCD patients (Kempe et al., 2007). Results of long-term naturalistic studies vary widely due to differences in outcome definition and methodology. In summary, 10-30% of the OCD patients achieve complete recovery and about 25% suffer from chronic persisting or deteriorating symptoms. While the majority of the OCD patients experience partial improvement over the years, more than half of the remitted patients subsequently relapse (Eisen et al., 2013; Garnaat et al., 2015; Skoog et Skoog, 1999).

In sum, the course of OCD varies widely among different individuals. Several studies investigated factors associated with treatment outcome and course of OCD and aimed to find predictors for remission, relapse, and chronicity of obsessive-compulsive symptoms. Several hypotheses including various factors such as OCD symptom severity, OCD symptom dimensions, course, insight, comorbidities, OCD-related cognitions, or social circumstances were investigated. However, results are inconclusive, often contradictory, and mostly not replicated (Hazari et al., 2016; Keeley et al., 2008; Knopp et al., 2013). Thus, the possibility of making a prompt individual-level prediction of the clinical course of OCD is currently limited because reliable clinically relevant predictors are not available (Hazari et al., 2016; Knopp et al., 2013; Schuurmans et al., 2012).

In addition, different factors may contribute to the prognosis of OCD and thus predictions based on single factors are too restricted and inaccurate to be used in clinical practice.

Instead, models that simultaneously exploit the information coming from several potential predictors may achieve a better predictive capability.

Machine learning (ML) techniques can be used to create precisely such models. ML techniques use known training examples to create algorithms able to provide the best possible prediction when applied to new cases whose outcome is still unknown. It is a fast-growing field at the crossroads of computer science, engineering, and statistics "that gives computers the ability to learn without being explicitly programmed" (Samuel, 1959).

A few attempts to apply such techniques to achieve clinically relevant predictions in OCD patients have already been made (Agne et al., 2020; Askland et al., 2015; Hoexter et al., 2013; Lenhard et al., 2018; Mas et al., 2016; Metin et al., 2020; Reggente et al., 2018; Salomoni et al., 2009; Yun et al., 2015). Although some of the algorithms showed high preliminary predictive accuracy, they have remained just proofs-of-concept, with a lack of any testing in further independent samples. Evidence from independent test sets is necessary before an algorithm can be safely translated into clinical practice, especially if its application aims to be generalized in multiple clinical centers (Cearns et al., 2019). In addition, some of these algorithms are based on predictors that may represent a significant barrier to their clinical adoption due to their high costs or non-routine assessment in current clinical practice (Hoexter et al., 2013; Lenhard et al., 2018; Mas et al., 2016; Reggente et al., 2018; Yun et al., 2015). Besides, two of them are focused on very peculiar treatments or OCD populations (Lenhard et al., 2018; Metin et al., 2020). Nevertheless, three studies showed promising predictive performances using only information easy to be assessed in clinical practice (Agne et al., 2020; Askland et al., 2015; Salomoni et al., 2009), demonstrating the feasibility of developing a clinically translatable ML algorithm for the prediction of OCD clinical course and treatment response prediction.

The present study aims to develop and test a ML algorithm for the prediction of OCD remission after 2 years. To facilitate clinical adoption, only predictors that are easily accessible in the daily clinical routine, such as anamnestic information and questionnaires, were used. The present article reports the results of the first phase with a focus on the preliminary investigation of the generalized predictive performance of the algorithm when applied to new different clinical centers.

METHODS

Subjects

Both the training and testing of the algorithm have been performed using data from the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study, a large multi-center naturalistic cohort study of the biological, psychological, and social determinants of chronicity in a clinical sample (Schuurmans et al., 2012). All subjects recruited in the NOCDA study are adult patients with a lifetime diagnosis of OCD which referred to one of the participating mental health care centers for evaluation and treatment. In all recruiting centers, the same study protocol and assessment procedures have been followed. No formal exclusion criteria were applied except for an inadequate understanding of the Dutch language. The study was conducted in accordance with the Helsinki Declaration and approved by the local ethics committees. All participants gave written informed consent. More details about the rationale, objectives, and methods of NOCDA can be found elsewhere (Schuurmans et al., 2012).

The present study included all NOCDA participants who fulfilled DSM-IV-TR criteria for OCD either at the baseline or at the two-year follow-up assessment, and whose diagnostic status was reassessed respectively at the two-year and four-year follow-up (n= 287). The latter reassessment was used as the two-year outcome that the algorithm aims to predict. In case a subject took part in all baseline, two-year, and four- year assessments and fulfilled diagnostic criteria for OCD both at baseline and the two-year follow-up, it was included twice in the analyses. Thus, a total of 462 observations were used in the study.

Remission was defined as an absence of the previously present diagnosis of OCD according to the DSM-IV-TR criteria, assessed by the Structured Clinical Interview for the DSM-IV-TR (SCID-I/P) (First et al., 2002), as suggested by international expert consensus (Mataix-Cols et al., 2016).

The subjects have been recruited from eight different clinical centers. Almost half of the sample has been recruited in one center (center Tr: subjects = 131/45.64%, observation = 213/46.10%) and the remaining part from the seven other ones, with a large variation in their contribution, ranging from 10 to 53 subjects and 15 to 87 observations. A detailed description of the number of subjects recruited in each center and the distribution of the remission variable can be found in Table 1.

Table 1. Description of test centers.

	Center	Subjects	total observations	Remitters N	%
Included in testing	Test - A	27	45	11	24.44%
	Test - B	20	30	10	33.33%
	Test - C	53	87	20	22.99%
	Test - D	17	28	4	14.29%
	Test - G	19	25	12	48.00%
	Mean	27	43	11	28.61%
	Standard deviation	13.33	23.06	5.12	11.42%
	Minimum	17	25	4	14.29%
	Maximum	53	87	20	28.00%
Excluded from testing	Test - E	10	19	1	5.26%
	Test - F	10	15	3	20.00%

Features

A detailed description of the information assessed in the NOCDA study is available in the paper addressing the design and rationale of the study (Schuurmans et al., 2012). Only variables available both at baseline and at two-year assessment were included in the present study. Genetic and biomarker-based variables were discarded because this study aimed to use only information collectible in a clinical interview and with psychometric scales. Two additional variables were defined: current use of a serotonergic antidepressant and current pharmacological treatment according to the clinical guidelines (Balkom et al., 2013).

Some of the variables were not available for all observations, and it was a priori decided to remove variables with greater than 20% missing values in the train set (i.e., data coming from the center Tr). Moreover, we included only the categorical predictors in which at least two of the classes had a frequency of at least 5% in the training set, excluding missing values. This was applied to avoid the inclusion of categorical variables whose variation was too small. All variables initially included as predictors during the training of the algorithm are reported in Table S1 of the supplementary materials. Two hundred twenty-seven (n=227) features were initially considered.

Machine learning algorithm: Training

A detailed explanation of the methods regarding the development and training of the ML model is available as supplementary material. In brief, standardization of continuous features and encoding of categorical features were performed, and missing data were imputed using the MissForest technique (Stekhoven et Bühlmann, 2011). These pre-processing steps were developed with the data in the train set and applied to both train and test identically.

Gradient boosted decision trees (GBDT) (Friedman, 2001), as implemented the eXtreme Gradient Boosting (XGBoost) library (Chen et Guestrin, 2016), was used as ML technique. Hyper-parameter optimization was performed via Bayesian optimization employing the Scikit-Optimized library (https://scikit-optimize.github.io/) to identify the configuration that resulted in the best Area Under the Receiving Operating Curve (AUROC) via a 10-fold cross-validation protocol, stratified (i.e., balancing) for the percentage of remitters and non-remitters in each fold. This procedure was performed using the data of the train set only (i.e., center Tr), and the hyper-parameter configuration that demonstrated the best cross-validated AUROC was retained and used to retrain a single algorithm with the entire train sample. Moreover, as the algorithm initially outputs a continuous prediction to which a threshold need to be applied to obtain the final dichotomous prediction of remission, and that different threshold values may result in different predictive performances in terms of sensitivity and specificity, the threshold value that maximizes the balanced accuracy (i.e., the average between sensitivity and specificity) of the cross-validated predictions in the training dataset was define.

Machine learning algorithm: Testing

The observations from the other seven centers (centers A-G) were used as an independent test set to investigate the predictive performance of the algorithm. Even if sometimes two observations from the same subjects have been included in the analysis (i.e., the baseline assessment information as predictors and the OCD diagnosis at the two-year follow-up as outcome, and the two-year follow-up assessment information as predictors and the OCD diagnosis at the four-year follow-up as outcome), the entire train and test sets are fully independent with respect to the subjects because the test set (Center A-G) includes observations from subjects that are distinct from those included in the training set (Center Tr). In every single center of the test set, the achieved AUROC, balance accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPA) were calculated separately. The 95% confidence intervals (CIs) were calculated with a stratified bootstrap procedure, with 10000 resamples (Efron, 1987). Only five of the seven centers were considered in these analyses, given that two centers provided a small number of observations (E=19; F=15), in which the observed cases of remissions were very limited (E=1; F=3). The bootstrap resampling technique was also used to investigate if the differences observed in the predictive performance between the different centers were statistically significant. For each statistic, we generated a stratified bootstrap distribution (10000 resamples) of the pairwise differences between two centers and subsequently calculated CIs of the differences, using the very conservative 99.5% range in order to correct for the ten pairwise comparisons for each statistic (alpha=0.05/10=0.005). A difference was considered statistically significant if both bounds of the CI being above or below the value 0.

Feature importance

Some of the predictors initially taken into consideration may be automatically discarded during the training process. As the NOCDA dataset includes a very extensive assessment, this step may help to reduce the amount of necessary information.

At first, we investigated which predictors were included in the final model. Subsequently, we ranked the retained predictors by importance using the gain feature importance metric provided by the XGBoost library. The gain metric indicates the relative contribution of a feature to the model, which is calculated by considering the improvement in accuracy brought by a feature at each split of the ensemble of decision-trees (https://xgboost.readthedocs.io/en/latest/R-package/discoverYo urData.html?highlight=gain).

Both the inclusion of a predictor in the model and its gain importance score cannot be considered absolute metrics of the strength of association between the predictor and the probability of the two-year remission. Both the inclusion and the gain score are closely related to the contribution that a particular predictor has in improving the predictive performance of the specific algorithm that has been developed. This contribution may substantially vary when using other ML techniques, or even with the same technique but with a different hyper-parameter configuration.

RESULTS

Descriptive statistics of all baseline assessment variables are available in Table S1 of the supplementary materials, separately for the training and test dataset. Statistics of continuous features are reported before the standardization was applied. In particular, in the train dataset (center Tr), the recruited subjects had a mean age of 39.95 years (SD= 10.75), a mean Y-BOCS total severity compulsions score of 10.26 (SD= 4.28), and a mean Y-BOCS total severity obsessions score of 9.95 (SD= 3.83). In the test dataset (center A-E), the recruited subjects had a mean age of 36.47 years (SD= 11.02), a mean Y-BOCS total severity compulsions score of 10.33 (SD= 4.28), and a mean Y-BOCS total severity obsessions score of 10.6 (SD= 4.09). In the train dataset 118 (55%) were female, while in the test dataset 130 (52.21%) were female.

Performance of the predictive algorithm

The hyper-parameter optimization identified the best hyper-parameter configuration[1] that resulted in an average cross-validated AUROC of 0.7392. The cross-validated predictions obtained with this configuration were pooled together and used to identify the cut-off threshold that maximized the cross-validated balanced accuracy. The obtained threshold value was 0.2193. Applying this threshold to the cross-validated predictions, a balanced accuracy of 71.90%, a sensitivity of 80.00%, a specificity of 68.71%, a positive predictive value of 40.40%, and a negative predictive value of 91.23% were observed. This hyper-parameter configuration was subsequently used to train the final model using the entire train set without cross-validation.

When the final model was tested using the data collected in the centers A, B, C, D, and G, the average AUROC among the centers resulted 0.7820 (95% bootstrap CI= 0.7119-0.8267). Considering the categorical predictions generated with the threshold identified above, results indicated an average balanced accuracy of 72.44% (95% bootstrap C= 66.81%-77.73%), an average sensitivity of 73.42% (95% bootstrap CI= 65.84%-82.91%), an average specificity of 71.45% (95% bootstrap CI= 63.27%-76.74%), an average positive predictive value of 48.52% (95% bootstrap CI= 40.76%-54.75%), and an average negative predictive value of 87.33% (95% bootstrap CI= 83.94%-92.12%).

When testing the distinct predictive performance of the algorithm per center, results demonstrated a large between-center variation with the AUROC ranging from 0.6364 (A) to 0.9063 (D), the balanced accuracy from 58.02% (A) to 87.50% (D), the sensitivity from 45.45% (A) to 100% (D), the specificity from 62.69% (C) to 76.92% (G), the positive predictive value from 31.25% (A) to 78.57% (G), and the negative predictive value from 78.95% (B) to 100% (D). All point estimates and the 95% bootstrap CIs of the results per center are summarized in Table 3.

Bootstrap analyses revealed significantly different balanced accuracies between center A and center D (58.02% versus 87.50%) and between center C and center D (66.34% versus 87.50%), significantly different sensitivities between center A and center D (45.45% versus 100%) and between center C and center D (70.00% versus 100%), significantly different

1 The resulted best hyperparameter configuration is: base_score=0.5, booster='gbtree', colsample_bylevel=0.42115547404634657, colsample_bynode=0.3067377514618746, colsample_bytree=0.4082812237129432, gamma=0.9, learning_rate=0.3, max_delta_step=1, max_depth=2, min_child_weight=0.99, n_estimators=231, num_parallel_tree=10, reg_ alpha=0.11711395279718309, reg_lambda=15.276374168654078, subsample=0.2

positive predictive values between center A and center G (31.25% versus 78.57%) and between center C and center G (35.90% versus 78.57%), and significantly different negative predictive values between center A and center D (79.31% versus 100.00%) and between center C and center D (87.50% versus 100.00%). Bootstrap median and 99.5% CIs of the differences are reported in Table 4. In summary, despite the conservative multiple-comparison correction applied in these analyses, the performance of the algorithm sometimes differs considerably between different clinical centers, even though all centers followed the assessment protocol as demanded by the NOCDA study.

Feature importance

The final model included 217 out of the 227 initial features (95.59%), while only 10 variables (4.41%) were discarded. A detailed description of the retained variables, the associated gain feature importance score, and the ranking are reported in Table S1 of the supplementary materials.

Based on the gain feature importance metric, the variables ranked as the ten most important predictors in the present algorithm are (Table 2): the total score Y-BOCS severity (Goodman et al., 1989a; Goodman et al., 1989b); hours spent every week by the respondent as an organizer of social organizations and clubs (e.g., employers, religious, sport, political or patients organizations); the use of antidepressant drugs on doctors order in the last two weeks; whether the respondent had a paid job at the moment of the baseline assessment; chronic course of OCD in the last two years; the use of any psychotropic drug on doctors order in the last two weeks; participation in sports clubs; the use of psychoanaleptic drugs on doctors order in the last two weeks (defined according to the ATC classification; (World Health Organization, 2011)); the number of different psychotropic drugs currently taken by the subject (defined according to the ATC classification; (World Health Organization, 2011)); and the number of hours the subject work in a week.

Table 2. Description of the ten most important predictors.

Variable	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
Total severity of Y-BOCS	Mean: 19.96, SD: 6.94	Mean: 19.9, SD: 7.35	0.0077	1
How many hours a week the respondent is involved in an executive role in a club or organizations (e.g., sport club, music band, organization for patient, social organization, religious organization, political party)?	Mean: 0.17, SD: 0.92	Mean: 0.16, SD: 0.96	0.0076	2
Antidepressant use on doctors order in the last two weeks	No: 92 (43%), Yes: 110 (52%), Missing value: 11 (5.16%)	No: 75 (30.12%), Yes: 165 (66.27%), Missing values: 9 (4%)	0.0076	3
Do you have a paid job at the moment?	No, I have never had a paid job: 5 (2%), No, I had a paid job in the past: 71 (33%), Yes: 126 (59%), Missing values: 11 (5.16%)	No, I have never had a paid job: 9 (3.61%), No, I had a paid job in the past: 116 (46.59%), Yes: 115 (46.18%), Missing values: 9 (4%)	0.0075	4
Chronical course of OCD in the last 2 years	Too many omitted answers from the respondent: 3 (1%), No: 90 (42%), Yes: 120 (56%)	Too many omitted answers from the respondent: 3 (1.2%), No: 97 (38.96%), Yes: 146 (58.63%), Missing values: 3 (1%)	0.0070	5
Psychotropic use on doctors order in the last two weeks	No: 80 (38%), Yes: 122 (57%), Missing values: 11 (5.16%)	No: 66 (26.51%), Yes: 174 (69.88%), Missing values: 9 (4%)	0.0070	6
Are you involved in sports clubs?	Asked but the respondent did not answer: 5 (2%), No: 134 (63%), Yes: 71 (33%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 165 (66.27%), Yes: 78 (31.33%)	0.0068	7
Psychoanaleptic use on doctors order in the last two weeks	No: 92 (43%), Yes: 110 (52%), Missing values: 11 (5.16%)	No: 72 (28.92%), Yes: 168 (67.47%), Missing values: 9 (4%)	0.0068	8
Total number of different psychotropic medications currently used by the subjects	Mean: 0.99, SD: 1.08	Mean 1.15, SD: 1.2	0.0066	9
How many hours did you work a week recently?	Mean: 16.98, SD: 16.75	Mean: 12.93, SD: 16.37	0.0064	10

Table 3. Test predictive performance.

Center	AUROC			BALANCED ACCURACY			SENSITIVITY			SPECIFICITY			POSITIVE PREDICTIVE VALUE			NEGATIVE PREDICTIVE VALUE		
	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)	Observed Point Estimate	95% Bootstrap CI (Lower)	95% Bootstrap CI (Higher)
Test - A	0,6364	0,4412	0,8155	58,02%	39,97%	73,13%	45,45%	18,18%	72,73%	67,65%	52,94%	82,35%	31,25%	13,33%	50,00%	79,31%	70,00%	89,66%
Test - B	0,7300	0,525	0,915	67,50%	50,00%	85,00%	60,00%	30,00%	90,00%	75,00%	55,00%	95,00%	54,55%	33,33%	81,82%	78,95%	66,67%	93,75%
Test - C	0,7336	0,6187	0,8381	66,34%	54,37%	77,57%	70,00%	50,00%	90,00%	62,69%	50,75%	74,63%	35,90%	26,47%	46,15%	87,50%	80,00%	95,35%
Test - D	0,9063	0,7708	1	87,50%	79,17%	95,83%	100,00%	100,00%	100,00%	75,00%	58,33%	91,67%	40,00%	28,57%	66,67%	100,00%	100,00%	100,00%
Test - G	0,9038	0,7628	1	84,29%	68,59%	96,15%	91,67%	75,00%	100,00%	76,92%	53,85%	100,00%	78,57%	62,50%	100,00%	90,91%	75,00%	100,00%
Mean	0,7820			72,73%			73,42%			71,45%			48,05%			87,33%		
Standard Deviation	0,1063			11,28%			20,07%			5,41%			17,14%			7,85%		
Minumum	0,6364			58,02%			45,45%			62,69%			31,25%			78,95%		
Maximum	0,9063			87,50%			100,00%			76,92%			78,57%			100,00%		

AUROC = Area under the receiving operating curve. 95% Bootstrap CI (Lower) = lower bound of the 95% bootstrap confidence interval. 95% Bootstrap CI (Higher) = higher bound of the 95% bootstrap confidence interval.

Table 4. Pairwise between-centers differences of test predictive performance.

AUROC	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Boots-trap CI (Lower)	99.5% Boots-trap CI (Higher)	99.5% Boots-trap CI (Lower)	99.5% Boots-trap CI (Higher)	99.5% Boots-trap CI (Lower)	99.5% Boots-trap CI (Higher)	99.5% Boots-trap CI (Lower)	99.5% Boots-trap CI (Higher)	99.5% Boots-trap CI (Lower)	99.5% Boots-trap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-0,2844	0,4676	/	/	/	/	/	/	/	/
Test - C	-0,2087	0,4298	-0,3035	0,3511	/	/	/	/	/	/
Test - D	-0,0506	0,5875	-0,1533	0,5079	-0,0998	0,3874	/	/	/	/
Test - G	-0,0606	0,5877	-0,1551	0,5062	-0,1005	0,3996	-0,2708	0,2516	/	/

Balanced Accuracy	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-23,58%	45,91%	/	/	/	/	/	/	/	/
Test - C	-19,18%	37,45%	-30,63%	29,59%	/	/	/	/	/	/
Test - D	*4,33%*	*57,10%*	-7,50%	48,33%	*1,00%*	*42,15%*	/	/	/	/
Test - G	-4,39%	57,31%	-16,60%	48,65%	-9,70%	42,65%	-28,69%	18,75%	/	/

Sensitivity	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-42,73%	72,73%	/	/	/	/	/	/	/	/
Test - C	-26,82%	71,82%	-40,00%	60,00%	/	/	/	/	/	/
Test - D	*9,09%*	*90,91%*	0,00%	80,00%	*5,00%*	*60,00%*	/	/	/	/
Test - G	-6,06%	90,91%	-16,67%	80,00%	-18,33%	55,00%	-41,67%	33,25%	/	/

Specificity	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-27,65%	41,77%	/	/	/	/	/	/	/	/
Test - C	-31,61%	23,13%	-41,79%	20,67%	/	/	/	/	/	/
Test - D	-26,96%	39,95%	-36,67%	36,67%	-18,66%	40,61%	/	/	/	/
Test - G	-34,39%	45,25%	-41,54%	42,31%	-25,72%	44,78%	-40,71%	41,67%	/	/

Positive Predictive Value	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-19,23%	70,83%	/	/	/	/	/	/	/	/
Test - C	-28,18%	35,39%	-61,77%	17,56%	/	/	/	/	/	/
Test - D	-25,00%	58,98%	-58,93%	36,25%	-18,75%	48,75%	/	/	/	/
Test - G	*11,11%*	*83,33%*	-22,79%	65,03%	*16,30%*	*71,05%*	-9,41%	69,23%	/	/

Negative Predictive Value	Test - A		Test - B		Test - C		Test - D		Test - G	
	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)	99.5% Bootstrap CI (Lower)	99.5% Bootstrap CI (Higher)
Test - A	/	/	/	/	/	/	/	/	/	/
Test - B	-22,86%	25,69%	/	/	/	/	/	/	/	/
Test - C	-9,95%	25,18%	-14,44%	29,66%	/	/	/	/	/	/
Test - D	*5,26%*	*34,62%*	0,00%	38,89%	*2,17%*	*24,00%*	/	/	/	/
Test - G	-17,21%	33,33%	-20,77%	36,84%	-23,56%	22,00%	-33,33%	22,32%	/	/

Difference is calculated as center in the row minus center in the column. Statistical singificance (i.e. both bounds of the 99.5% boostrap CI higher or lower than 0) evidence in italic. 99.5% Bootstrap Ci (Lower) = lower bound of the 99.5% bootstrap confidence interval of the pairwise centres difference. 99.5% Bootstrap Ci (Higher) = higher bound of the 99.5% bootstrap confidence interval of the pairwise centres difference.

DISCUSSION

The present study aimed to develop and test a preliminary ML algorithm for the prediction of the two-year remission in subjects with OCD using data from a large naturalistic multi-center study (NOCDA). Solely predictors based on information from clinical interviews and psychometric scales were included as features. The algorithm was developed and trained using a large sample of subjects recruited in a single center, which represented almost half of the entire dataset. Subsequently, the algorithm was tested in the other participating NOCDA centers. This was done to mimic the translation from a research environment into clinical practice, where new algorithms or protocols are commonly developed in one large center and subsequently applied in different clinical centers.

The strict separation between the training and the test set was chosen to increase independence between both datasets. It ensures a sound testing of the generalized performance of the algorithm when applied to clinical centers distinct from the training center.

In this preliminary phase, we arbitrary decided to give equal importance to sensitivity and specificity by defining the predictive threshold that maximized the balanced accuracy in the training dataset. Results showed a moderate predictive performance, with a similar crossvalidated and average test balanced accuracy of respectively 71.90% and 72.44%. There is one previous study (Askland et al., 2015) which also aimed to develop a ML model to predict OCD remission based on features assessed by an extensive clinical interview and several psychometric questionnaires. They reported an unbalanced accuracy of 75.4% as the performance of their algorithm. Although there are similarities in the study designs (e.g., both studies are large naturalistic multi-center follow-up studies), this study is not fully comparable to ours because of the performance metrics Askland and colleagues used (e.g., unbalanced accuracy in their study, and balanced accuracy in the current study), and a different definition of OCD remission (at least one period of eight consecutive weeks of sub-threshold symptoms during the entire study enrollment, versus lack of fulfillment of DSM-IV-TR criteria for OCD at the 2-year follow-up assessment in the current study).

The other performance statistics also resulted somewhat similar between cross-validation and testing, with a partial reduction in the average sensitivity and average negative predictive value, and partial improvement in the average specificity and average positive predictive value in the test dataset compared to the cross-validated results obtained in the training dataset. Thus, when the average test performance is taken into account, it might

be concluded that the algorithm maintained its performance levels when applied to new clinical centers.

However, in subsequent testing using every single center as a distinct test data set, a substantial variation in the performance statistics was observed between the five centers. The predictive performance of the algorithm was particularly good in some of them, while quite reduced and poor in others. Some between-center differences resulted statistically significant even after a conservative Bonferroni correction for multiple comparisons. Based on these results, any expected performance cannot be guaranteed when the current version of the algorithm is applied to new clinical settings.

Differences in remission rates between the centers (varying from 14.3% to 48%) may affect the predictive performance, but it does not sufficiently explain all of the variability, because also statistics that are in theory unaffected by the rate of remissions occurring in a specific center, such as the balanced accuracy, sensitivity, and specificity showed this variation. The distribution of the characteristics of the OCD subjects may also affect the predictive performance. OCD often is described as a heterogeneous disorder (Mataix-Cols et al., 2005), and also the participants of the NOCDA study were a diverse group. OCD patients referred to a certain clinical center might differ significantly from those referred to another center. The predictive accuracy of a ML algorithm is not necessarily constant among subjects with different characteristics, and some centers may present a higher prevalence of subjects in which the algorithm tends to be less accurate in its predictions. Moreover, variations in the distribution of the predictors (i.e. covariate shift (Shimodaira, 2000)) or of the outcome variable (i.e. label shift (Lipton et al., 2018)) are known to potentially affect the performance of ML algorithms. Besides, even a change in the relationship between the predictor and outcome variables (i.e. concept drift (Gama et al., 2014)) can occur over time and among different populations.

Thus, before a medical predictive model can be safely applied in clinical practice, it is crucial to test it not only in a single but in multiple datasets that are independent both to each other and to the data used during the development of the algorithm. As a matter of facts, the majority of medical device filings to regulatory bodies such as the US Food and Drugs Administration are based on multi-center clinical studies (Johnston et al., 2020), and multi-centric testing seems to have progressively become more and more used in the recent literature of ML for medical applications (Abraham et al., 2017; Gabr et al., 2019; Meyer et al., 2017).

However, previous studies using ML to predict clinical course and treatment response prediction in OCD patients are mostly based on data recruited in a single center (Hoexter et al., 2013; Lenhard et al., 2018; Mas et al., 2016; Metin et al., 2020; Reggente et al., 2018; Salomoni et al., 2009; Yun et al., 2015). Only Askland and colleagues (Askland et al., 2015) used a large multi-center dataset from a longitudinal study of OCD (The Brown Longitudinal Obsessive-Compulsive Study (Pinto et al., 2006)). However, pooled data from all centers were used both for training and testing. Their test dataset was not independent from the data used during the training of the algorithm and thus the predictive performance may differ when the algorithm is applied to new, independent data sets. In conclusion, the present study is the first one using ML in OCD course prediction which tested the algorithm in an independent test sample consisting of data from other centers than the training center.

Some strategies that attempt to reduce the impact of the above-mentioned distribution shift/drift have been proposed in the ML literature (Gama et al., 2014; Lipton et al., 2018; Shimodaira, 2000). However, any application of such correction strategies requires advanced knowledge of the predictor and/or target variable distributions in the particular setting where the algorithms will be used. Thus, a relevant amount of data has to be preliminary available for any new center, or these data have to be collected in advance for the sole purpose of developing the center-specific correction of the algorithm. Especially for the outcome variable, which is based on a 2-year follow-up, this preliminary data collection would be particularly burdensome and may delay the introduction of the algorithm in a particular clinical center.

Another potential strategy to reduce the impact of variable distribution shifts/drifts is to include only predictive variables in the algorithm with more stable distributions among clinical centers, and a stable relationship with the outcome variable. A reduction of the number of predictors may also help to improve the applicability of the algorithm in the daily clinical practice. Although the present algorithm only uses information from clinical interviews and questionnaires, the extensive NOCDA assessment protocol is time-consuming and may be exhausting for patients. Unfortunately, less than 5% of the features were automatically discarded during the training process, which is a characteristic of the GBDT technique, and the algorithm still relies on 217 predictors. A further reduction of the predictive variables will be later performed by applying some additional feature selection strategies, by taking into account the gain feature importance metric, and by evaluating the clinical importance and availability of the predictors. This may lead to the development of a more robust algorithm while maintaining or perhaps even improving its predictive performance.

The ranking of importance of the predictors based on the gain feature importance metric confirms that factors of different nature may contribute to the prognosis of OCD, without one domain being the sole or preliminary source of it. For example, the ten features that resulted as most relevant are related to very different domains, such as clinical severity and characterizations, medications, work, and social activities. This also supports the necessity of using models that simultaneously consider multiple predictors rather than individual factors to achieve relevant prediction of OCD remission and prognosis.

Some limitations should be taken into account. We used GBDT as the sole ML technique in our study. Several other supervised ML techniques exist, all of which may have led to different results. Some of these other techniques may have even resulted in better predictive performance, and an ensemble of different techniques can also be used in the attempt of achieving better results (Grassi et al., 2019). In this preliminary phase, we opted to focus on the GBDT technique for several reasons. First, it has proved to be a powerful technique even if used individually (Natekin et Knoll, 2013). Moreover, given the large number of categorical variables we used as predictors, this technique was chosen because it can handle non-dichotomous categorical variables with efficient coding strategies (e.g., label encoding), allowing to use of a single predictor per categorical variable instead of a single predictor per class of each categorical variable (i.e., one-hot encoding), as it is required by most of the other supervised ML techniques. Furthermore, a metric of the importance of the predictive variables, i.e., the gain feature importance metric, can be derived natively and computationally efficiently directly from the algorithm, which takes into account the interactions between the predictive variables and does not require additional analyses to be performed after the final model has been trained. Finally, less important features are expected to be discarded automatically during the development of the algorithm, with the GBDT technique operating an automatic and model-tailored feature selection. Considering all these characteristics of the GBDT technique, it seemed convenient to use this single technique in this preliminary step, leaving the use of further techniques and their ensembling to the following phases of our research.

Another limitation is that, although independent to each other, the clinical centers of the NOCDA study all collected the data following the same assessment protocol. Moreover, they are all located in The Netherlands. Thus, these centers may share more similarities than other clinical centers not following the standardized assessment protocol or centers from other countries. Therefore, when the algorithm is applied to new clinical centers, the predictive performance may vary even more compared to the variation observed in the present study.

An additional limitation is that, although two centers with a very limited number of cases were excluded, the sample size of the data from some of the five test centers was small. In the next phase, we plan to include the final follow-up assessment (predictor variables from the four-year follow-up assessment and remission at the six-year follow-up assessment) to enlarge the sample size for both in training and testing of the algorithm.

Finally, the definition of remission used in this study is the absence of an OCD diagnosis at the two-year follow-up assessment. As the course is not unidirectional but shows periods of remission and subsequent relapse in the majority of the OCD patients (Eisen et al., 2013; Garnaat et al., 2015; Reddy et al., 2005), the current prediction of the algorithm may not be able to provide an exhaustive description of the clinical course of the subject. A more complex modeling of the course of OCD may be desirable, based on information about the course of OCD assessed longitudinally during several follow-ups.

Some strengths may also be mentioned. Data are based on a large naturalistic multi-center study. The longitudinal design, with baseline and successive follow-up assessments, makes the application of ML techniques particularly suitable to examine predictors of the course of OCD. The naturalistic investigation of the illness course contributes to the clinical validity of the ML algorithms developed with data from the NOCDA study. All features can be assessed during the daily routine using interviews and questionnaires, which makes it easily accessible. With a total of 462 observations, it is one of the largest ML studies in the field of OCD research. Approximately half of the subjects were recruited from a single center, and the remaining part of the sample from the other seven centers, with a large variation in the numbers of subjects recruited in each one of them. This mimics the common scenario in which a larger dataset coming from one or a few centers is used to train a ML algorithm, which will be later applied to other centers. In contrast to previous studies in this field, the present study did not only develop an algorithm for OCD course prediction and tested it within the training set but also applied a thorough testing by subsequently validating the algorithm in a test sample consisting of data from other centers than the training center.

The present study aimed to develop a clinically accessible algorithm that predicts remission of OCD, which is based on information that can be easily assessed in the daily clinical routine. However, if this information is not sufficient to achieve a good level of prediction, the inclusion of additional predictors, such as genetic or neuroimaging biomarkers, should be investigated. Although costs and availability can make their introduction in the clinical routine quite challenging, it may be justified if they significantly increase the predictive

performance of the algorithm given the contribution that a prediction of the OCD course may bring to treatment planning and appropriate support of OCD patients. In the NOCDA study, further biological and genetic information has been collected and we also plan as a further next step to investigate if the addition of such information may relevantly increase the accuracy of our algorithm.

In conclusion, the present study developed and tested a ML algorithm for the prediction of the 2-year remission of the diagnosis of OCD using data from a large, multi-center study (NOCDA). The development of the algorithm in one large clinical center and subsequently testing it in different smaller centers resulted in a moderate average generalized performance but showed a large variation between the centers when investigated per distinct center. This demonstrates the difficulties algorithms have to overcome before they can be safely translated from the research environment into clinical practice. It also emphasizes the need for independent test samples from different centers during further research.

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SUPPLEMENTARY MATERIAL

Supplementary Methods

1. Feature preprocessing

Two hundred twenty-seven (n= 227) features were initially considered. Continuous variables were standardized (mean= 0, standard deviation= 1). Categorical variables were re-coded with the so-called label-encoding strategy, i.e., all cases of each categorical variable have been assigned to an integer number starting from 0. If the variable was ordinal, the class-to-integer conversion respected the order of the classes. In case a "Not answered" class was present, this was not coded as a missing value but the value 0 and other classes starting from 1, because the "Not answered" class may give an additional piece of information rather than a pure missing value (i.e., the subject decided to actively decline to answer instead of that the answer was not collected). The encoding was performed using only the classes occurring in the data used for training. The test data were coded following the coding scheme used for the training data. Any additional class that occurred only in the test dataset was coded as a missing value. This coding strategy for categorical variables is justified by the use of a tree-based ML technique.

Missing values were imputed using the MissForest technique (Stekhoven et Bühlmann, 2011), implemented with the *IterativeImputer* function of the Scikit-Learn library version 0.22.2 (Pedregosa et al., 2011) and using Random Forest (Breiman, 2001) as estimator. The imputation model was first trained using only the train set and then applied also to the test set.

2. Gradient boosting technique

Boosting is an ML technique that produces a prediction model in the form of an ensemble of several simpler and consecutively developed prediction models, which are expected to show weaker predictive performance if applied singularly. In our study, we used decision tree models, which are the most common choice within the gradient boosting ensemble technique. Several decision trees are iteratively built, each one consecutively trained to predict better the cases misclassified by the previous model or, as in the case of the gradient boosting approach we used in this study, to predict the error in the prediction performed by the previous model (Friedman, 2001). In the end, the final prediction is the result of a weighted sum of the prediction performed by all weaker (up to hundreds) models.

The present study used the implementation of gradient boosted decision trees (GBDT) provided in the eXtreme Gradient Boosting (XGBoost) library (Chen et Guestrin, 2016), which is an optimized distributed gradient boosting library designed to be highly efficient, flexible, and portable. This library implements several advancements compared to the standard GBDT technique, among which the possibility of adding stochasticity (Blagus et Lusa, 2015) and the use of parallel decision trees (bagging) in each bagging iteration.

Several other supervised ML techniques exist. In this preliminary phase, we opted to focus on the GBDT technique for several reasons. First, it has proved to be a powerful technique even if used individually (Natekin et Knoll, 2013). Moreover, given the large number of categorical variables we used as predictors, this technique was chosen because it can handle non-dichotomous categorical variables with efficient coding strategies (e.g., label encoding), allowing to use of a single predictor per categorical variable instead of a single predictor per class of each categorical variable (i.e., one-hot encoding), as it is required by most of the other supervised ML techniques. Furthermore, as discussed later, a metric of the importance of the predictive variables, i.e., the gain feature importance metric, can be derived natively and computationally efficiently directly from the algorithm, which takes into account the interactions between the predictive variables and does not require additional analyses to be performed after the final model has been trained. Finally, less important features are expected to be discarded automatically during the development of the algorithm, with the GBDT technique operating an automatic and model-tailored feature selection. Considering all these characteristics of the GBDT technique, it seemed convenient to use this single technique in this preliminary step, leaving the use of further techniques and their ensembling to the following phases of our research.

3. Hyper-parameter optimization

As for most of the ML techniques, several hyper-parameters are available for XGBoost, which allow a different tuning of the algorithm during the training process. Different values of these hyper-parameters lead to different predictive performances. The aim is to identify the configuration that produces the best possible performance when applied to cases that are not part of the training set. In order to optimize such hyper-parameters, the algorithm was first trained with 50 random hyperparameter configurations. Subsequently, 150 further configurations were progressively estimated with a Bayesian optimization approach. Bayesian optimization aims to estimate the hyper-parameter design that maximizes the performance of the algorithm starting from the previous estimates. It is based on the assumption of a relationship between the various hyper-parameter values and the performance achieved by the algorithm. Bayesian optimization is expected to identify better hyper-parameter

configurations with fewer attempts than a random generation of configurations. Estimation was performed with Gaussian Processes, as implemented in the Scikit-Optimized library (https://scikit-optimize.github.io/).

The Area Under the Receiving Operating Curve (AUROC) was used as the performance metric to be maximized. The algorithm outputs a continuous prediction score (range: 0-1; the closer to 1, the higher the predicted probability of remission for that subject). The AUROC value can be interpreted as the probability that a randomly selected remitted subject will receive a higher output score than a randomly selected non-remitted subject. The AUROC value is 0.5 when the algorithm makes random predictions and 1 in case it is always correct in making predictions. AUROC is not affected by class imbalance, and it is independent of any specific threshold that is applied to perform a dichotomous prediction.

4. Cross-validation

The aim is to train an algorithm that achieves the best possible generalized performance and that also performs well beyond the cases used in the training process. Cross-validation provides an estimate of such generalized performance for every hyper-parameter configuration. In cross-validation, the training sample is divided into several folds of cases that are held-out from the training process, with training iteratively performed with the remaining cases. After the training, the algorithm is finally applied to the held-out cases.

In this study, the commonly used 10-fold cross-validation procedure was applied. The fold creation was performed at random, stratifying (i.e., balancing) for the percentage of remitters and non-remitters in each fold. Finally, the ten performance estimates of the algorithm available for each hyper-parameter configuration were averaged to provide a final point estimate of the generalized performance. The hyper-parameter configuration that demonstrated the best average cross-validated AUROC was retained and used to retrain a single algorithm with the entire train sample.

The algorithm initially outputs a continuous prediction to which a threshold is applied to obtain the final dichotomous prediction of remission. Different threshold values may result in different predictive performances in terms of sensitivity and specificity. In this preliminary investigation, we chose the threshold value that maximizes the balanced accuracy (i.e., the average between sensitivity and specificity) of the cross-validated predictions in the training dataset.

Table S1. Description of the predictor variables.

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
ADHD rating scale IV (DuPaul et al., 1998)	ADHD symptoms in the past	1	Mean: 4.62, SD: 4.48	Mean: 3.92, SD: 4.21	0.0039	160
	Hyperactivity Impulsiveness symptoms in the past	1	Mean: 2.06, SD: 2.38	Mean: 1.73, SD: 2.21	0.0039	166
	Attention deficit symptoms in the past	1	Mean: 2.57, SD: 2.7	Mean: 2.19, SD: 2.41	0.0035	184
	ADHD inattentive type in the past	1	No: 169 (79%), Yes: 43 (20%), Missing values: 1 (0.47%)	No: 217 (87.15%), Yes: 32 (12.85%)	0.0028	209
	ADHD combined type in the past	1	No: 197 (92%), Yes: 15 (7%), Missing values: 1 (0.47%)	No: 235 (94.38%), Yes: 14 (5.62%)	0.0028	211
	ADHD hyperactive type in the past	0	No: 186 (87%), Yes: 26 (12%), Missing values: 1 (0.47%)	No: 229 (91.97%), Yes: 20 (8.03%)	-	-
Beck Anxiety Inventory (Beck et al., 1988)	Becks Anxiety Inventory - total scale score	1	Mean: 15.64, SD: 10.57	Mean: 17.6, SD: 12.06	0.0046	104
Beck Depression Inventory (Beck et al., 1961)	Becks Depression Inventory - total scale score	1	Mean: 13.63, SD: 8.6	Mean: 15.73, SD: 10.46	0.0059	24
Clinical Interview	How many hours a week the respondent is involved in an executive role in a club or organizations (e.g., sport club, music band, organization for patient, social organization, religious organization, political party)?	1	Mean: 0.17, SD: 0.92	Mean: 0.16, SD: 0.96	0.0076	2
	Antidepressant use on doctor's order in the last two weeks	1	No: 92 (43%), Yes: 110 (52%), Missing values: 11 (5.16%)	No: 75 (30.12%), Yes: 165 (66.27%), Missing values: 9 (4%)	0.0076	3

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Do you have a paid job at the moment?	1	No, I have never had a paid job: 5 (2%), No, I had a paid job in the past: 71 (33%), Yes: 126 (59%), Missing values: 11 (5.16%)	No, I have never had a paid job: 9 (3.61%), No, I had a paid job in the past: 116 (46.59%), Yes: 115 (46.18%), Missing values: 9 (4%)	0.0075	4
	Psychotropic drug use on doctor's order in the last two weeks	1	No: 80 (38%), Yes: 122 (57%), Missing values: 11 (5.16%)	No: 66 (26.51%), Yes: 174 (69.88%), Missing values: 9 (4%)	0.0070	6
	The respondent participates in a sports club	1	Asked but the respondent did not answer: 5 (2%), No: 134 (63%), Yes: 71 (33%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 165 (66.27%), Yes: 78 (31.33%)	0.0068	7
	Psychoanaleptic use on doctor's order in the last two weeks	1	No: 92 (43%), Yes: 110 (52%), Missing values: 11 (5.16%)	No: 72 (28.92%), Yes: 168 (67.47%), Missing values: 9 (4%)	0.0068	8
	Total number of different psychotropic medications used by the respondent	1	Mean: 0.99, SD: 1.08	Mean: 1.25, SD: 1.2	0.0066	9
	How many hours did you work a week recently?	1	Mean: 16.98, SD: 16.75	Mean: 12.93, SD: 16.37	0.0064	10
	How many different antidepressants are used by the respondent?	1	Mean: 0.6, SD: 0.64	Mean: 0.76, SD: 0.58	0.0064	11
	Age at the time of the interview	1	Mean: 39.95, SD: 10.75	Mean: 36.47, SD: 11.02	0.0063	13
	Antipsychotic use on doctor's order the last two weeks	1	No: 183 (86%), Yes: 19 (9%), Missing values: 11 (5.16%)	No: 196 (78.71%), Yes: 44 (17.67%), Missing values: 9 (4%)	0.0061	20
	How many different psychoanaleptic medications are used by the respondent?	1	Mean: 0.62, SD: 0.65	Mean: 0.79, SD: 0.6	0.0060	21
	Do you take classes aimed at a diploma at the moment or in the last year?	1	Asked but the respondent did not answer: 7 (3%), No: 185 (87%), Yes: 18 (8%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), No: 217 (87.15%), Yes: 27 (10.84%)	0.0058	27

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	The respondent participates in a political party, organization or club	1	Asked but the respondent did not answer: 5 (2%), No: 194 (91%), Yes: 11 (5%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 230 (92.37%), Yes: 13 (5.22%)	0.0058	28
	Number of children	1	Mean: 0.4, SD: 0.91	Mean: 0.45, SD: 0.93	0.0057	32
	How many different anxiolytic medications are used by the respondent?	1	Mean: 0.13, SD: 0.34	Mean: 0.14, SD: 0.39	0.0057	33
	How often do you have contact (phone, email, writing a letter, etc.) with your best friend?	1	Asked but the respondent did not answer: 10 (5%), No friend: 54 (25%), Less than a few times a year: 2 (1%), A few times a year: 18 (8%), A few times a month: 61 (29%), A few times a week: 54 (25%), Daily: 10 (5%), We live in the same house: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 14 (5.62%), No friend: 57 (22.89%), Less than a few times a year: 5 (2.01%), A few times a year: 19 (7.63%), A few times a month: 63 (25.3%), A few times a week: 67 (26.91%), Daily: 15 (6.02%), We live in the same house: 4 (1.61%), Missing values: 5 (2%)	0.0057	34
	Participant currently taking serotonergic antidepressiant according to clinical guidelines for OCD	1	Missing: 15 (7%), None: 97 (46%), Yes, dosage not reported: (1%), Yes, subtherapeutic dosage according to guidelines: 38 (18%), Yes, adequate OCD dosage according to guidelines: 60 (28%)	Missing: 14 (5.62%), None: 79 (31.73%), Yes, subherapeutic dosage according to guidelines: 75 (30.12%), Yes, adequate OCD dosage according to guidelines: 81 (32.53%)	0.0055	44
	Psycholeptic use on doctor's order in the last two weeks	1	No: 158 (74%), Yes: 44 (21%), Missing values: 11 (5.16%)	No: 175 (70.28%), Yes: 65 (26.1%), Missing values: 9 (4%)	0.0054	49

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	How often does the respondent visit a sport match?	1	Asked but the respondent did not answer: 9 (4%), Practically never: 164 (77%), A few times a year: 24 (11%), Every month: 4 (2%), A few times a month: 5 (2%), Every week: 2 (1%), A few times a week: 2 (1%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), Practically never: 179 (71.89%), A few times a year: 30 (12.05%), Every month: 9 (3.61%), A few times a month: 12 (4.82%), Every week: 12 (4.82%), A few times a week: 1 (0.4%)	0.0053	52
	How many minutes a week do you volunteer for a club or organizations (e.g., sport club, music band, organization for patient, social organization, religious organization, political party)?	1	Mean: 0.52, SD: 3.02	Mean: 1.37, SD: 5.75	0.0053	54
	Total household income of the respondent (excluding holiday allowance, refunding of traveling or payment of expense)	1	Asked, no answer: 26 (12%), 0-750 euro: 14 (7%), 750-1000 euro: 18 (8%), 1000-1250 euro: 18 (8%), 1250-1500 euro: 21 (10%), 1500-2000 euro: 25 (12%), 2000-2500 euro: 11 (5%), 2500-3000 euro: 24 (11%), 3000-4000 euro: 28 (13%), more than 4000 euro: 14 (7%), Missing values: 14 (6.57%)	Asked, no answer: 45 (18.07%), 0-750 euro: 7 (2.81%), 750-1000 euro: 21 (8.43%), 1000-1250 euro: 17 (6.83%), 1250-1500 euro: 19 (7.63%), 1500-2000 euro: 26 (10.44%), 2000-2500 euro: 21 (8.43%), 2500-3000 euro: 30 (12.05%), 3000-4000 euro: 34 (13.65%), more than 4000 euro: 18 (7.23%), Missing values: 11 (4%)	0.0052	59
	Of the friends you have, how many are people you work with?	1	Mean: 0.34, SD: 1.23	Mean: 0.36, SD: 1.26	0.0052	61

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Does the respondent have an executive role in a club or organizations (e.g., sport club, music band, organization for patient, social organization, religious organization, political party)?	1	Asked but the respondent did not answer: 6 (3%), No: 189 (89%), Yes: 15 (7%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 7 (2.81%), No: 219 (87.95%), Yes: 23 (9.24%)	0.0051	62
	How often do you see/visit your best friend?	1	Asked but the respondent did not answer: 6 (3%), No friend: 54 (25%), Less than a few times a year: 1 (0%), A few times a year: 52 (24%), A few times a month: 56 (26%), A few times a week: 35 (16%), Daily: 5 (2%), We live in the same house: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 3 (1.2%), No friend: 57 (22.89%), Less than a few times a year: 5 (2.01%), A few times a year: 46 (18.47%), A few times a month: 76 (30.52%), A few times a week: 45 (18.07%), Daily: 8 (3.21%), We live in the same house: 4 (1.61%), Missing values: 5 (2%)	0.0051	66
	How many hours a day do you spend with hobbies, doing "odd" jobs or other creative activities around the house?	1	Mean: 0.86, SD: 1.29	Mean: 0.85, SD: 1.32	0.0050	69
	How among your friends are neighbors or live in the neighborhood?	1	Mean: 1.26, SD: 1.9	Mean: 1.2, SD: 2.28	0.0050	70

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Employment status of the respondent	1	Incapacitated for work: 42 (20%), Paid work, 12 hours a week or more: 98 (46%), Paid work, but less than 12 hours a week: 4 (2%), Retired: 5 (2%), Housewife/ house husband: 6 (3%), Student: 12 (6%), Unemployed: 7 (3%), Working as a volunteer: 5 (2%), Independent worker: 9 (4%), Independent worker: 14 (7%), Missing values: 11 (5.16%)	Incapacitated for work: 67 (26.91%), Paid work, 12 hours a week or more: 89 (35.74%), Paid work, but less than 12 hours a week: 7 (2.81%), Retired: 4 (1.61%), Housewife/house husband: 10 (4.02%), Student: 20 (8.03%), Unemployed: 7 (2.81%), Working as a volunteer: 9 (3.61%), Independent worker: 5 (2.01%), Sickness Benefits Act: 22 (8.84%), Missing values: 9 (4%)	0.0050	72
	How many minutes a day do you spend with hobbies, doing odd jobs or other creative activities around the house?	1	Mean: 7.44, SD: 12.55	Mean: 7.86, SD: 12.55	0.0050	73
	Total number of different benzodiazepines used by the respondent	1	Mean: 0.19, SD: 0.44	Mean: 0.18, SD: 0.48	0.0050	75
	How many friends do you have or how many friends do you think you have?	1	Mean: 5.5, SD: 5.26	Mean: 5.28, SD: 4.77	0.0050	77
	How many times a week you read the newspaper?	1	Asked but the respondent did not answer: 9 (4%), Never: 46 (22%), Less than once a week: 21 (10%), 1-2 times a week: 33 (15%), 3-4 times a week: 31 (15%), Daily: 70 (33%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), Never: 86 (34.54%), Less than once a week: 26 (10.44%), 1-2 times a week: 46 (18.47%), 3-4 times a week: 20 (8.03%), Daily: 66 (26.51%)	0.0049	88

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Do you have a partner at the moment?	1	Questionnaire not present: 14 (7%), No: 70 (33%), Yes: 129 (61%)	Questionnaire not present: 11 (4.42%), No: 86 (34.54%), Yes: 152 (61.04%)	0.0048	91
	Living arrangements of the respondent	1	Other: 9 (4%), Alone: 74 (35%), Partner with children: 49 (23%), Partner without children: 45 (21%), Single with children: 8 (4%), With parents: 10 (5%), Missing values: 18 (8.45%)	Other: 9 (3.61%), Alone: 68 (27.31%), Partner with children: 68 (27.31%), Partner without children: 63 (25.3%), Single with children: 5 (2.01%), With parents: 25 (10.04%), Missing values: 11 (4%)	0.0048	93
	Do you use a computer?	1	Asked but the respondent did not answer: 7 (3%), No: 28 (13%), Yes: 175 (82%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), No: 28 (11.24%), Yes: 216 (86.75%)	0.0048	95
	Type of residence of the respondent	1	Other: 2 (1%), In parents house: 8 (4%), Lodgings: 7 (3%), Own house (rented or owner-occupied): 121 (57%), Not pertinent: 58 (27%), Missing values: 17 (7.98%)	Other: 8 (3.21%), In parents house: 18 (7.23%), Lodgings: 7 (2.81%), Own house (rented or owner-occupied): 140 (56.22%), Not pertinent: 64 (25.7%), Missing values: 12 (5%)	0.0047	96
	How many hours a week do you use a computer?	1	Mean: 6.65, SD: 9.93	Mean: 7.42, SD: 10.0	0.0047	98
	If you participate in clubs or organizations, how often do you attend activities or meetings of these clubs or organizations?	1	Asked but the respondent did not answer: 6 (3%), Never: 104 (49%), Practically never: 4 (2%), A few times a year: 21 (10%), Every month: 10 (5%), A few times a month: 11 (5%), Every week: 28 (13%), A few times a week: 25 (12%), Every day: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 7 (2.81%), Never: 105 (42.17%), Practically never: 6 (2.41%), A few times a year: 23 (9.24%), Every month: 12 (4.82%), A few times a month: 17 (6.83%), Every week: 41 (16.47%), A few times a week: 37 (14.86%), Every day: 1 (0.4%)	0.0046	101

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Number of benzodiazepines from different groups used by the respondent	1	Mean: 0.18, SD: 0.42	Mean: 0.17, SD: 0.42	0.0046	102
	Body Mass Index (BMI) of the respondent	1	Mean: 24.7, SD: 4.8	Mean: 25.95, SD: 5.67	0.0045	112
	How often does the respondent go to a cafe, restaurant, etc.?	1	Asked but the respondent did not answer: 9 (4%), Practically never: 26 (12%), A few times a year: 48 (23%), Every month: 45 (21%), A few times a month: 33 (15%), Every week: 33 (15%), A few times a week: 15 (7%), Every day: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), Practically never: 38 (15.26%), A few times a year: 64 (25.7%), Every month: 51 (20.48%), A few times a month: 48 (19.28%), Every week: 37 (14.86%), A few times a week: 5 (2.01%), Every day: 1 (0.4%)	0.0045	114
	The respondent participates in a Trade Union, a employers' organization, or a professional organization	1	Asked but the respondent did not answer: 5 (2%), No: 186 (87%), Yes: 19 (9%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 224 (89.96%), Yes: 19 (7.63%)	0.0044	116
	How many different psycholeptic medications are used by the respondent?	1	Mean: 0.28, SD: 0.6	Mean: 0.4, SD: 0.77	0.0044	118
	How many different benzodiazepines are used by the respondent?	1	Mean: 0.13, SD: 0.34	Mean: 0.14, SD: 0.39	0.0044	121
	How often do you watch the news or the newsreel on TV?	1	Asked but the respondent did not answer: 9 (4%), Never: 10 (5%), Less than once a week: 14 (7%), 1-2 times a week: 20 (9%), 3-4 times a week: 41 (19%), Daily: 116 (54%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), Never: 21 (8.43%), Less than once a week: 15 (6.02%), 1-2 times a week: 25 (10.04%), 3-4 times a week: 55 (22.09%), Daily: 127 (51%)	0.0044	122

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Is your best friend a man or a woman?	1	Asked but the respondent did not answer: 6 (3%), No best friend: 54 (25%), Man: 55 (26%), Woman: 95 (45%), Missing values: 3 (1.41%)	No best friend: 57 (22.89%), Man: 76 (30.52%), Woman: 111 (44.58%), Missing values: 5 (2%)	0.0043	123
	How many persons in your household have a regular income? (Don't include children with only a job on Saturday or in their holidays)	1	Mean: 1.39, SD: 0.65	Mean: 1.6, SD: 0.78	0.0043	124
	If you participate in clubs or organizations, do you volunteer for these clubs or organizations?	1	Asked but the respondent did not answer: 5 (2%), No: 168 (79%), Yes: 37 (17%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 7 (2.81%), No: 178 (71.49%), Yes: 64 (25.7%)	0.0043	127
	How many different SSRIs are used by the respondent?	1	Mean: 0.37, SD: 0.49	Mean: 0.48, SD: 0.52	0.0042	131
	How often does the respondent go to the forest, dunes, zoo, etc.?	1	Asked but the respondent did not answer: 7 (3%), Practically never: 34 (16%), A few times a year: 59 (28%), Every month: 32 (15%), A few times a month: 35 (16%), Every week: 26 (12%), A few times a week: 10 (5%), Every day: 7 (3%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), Practically never: 46 (18.47%), A few times a year: 98 (39.36%), Every month: 37 (14.86%), A few times a month: 24 (9.64%), Every week: 20 (8.03%), A few times a week: 10 (4.02%), Every day: 9 (3.61%)	0.0042	134
	Sex of the respondent	1	Male: 95 (45%), Female: 118 (55%)	Male: 119 (47.79%), Female: 130 (52.21%)	0.0042	136
	Did the respondent experience one or more negative events in the past year?	1	No: 54 (25%), Yes: 159 (75%)	No: 54 (21.69%), Yes: 191 (76.71%), Missing values: 4 (2%)	0.0042	139

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	How often does the respondent go shopping for fun?	1	Asked but the respondent did not answer: 7 (3%), Practically never: 43 (20%), A few times a year: 38 (18%), Every month: 47 (22%), A few times a month: 40 (19%), Every week: 24 (11%), A few times a week: 10 (5%), Every day: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 7 (2.81%), Practically never: 60 (24.1%), A few times a year: 49 (19.68%), Every month: 44 (17.67%), A few times a month: 45 (18.07%), Every week: 33 (13.25%), A few times a week: 10 (4.02%), Every day: 1 (0.4%)	0.0041	149
	Do you take classes at the moment or in last year?	1	Asked but the respondent did not answer: 7 (3%), No: 138 (65%), Yes: 65 (31%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), No: 161 (64.66%), Yes: 83 (33.33%)	0.0041	151
	How often does the respondent visit a cultural organization, like a movie theater, museum, concert, etc.?	1	Asked but the respondent did not answer: 7 (3%), Practically never: 44 (21%), A few times a year: 93 (44%), Every month: 34 (16%), A few times a month: 21 (10%), Every week: 7 (3%), A few times a week: 4 (2%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), Practically never: 71 (28.51%), A few times a year: 133 (53.41%), Every month: 26 (10.44%), A few times a month: 12 (4.82%), Every week: 2 (0.8%)	0.0040	153
	Number of positive recent events in the past year	1	Mean: 2.2, SD: 1.63	Mean: 2.16, SD: 1.62	0.0040	154
	How many different antipsychotic medications are used by the respondent?	1	Mean: 0.1, SD: 0.37	Mean: 0.22, SD: 0.51	0.0040	158
	Did the respondent experience one or more lingering conflicts or problems in the past year?	1	No: 81 (38%), Yes: 132 (62%)	No: 115 (46.18%), Yes: 129 (51.81%), Missing values: 5 (2%)	0.0039	159
	Do you have financial troubles?	1	No: 174 (82%), Yes: 24 (11%), Missing values: 15 (7.04%)	No: 215 (86.35%), Yes: 23 (9.24%), Missing values: 11 (4%)	0.0039	161
	Number of negative recent events in the past year	1	Mean: 1.63, SD: 1.5	Mean: 1.64, SD: 1.43	0.0039	164

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	If you participate in clubs or organizations, how many minutes a week are you involved in an executive role in these clubs or organizations?	1	Mean: 0.19, SD: 2.16	Mean: 1.08, SD: 5.6	0.0039	167
	Other antidepressant (different than SSRIs and non-selective monoamine reuptake inhibitors) use on doctor's order in the last two weeks	1	No: 174 (82%), Yes: 28 (13%), Missing values: 11 (5.16%)	No: 220 (88.35%), Yes: 20 (8.03%), Missing values: 9 (4%)	0.0038	168
	How often does the respondent visit a social-cultural organization?	1	Asked but the respondent did not answer: 9 (4%), Practically never: 164 (77%), A few times a year: 13 (6%), Every month: 10 (5%), A few times a month: 4 (2%), Every week: 9 (4%), A few times a week: 1 (0%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), Practically never: 204 (81.93%), A few times a year: 17 (6.83%), Every month: 7 (2.81%), A few times a month: 6 (2.41%), Every week: 6 (2.41%), A few times a week: 4 (1.61%)	0.0038	169
	How often does the respondent do outdoor activities, like swimming, walking, fishing, etc.?	1	Asked but the respondent did not answer: 7 (3%), Practically never: 33 (15%), A few times a year: 13 (6%), Every month: 11 (5%), A few times a month: 15 (7%), Every week: 51 (24%), A few times a week: 55 (26%), Every day: 25 (12%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), Practically never: 56 (22.49%), A few times a year: 27 (10.84%), Every month: 10 (4.02%), A few times a month: 25 (10.04%), Every week: 55 (22.09%), A few times a week: 45 (18.07%), Every day: 25 (10.04%)	0.0038	171
	Benzodiazepines (all types) use on doctor's order the last two weeks	1	No: 168 (79%), Yes: 34 (16%), Missing values: 11 (5.16%)	No: 205 (82.33%), Yes: 35 (14.06%), Missing values: 9 (4%)	0.0038	174

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Number of lingering conflicts or problems in the past year	1	Mean: 0.85, SD: 0.79	Mean: 0.74, SD: 0.81	0.0037	177
	The respondent participates in other kind of clubs and organizations	1	Asked but the respondent did not answer: 5 (2%), No: 179 (84%), Yes: 26 (12%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 220 (88.35%), Yes: 23 (9.24%)	0.0035	183
	The respondent participates in a choral society, music band, theatre company	1	Asked but the respondent did not answer: 5 (2%), No: 182 (85%), Yes: 23 (11%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 223 (89.56%), Yes: 20 (8.03%)	0.0035	185
	Did the respondent experience one or more positive recent events in the past year?	1	No: 34 (16%), Yes: 179 (84%)	No: 40 (16.06%), Yes: 205 (82.33%), Missing values: 4 (2%)	0.0034	188
	The respondent participates in an organization for patients	1	Asked but the respondent did not answer: 5 (2%), No: 183 (86%), Yes: 22 (10%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 217 (87.15%), Yes: 26 (10.44%)	0.0034	189
	SSRI use on doctor's order the last two weeks	1	No: 128 (60%), Yes: 74 (35%), Missing values: 11 (5.16%)	No: 127 (51%), Yes: 113 (45.38%), Missing values: 9 (4%)	0.0034	190
	Participant currently taking psychotropic pharmacotherapy according to guidelines	1	Missing: 18 (8%), No: 135 (63%), Yes: 60 (28%)	Missing: 13 (5.22%), No: 154 (61.85%), Yes: 81 (32.53%), Missing values: 1 (0%)	0.0034	192
	If you participate in clubs or organizations, how many hours a week do you volunteer for these clubs and organizations?	1	Mean: 0.6 SD: 2.43	Mean: 0.88, SD: 2.62	0.0033	193
	Anxiolytic use on doctor's order the last two weeks	1	No: 175 (82%), Yes: 27 (13%), Missing values: 11 (5.16%)	No: 210 (84.34%), Yes: 30 (12.05%), Missing values: 9 (4%)	0.0033	194
	If you participate in clubs or organizations, do you participate in activities or meetings of these clubs or organizations?	1	Asked but the respondent did not answer: 5 (2%), No: 104 (49%), Yes: 101 (47%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 105 (42.17%), Yes: 138 (55.42%)	0.0033	195

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	How many different non-selective monoamine reuptake inhibitors are used by the respondent?	1	Mean: 0.09, SD: 0.32	Mean: 0.19, SD: 0.43	0.0032	199
	The respondent participates in an action committee or organization with social goals	1	Asked but the respondent did not answer: 5 (2%), No: 186 (87%), Yes: 19 (9%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 232 (93.17%), Yes: 11 (4.42%)	0.0030	203
	How many minutes a week do you use a computer?	1	Mean: 3.08, SD: 9.37	Mean: 5.59, SD: 12.24	0.0030	204
	Do you take other kind of classes at the moment or in the last year?	1	Asked but the respondent did not answer: 7 (3%), No: 168 (79%), Yes: 35 (16%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 5 (2.01%), No: 206 (82.73%), Yes: 38 (15.26%)	0.0030	205
	The respondent participates in a church or organization with religious or ideological goal	1	Asked but the respondent did not answer: 5 (2%), No: 186 (87%), Yes: 19 (9%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 177 (71.08%), Yes: 66 (26.51%)	0.0029	206
	The respondent participates in a hobby or social club	1	Asked but the respondent did not answer: 5 (2%), No: 187 (88%), Yes: 18 (8%), Missing values: 3 (1.41%)	Asked but the respondent did not answer: 6 (2.41%), No: 222 (89.16%), Yes: 21 (8.43%)	0.0029	207
	Benzodiazepine (anxiolytic type) use on doctor's order in the last two weeks	1	No: 175 (82%), Yes: 27 (13%), Missing values: 11 (5.16%)	No: 210 (84.34%), Yes: 30 (12.05%), Missing values: 9 (4%)	0.0029	208
	Non-selective monoamine reuptake inhibitor use on doctor's order in the last two weeks	1	No: 185 (87%), Yes: 17 (8%), Missing values: 11 (5.16%)	No: 197 (79.12%), Yes: 43 (17.27%), Missing values: 9 (4%)	0.0025	216
	How many different hypnotics sedatives are used by the respondent?	1	Mean: 0.04, SD: 0.22	Mean: 0.03, SD: 0.18	0.0010	217
	How many different antiepileptic medications are used by the respondent?	0	Mean: 0.03, SD: 0.23	Mean: 0.02, SD: 0.14	-	-

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	How many different hypnotic benzodiazepines are used by the respondent?	0	Mean: 0.03, SD: 0.2	Mean: 0.03, SD: 0.18	-	-
	How many different nervous system drugs are used by the respondent??	0	Mean: 0.0, SD: 0.12	Mean: 0.0, SD: 0.14	-	-
	How many different addictive disorders drug are used by the respondent??	0	Mean: 0.0, SD: 0.12	Mean: 0.0, SD: 0.14	-	-
EuroQol (EuroQol, 1990)	EQ-5D score	1	Mean: 0.7, SD: 0.26	Mean: 0.68, SD: 0.27	0.0057	31
Interpretation of Intrusion Inventory (O.C.C.W. Group, 2001)	Interpretation of Intrusions Inventory: Responsibility subscale score	1	Mean: 448.26, SD: 277.36	Mean: 488.28, SD: 281.01	0.0047	99
	Interpretation of Intrusions Inventory: Importance of Thoughts subscale score	1	Mean: 359.0, SD: 228.58	Mean: 371.73, SD: 246.24	0.0046	100
	Interpretation of Intrusions Inventory: Control subscale score	1	Mean: 519.52, SD: 246.79	Mean: 554.96, SD: 260.81	0.0041	147
Level of Expressed Emotion (Cole et Kazarian, 1988)	Percieved lack of emotional support scale	1	Mean: 31.02, SD: 9.52	Mean: 31.69, SD: 12.11	0.0050	76
	Percieved irritation scale	1	Mean: 12.9, SD: 4.64	Mean: 13.27, SD: 5.01	0.0049	79
	Percieved intrusiveness scale	1	Mean: 11.77, SD: 5.31	Mean: 12.6, SD: 5.79	0.0049	89
	Percieved criticism scale	1	Mean: 8.45, SD: 2.79	Mean: 8.78, SD: 3.15	0.0047	97
Life Chart (Eaton et al., 1997)	Chronical Course of OCD in the last 2 years	1	Too many omitted answers from the respondent: 3 (1%), No: 90 (42%), Yes: 120 (56%)	Too many omitted answers from the respondent: 3 (1.2%), No: 97 (38.96%), Yes: 146 (58.63%), Missing values: 3 (1%)	0.0070	5

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Late onset OCD (20 years or older)?	1	Asked but the respondent did not answer: 11 (5%), No: 126 (59%), Yes: 59 (28%), Missing values: 17 (7.98%)	Asked but the respondent did not answer: 15 (6.02%), No: 144 (57.83%), Yes: 87 (34.94%), Missing values: 3 (1%)	0.0057	30
Loneliness Scale (De Jong-Gierveld et Kamphuls, 1985)	Emotional loneliness score	1	Mean: 2.66, SD: 2.18	Mean: 2.69, SD: 2.22	0.0056	38
	Total score	1	Mean: 5.18, SD: 3.6	Mean: 5.42, SD: 3.61	0.0050	74
	Social loneliness score	1	Mean: 2.53, SD: 1.86	Mean: 2.73, SD: 1.82	0.0049	85
Montgomery-Asberg Depression Rating Scale (Montgomery et Asberg, 1979)	MADRS total score	1	Mean: 11.92, SD: 8.09	Mean: 12.04, SD: 9.3	0.0062	14
Padua Inventory (Sanavio, 1988)	Padua Inventory: precision subscale score	1	Mean: 6.45, SD: 5.9	Mean: 6.75, SD: 6.2	0.0062	15
	Padua Inventory: rumination subscale score	1	Mean: 20.85, SD: 9.5	Mean: 22.84, SD: 8.89	0.0051	63
	Padua Inventory: checking subscale score	1	Mean: 13.07, SD: 7.91	Mean: 13.94, SD: 7.16	0.0051	65
	Padua Inventory: washing subscale score	1	Mean: 11.87, SD: 11.92	Mean: 10.73, SD: 10.16	0.0051	67
	Padua Inventory: impulses subscale score	1	Mean: 6.07, SD: 5.98	Mean: 5.62, SD: 6.52	0.0050	68
Structured Clinical Interview for DSM-IV-R (First et Gibbon, 2004)	Diagnosis of Somatoform disorders - lifetime	1	No: 203 (95%), Yes: 10 (5%)	No: 236 (94.78%), Yes: 13 (5.22%)	0.0064	12
	Diagnosis of Major depressive disorder - lifetime	1	No: 83 (39%), Yes: 130 (61%)	No: 96 (38.55%), Yes: 153 (61.45%)	0.0052	58
	Diagnosis of Specific Phobia - current	1	No: 189 (89%), Yes: 24 (11%)	No: 240 (96.39%), Yes: 9 (3.61%)	0.0049	84

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Any current diagnosis of Anxiety disorder besides OCD diagnosis	1	No: 140 (66%), Yes: 73 (34%)	No: 172 (69.08%), Yes: 77 (30.92%)	0.0046	103
	Any lifetime diagnosis of anxiety disorder besides OCD diagnosis	1	No: 112 (53%), Yes: 101 (47%)	No: 138 (55.42%), Yes: 111 (44.58%)	0.0046	109
	Diagnosis of Social phobia - lifetime	1	No: 161 (76%), Yes: 52 (24%)	No: 179 (71.89%), Yes: 70 (28.11%)	0.0044	117
	Number of current diagnosis	1	Mean: 1.84, SD: 1.11	Mean: 1.77, SD: 1.02	0.0042	129
	Diagnosis of Dysthymic disorder - lifetime	1	No: 197 (92%), Yes: 16 (8%)	No: 234 (93.98%), Yes: 15 (6.02%)	0.0042	137
	Diagnosis of Panic disorder with agoraphobia - lifetime	1	No: 177 (83%), Yes: 36 (17%)	No: 226 (90.76%), Yes: 23 (9.24%)	0.0042	142
	Number of lifetime diagnosis	1	Mean: 2.74, SD: 1.46	Mean: 2.63, SD: 1.36	0.0041	150
	Diagnosis of Substance related disorders dependence - lifetime	1	No: 194 (91%), Yes: 19 (9%)	No: 222 (89.16%), Yes: 27 (10.84%)	0.0040	157
	Diagnosis of Social phobia - current	1	No: 182 (85%), Yes: 31 (15%)	No: 204 (81.93%), Yes: 45 (18.07%)	0.0038	172
	Diagnosis of Specific Phobia - lifetime	1	No: 179 (84%), Yes: 34 (16%)	No: 230 (92.37%), Yes: 19 (7.63%)	0.0036	180
	Diagnosis of Eating disorders - lifetime	1	No: 186 (87%), Yes: 27 (13%)	No: 223 (89.56%), Yes: 26 (10.44%)	0.0035	187
	Diagnosis of Major depressive disorder - current	1	No: 175 (82%), Yes: 38 (18%)	No: 210 (84.34%), Yes: 39 (15.66%)	0.0032	197
	Diagnosis of Generalized anxiety disorder - lifetime	1	No: 187 (88%), Yes: 26 (12%)	No: 228 (91.57%), Yes: 21 (8.43%)	0.0032	198
	Diagnosis of Panic disorder without agoraphobia - lifetime	1	No: 194 (91%), Yes: 19 (9%)	No: 222 (89.16%), Yes: 27 (10.84%)	0.0032	200
	Diagnosis of Dysthymic disorder - current	1	No: 202 (95%), Yes: 11 (5%)	No: 239 (95.98%), Yes: 10 (4.02%)	0.0028	210
	Diagnosis of Panic disorder with agoraphobia - current	1	No: 200 (94%), Yes: 13 (6%)	No: 238 (95.58%), Yes: 11 (4.42%)	0.0027	214

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Diagnosis of Generalized anxiety disorder - current	0	No: 195 (92%), Yes: 18 (8%)	No: 231 (92.77%), Yes: 18 (7.23%)	-	-
Self-reported general attachment style (Griffin et Bartholomew, 1994)	W*hich attachment style most appropriately describes you?*	1	Asked but the respondent did not answer: 4 (2%), Dismissing: 21 (10%), Fearful: 65 (31%), Preoccupied: 52 (24%), Secure: 66 (31%), Missing values: 5 (2.35%)	Asked but the respondent did not answer: 9 (3.61%), Dismissing: 21 (8.43%), Fearful: 104 (41.77%), Preoccupied: 48 (19.28%), Secure: 57 (22.89%), Missing values: 10 (4%)	0.0052	60
	Attachment Style Fearful score: *I am wary to get engaged in close relationships because I am afraid to get hurt*	1	Mean: 4.05, SD: 2.01	Mean: 4.38, SD: 1.88	0.0059	25
	Attachment Style Preoccupied score: *I have the impression that usually I like others better than they like me*	1	Mean: 3.74, SD: 1.77	Mean: 3.9, SD: 1.68	0.0055	42
	Attachment Style Dismissing score: *I prefer that others are independent of me and I am independent of them*	1	Mean: 3.24, SD: 1.86	Mean: 2.96, SD: 1.85	0.0049	86
	Attachment Style Secure score: *I feel at ease in intimate relationships*	1	Mean: 4.08, SD: 1.83	Mean: 3.7, SD: 1.78	0.0042	138
Social Support Inventory (Timmerman et al., 2000)	Informative Support subscale score	1	Mean: 12.84, SD: 2.22	Mean: 12.55, SD: 2.46	0.0046	110
	Instrumental Support subscale score	1	Mean: 13.25, SD: 2.19	Mean: 13.16, SD: 2.51	0.0042	141
	Emotional Support subscale score	1	Mean: 12.6, SD: 2.65	Mean: 12.2, SD: 2.75	0.0041	144
	Social Companionship subscale score	1	Mean: 12.0, SD: 2.56	Mean: 12.15, SD: 2.68	0.0041	145

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
Structured Trauma Interview (Draijer et Langeland, 1999)	Mother was (sometimes) dysfuctioning or unavailable?	1	Too many omitted answers from the respondent: 5 (2%), No: 90 (42%), Yes: 112 (53%), Missing values: 6 (2.82%)	No: 101 (40.56%), Yes: 148 (59.44%)	0.0060	22
	Mother and/or father was (sometimes) dysfuctioning or unavailable	1	Too many omitted answers from the respondent: 5 (2%), No: 57 (27%), Yes: 145 (68%), Missing values: 6 (2.82%)	No: 72 (28.92%), Yes: 177 (71.08%)	0.0059	23
	Physical abuse (domestic) after age 16	1	Asked but the respondent did not answer: 30 (14%), No: 156 (73%), Yes: 21 (10%), Missing values: 6 (2.82%)	Asked but the respondent did not answer: 28 (11.24%), No: 186 (74.7%), Yes: 35 (14.06%)	0.0057	29
	Abuse before or after age 16	1	Asked but the respondent did not answer: 30 (14%), No: 164 (77%), Yes: 13 (6%), Missing values: 6 (2.82%)	Asked but the respondent did not answer: 29 (11.65%), No: 206 (82.73%), Yes: 14 (5.62%)	0.0057	36
	Father was (sometimes) dysfuctioning or unavailable?	1	Too many omitted answers from the respondent: 9 (4%), No: 101 (47%), Yes: 97 (46%), Missing values: 6 (2.82%)	No: 136 (54.62%), Yes: 113 (45.38%)	0.0054	46
	Total score dysfunctioning or unavailability mother	1	Mean: 1.14, SD: 1.31	Mean: 1.16, SD: 1.31	0.0050	71
	Childhood witnessing of interparental violence	1	Asked but the respondent did not answer: 5 (2%), No: 167 (78%), Yes: 35 (16%), Missing values: 6 (2.82%)	Asked but the respondent did not answer: 5 (2.01%), No: 212 (85.14%), Yes: 32 (12.85%)	0.0049	80
	Number of questions unanswered	1	Mean: 0.25, SD: 1.02	Mean: 0.02, SD: 0.14	0.0049	87
	Total score dysfunctioning or unavailability father	1	Mean: 0.94, SD: 1.21	Mean: 0.78, SD: 1.12	0.0048	90
	Number of different kind of childhood trauma exposures before age 16 (0-6: mother and father disfunctioning is counted separately)	1	Mean: 1.5, SD: 1.22	Mean: 1.4, SD: 1.17	0.0046	105

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Number of different kind of childhood trauma exposures before age 16 (0-5: mother and father disfunctioning is counted together)	1	Mean: 1.2, SD: 0.96	Mean: 1.07, SD: 0.88	0.0044	119
	Sexual abuse after age 16	1	Asked but the respondent did not answer: 13 (6%), No: 162 (76%), Yes: 32 (15%), Missing values: 6 (2.82%)	Asked but the respondent did not answer: 5 (2.01%), No: 210 (84.34%), Yes: 34 (13.65%)	0.0044	120
	Physical abuse but no sexual abuse before age 16	1	No: 188 (88%), Yes: 19 (9%), Missing values: 6 (2.82%)	No: 231 (92.77%), Yes: 18 (7.23%)	0.0043	125
	Sexual and/or physical abuse before age 16	1	No: 180 (85%), Yes: 27 (13%), Missing values: 6 (2.82%)	No: 218 (87.55%), Yes: 31 (12.45%)	0.0040	155
	Physical (parental) abuse before age 16	1	No: 186 (87%), Yes: 21 (10%), Missing values: 6 (2.82%)	No: 228 (91.57%), Yes: 21 (8.43%)	0.0026	215
Systolic and diastolic blood pressure assessment	Diastolic pressure - arm - lying - measurement 1	1	Mean: 79.12, SD: 10.75	Mean: 79.89, SD: 12.78	0.0054	50
	Systolic pressure - arm - lying - measurement 2	1	Mean: 131.17, SD: 18.93	Mean: 131.12, SD: 17.25	0.0052	57
	Diastolic pressure - arm - standing - measurement 2	1	Mean: 83.74, SD: 10.52	Mean: 84.4, SD: 12.65	0.0050	78
	Systolic pressure - arm - standing - measurement 1	1	Mean: 128.88, SD: 17.61	Mean: 129.9, SD: 16.57	0.0049	82
	Diastolic pressure - arm - lying - measurement 2	1	Mean: 79.37, SD: 10.94	Mean: 81.04, SD: 13.28	0.0048	92
	Systolic pressure - arm - standing - measurement 2	1	Mean: 130.69, SD: 18.62	Mean: 131.83, SD: 18.38	0.0046	107
	Systolic pressure - arm - lying - measurement 1	1	Mean: 131.9, SD: 17.5	Mean: 131.26, SD: 17.2	0.0046	108
	Diastolic pressure - arm - standing - measurement 1	1	Mean: 82.16, SD: 10.59	Mean: 83.17, SD: 11.41	0.0041	152

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
Trimbos/iMTA Questionnaire for Costs Associated with Psychiatric Illness (Roijen et al., 2002)	Respondent doing houshold work	1	Did not do it, because of health problems: 11 (5%), Did not do it, for reasons other than health problems: 3 (1%), Done, hindered by health problems: 118 (55%), Done, not hindered by health problems: 81 (38%)	Did not do it, because of health problems: 6 (2.41%), Did not do it, for reasons other than health problems: 4 (1.61%), Done, hindered by health problems: 156 (62.65%), Done, not hindered by health problems: 80 (32.13%), Missing values: 3 (1%)	0.0062	16
	Hours of work missed/lost because of hindrance by health problems	1	Mean: 19.25, SD: 92.91	Mean: 10.15, SD: 53.65	0.0062	18
	With how many medical specialists did you have contact in the last 6 months?	1	Mean: 0.63, SD: 0.91	Mean: 0.54, SD: 0.84	0.0061	19
	Have you been admitted to a health care institution in the last 6 months?	1	No: 189 (89%), Yes: 24 (11%)	No: 169 (67.87%), Yes: 77 (30.92%), Missing values: 3 (1%)	0.0058	26
	Days per week the respondent is employed	1	Mean: 2.33, SD: 2.12	Mean: 1.86, SD: 2.23	0.0057	35
	I was at work, but due to health problems I had to postpone work for the past 6 months	1	Asked but the respondent did not answer: 1 (0%), Not pertinent: 129 (61%), Rarely: 43 (20%), Occasionally: 10 (5%), Sometimes: 22 (10%), Often: 6 (3%), Nearly all the time: 2 (1%)	Asked but the respondent did not answer: 2 (0.8%), Not pertinent: 177 (71.08%), Rarely: 43 (17.27%), Occasionally: 5 (2.01%), Sometimes: 12 (4.82%), Often: 5 (2.01%), Nearly all the time: 2 (0.8%), Missing values: 3 (1%)	0.0056	37

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Respondent doing “odd” jobs	1	Did not do it, because of health problems: 36 (17%), Did not do it, for reasons other than health problems: 38 (18%), Done, hindered by health problems: 76 (36%), Done, not hindered by health problems: 63 (30%)	Did not do it, because of health problems: 29 (11.65%), Did not do it, for reasons other than health problems: 56 (22.49%), Done, hindered by health problems: 96 (38.55%), Done, not hindered by health problems: 65 (26.1%), Missing values: 3 (1%)	0.0056	39
	Number of hours volunteers took over domestic work in past 6 months	1	Mean: 4.13, SD: 37.8	Mean: 3.63, SD: 24.14	0.0056	40
	If the respondent had contact with a psychiatrist, psychologist or psychotherapist in a policlinic of a general hospital in the last six months, in what type of hospital did the respondent have such contact?	1	Asked but the respondent did not answer: 1 (0%), General Hospital: 4 (2%), No contact with a psychiatrist, psychologist or psychotherapist in a policlinic of a general hospital: 119 (56%), Other type of hospital: 17 (8%), Psychiatric hospital: 63 (30%), University hospital: 9 (4%)	Asked but the respondent did not answer: 6 (2.41%), General Hospital: 10 (4.02%), No contact with a psychiatrist, psychologist or psychotherapist in a policlinic of a general hospital: 185 (74.3%), Other type of hospital: 4 (1.61%), Psychiatric hospital: 21 (8.43%), University hospital: 20 (8.03%), Missing values: 3 (1%)	0.0055	41
	Hours per week the respondent is employed	1	Mean: 17.67, SD: 16.14	Mean: 13.7, SD: 16.44	0.0055	43

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	If the respondent does not work, what is the best description of current status?	1	(early) Retirement: 4 (2%), Housekeeping: 6 (3%), No work beacuse of health related problems: 56 (26%), Other reasons: 8 (4%), Not pertinent: 134 (63%), Student: 5 (2%)	(early) Retirement: 5 (2.01%), Housekeeping: 15 (6.02%), No work beacuse of health related problems: 88 (35.34%), Other reasons: 7 (2.81%), Not pertinent: 118 (47.39%), Student: 13 (5.22%), Missing values: 3 (1%)	0.0055	45
	How many contacts with a social worker in the last six months?	1	Mean: 0.53, SD: 3.82	Mean: 1.14, SD: 6.91	0.0054	48
	Did you have any contact with a social worker in the last six months?	1	No: 201 (94%), Yes: 12 (6%)	No: 226 (90.76%), Yes: 19 (7.63%), Missing values: 4 (2%)	0.0054	51
	Do you have a paid job at the moment?	1	No: 79 (37%), Yes: 134 (63%)	No: 128 (51.41%), Yes: 118 (47.39%), Missing values: 3 (1%)	0.0053	53
	Did you have any contact with a psychiatrist, psychologist or psychotherapist in a policlinic of a general hospital without admission to the hospital in the last six months?	1	No: 119 (56%), Yes: 94 (44%)	No: 185 (74.3%), Yes: 58 (23.29%), Missing values: 6 (2%)	0.0053	55
	How many contacts did you have with psychiatrist, psychologist or psychotherapist in policlinic of a general hospital without admission to the hospital in the last six months?	1	Mean: 3.43, SD: 7.41	Mean: 2.66, SD: 7.29	0.0052	56
	Did you have any contact with a RIAGG or GGZ institute in the last six months?	1	No: 113 (53%), Yes: 100 (47%)	No: 88 (35.34%), Yes: 156 (62.65%), Missing values: 5 (2%)	0.0051	64

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Has the respondent being absent from work due to health problems in last 6 months?	1	No: 142 (67%), Yes: 70 (33%), Missing values: 1 (0.47%)	No: 169 (67.87%), Yes: 76 (30.52%), Missing values: 4 (2%)	0.0049	81
	I was at work, but due to health problems I had problems with concentration in the past 6 months	1	Not pertinent: 129 (61%), Rarely: 18 (8%), Occasionally: 9 (4%), Sometimes: 31 (15%), Often: 16 (8%), Nearly all the time: 9 (4%), Missing values: 1 (0.47%)	Not pertinent: 177 (71.08%), Rarely: 26 (10.44%), Occasionally: 10 (4.02%), Sometimes: 17 (6.83%), Often: 11 (4.42%), Nearly all the time: 4 (1.61%), Missing values: 4 (2%)	0.0049	83
	How many contacts did you have with a RIAGG or GGZ institute in the last six months?	1	Mean: 12.62, SD: 26.94	Mean: 13.8, SD: 29.02	0.0048	94
	If the respondent has children, did the respondent do things for or with the children living at home?	1	Asked but the respondent did not answer/not relevant: 104 (49%), Did not do it, because of health problems: 1 (0%), Did not do it, for reasons other than health problems: 47 (22%), Done, hindered by health problems: 32 (15%), Done, not hindered by health problems: 29 (14%)	Asked but the respondent did not answer/ not relevant: 74 (29.72%), Did not do it, because of health problems: 5 (2.01%), Did not do it, for reasons other than health problems: 86 (34.54%), Done, hindered by health problems: 43 (17.27%), Done, not hindered by health problems: 38 (15.26%), Missing values: 3 (1%)	0.0046	106
	I was at work, but due to health problems I had to work at a slower pace over the past 6 months	1	Not pertinent: 129 (61%), Rarely: 28 (13%), Occasionally: 9 (4%), Sometimes: 20 (9%), Often: 20 (9%), Nearly all the time: 6 (3%), Missing values: 1 (0.47%)	Not pertinent: 177 (71.08%), Rarely: 23 (9.24%), Occasionally: 9 (3.61%), Sometimes: 22 (8.84%), Often: 7 (2.81%), Nearly all the time: 7 (2.81%), Missing values: 4 (2%)	0.0045	111

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Volunteers took over domestic work of the respondent in past 6 months?	1	No: 190 (89%), Yes: 22 (10%), Missing values: 1 (0.47%)	No: 227 (91.16%), Yes: 18 (7.23%), Missing values: 4 (2%)	0.0045	113
	Did you have any contact with a medical specialist in a policlinic of a general hospital without admission to the hospital in the last six months?	1	No: 121 (57%), Yes: 91 (43%), Missing values: 1 (0.47%)	No: 152 (61.04%), Yes: 92 (36.95%), Missing values: 5 (2%)	0.0044	115
	I was at work, but due to health problems I had to isolate myself for the past 6 months	1	Not pertinent: 129 (61%), Rarely: 51 (24%), Occasionally: 8 (4%), Sometimes: 15 (7%), Often: 8 (4%), Nearly all the time: 1 (0%), Missing values: 1 (0.47%)	Not pertinent: 177 (71.08%), Rarely: 43 (17.27%), Occasionally: 5 (2.01%), Sometimes: 16 (6.43%), Often: 2 (0.8%), Nearly all the time: 2 (0.8%), Missing values: 4 (2%)	0.0043	126
	How many contacts did you have with a physiotherapist in the last six months?	1	Mean: 6.72, SD: 22.91	Mean: 2.69, SD: 7.89	0.0043	128
	In what type of health care institution have you been admitted?	1	General Hospital: 14 (7%), No admission to a health care institution: 189 (89%), Other type of hospital: 1 (0%), Psychiatric hospital: 4 (2%), University hospital: 5 (2%)	General Hospital: 17 (6.83%), No admission to a health care institution: 169 (67.87%), Other type of hospital: 26 (10.44%), Psychiatric hospital: 29 (11.65%), University hospital: 2 (0.8%), Missing values: 6 (2%)	0.0042	130
	Physical or psychological cause of absence/illness/ disability?	1	Not at all: 129 (61%), A little: 59 (28%), A lot: 24 (11%), Missing values: 1 (0.47%)	Not at all: 177 (71.08%), A little: 46 (18.47%), A lot: 22 (8.84%), Missing values: 4 (2%)	0.0042	132

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	How many contacts did you have with your physician in the last six months? (add all visits to doctor, telephonic consultations, and visits of the physician at the respondent's home)	1	Mean: 1.95, SD: 2.05	Mean: 1.94, SD: 2.24	0.0042	133
	Did you participate in a self-help group in the last six months? (e.g., Aa group, talk-group patient association)?	1	No: 196 (92%), Yes: 16 (8%), Missing values: 1 (0.47%)	No: 231 (92.77%), Yes: 14 (5.62%), Missing values: 4 (2%)	0.0042	135
	Did you have any contact with alternative caretakers in the last six months (like a homoeopath, acupuncturist, healer, manual therapist, haptonomist chiropractor, iriscopist?)	1	No: 173 (81%), Yes: 40 (19%)	No: 219 (87.95%), Yes: 26 (10.44%), Missing values: 4 (2%)	0.0042	140
	How many days have you been admitted to a health care institution in the last 6 months?	1	Mean: 4.36, SD: 31.62	Mean: 21.3, SD: 59.36	0.0042	143
	Did family members took over domestic work in past 6 months?	1	No: 152 (71%), Yes: 60 (28%), Missing values: 1 (0.47%)	No: 179 (71.89%), Yes: 67 (26.91%), Missing values: 3 (1%)	0.0041	146
	Respondent going to buy Groceries	1	Did not do it, because of health problems: 7 (3%), Did not do it, for reasons other than health problems: 4 (2%), Done, hindered by health problems: 88 (41%), Done, not hindered by health problems: 114 (54%)	Did not do it, because of health problems: 9 (3.61%), Did not do it, for reasons other than health problems: 4 (1.61%), Done, hindered by health problems: 127 (51%), Done, not hindered by health problems: 106 (42.57%), Missing values: 3 (1%)	0.0041	148

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Number of hours family members took over domestic work in past 6 months	1	Mean: 23.92, SD: 89.67	Mean: 19.94, SD: 61.76	0.0040	156
	Days in the last 6 months the respondent was hindered at work by health problems	1	Mean: 19.7, SD: 38.12	Mean: 20.18, SD: 43.59	0.0039	162
	Did you have any contact with a physiotherapist in the last six months?	1	No: 146 (69%), Yes: 66 (31%), Missing values: 1 (0.47%)	No: 196 (78.71%), Yes: 49 (19.68%), Missing values: 4 (2%)	0.0039	163
	I was at work, but due to health problems I had to have others take over work for the past 6 months	1	Not pertinent: 129 (61%), Rarely: 54 (25%), Occasionally: 10 (5%), Sometimes: 12 (6%), Often: 7 (3%), Missing values: 1 (0.47%)	Not pertinent: 177 (71.08%), Rarely: 47 (18.88%), Occasionally: 7 (2.81%), Sometimes: 9 (3.61%), Often: 5 (2.01%), Missing values: 4 (2%)	0.0039	165
	How many whole days did you have day-time or part-time treatment for mental problems in the last 6 months?	1	Mean: 4.3, SD: 22.92	Mean: 10.84, SD: 30.31	0.0038	170
	Did you have any contact with a company doctor in the last six months?	1	No: 164 (77%), Yes: 49 (23%)	Asked but the respondent did not answer: 9 (3.61%), No: 179 (71.89%), Yes: 58 (23.29%), Missing values: 3 (1%)	0.0038	173
	I was at work, but due to health issues, I had more trouble making decisions in the past 6 months	1	Asked but the respondent did not answer: 2 (1%), Not pertinent: 129 (61%), Rarely: 43 (20%), Occasionally: 9 (4%), Sometimes: 20 (9%), Often: 9 (4%), Nearly all the time: 1 (0%)	Asked but the respondent did not answer: 1 (0.4%), Not pertinent: 177 (71.08%), Rarely: 39 (15.66%), Occasionally: 9 (3.61%), Sometimes: 10 (4.02%), Often: 7 (2.81%), Nearly all the time: 3 (1.2%), Missing values: 3 (1%)	0.0038	175
	How many contacts did you have with a company doctor in the last six months?	1	Mean: 0.73, SD: 1.75	Mean: 0.88, SD: 2.11	0.0038	176

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	Others took over domestic work that the respondent normally does in past 6 months?	1	No: 130 (61%), Yes: 83 (39%)	No: 159 (63.86%), Yes: 87 (34.94%), Missing values: 3 (1%)	0.0037	178
	I was at work, but due to health problems I had other problems	1	Asked but the respondent did not answer: 1 (0%), Not pertinent: 129 (61%), Rarely: 60 (28%), Occasionally: 2 (1%), Sometimes: 9 (4%), Often: 7 (3%), Nearly all the time: 5 (2%)	Asked but the respondent did not answer: 2 (0.8%), Not pertinent: 178 (71.49%), Rarely: 51 (20.48%), Sometimes: 4 (1.61%), Often: 8 (3.21%), Nearly all the time: 3 (1.2%), Missing values: 3 (1%)	0.0037	179
	With how many alternative caretakers did you have contact in the last 6 months?	1	Mean: 0.2, SD: 0.45	Mean: 0.12, SD: 0.36	0.0036	181
	How many contacts did you have with an independent psychiatrist, psychologist or psychotherapist in the last six months?	1	Mean: 2.65, SD: 10.02	Mean: 2.06, SD: 11.2	0.0036	182
	Did you have any contact with an independent psychiatrist, psychologist or psychotherapist in the last six months?	1	No: 159 (75%), Yes: 53 (25%), Missing values: 1 (0.47%)	No: 208 (83.53%), Yes: 36 (14.46%), Missing values: 5 (2%)	0.0035	186
	How many different self-help groups?	1	No: 197 (92%), Yes: 16 (8%)	No: 235 (94.38%), Yes: 14 (5.62%)	0.0034	191
	Hours per week the respondent was employed in the past	1	Mean: 6.46, SD: 13.51	Mean: 9.78, SD: 16.19	0.0033	196
	Did you have contact with your physician in the last six months?	1	No: 49 (23%), Yes: 164 (77%)	No: 72 (28.92%), Yes: 174 (69.88%), Missing values: 3 (1%)	0.0032	201

Source	Variable	Included in the algorithm after training	Descriptive statistics in the train set	Descriptive statistics in the test set	Gain feature importance - score	Gain feature importance - rank
	In what type of institution did you have daytime- or part-time treatment for mental problems?	1	General Hospital: 1 (0%), No daytime- or parttime treatment for mental problems: 190 (89%), Other type of hospital: 15 (7%), Psychiatric hospital: 7 (3%)	Asked but the respondent did not answer: 6 (2.41%), General Hospital: 2 (0.8%), No daytime- or parttime treatment for mental problems: 183 (73.49%), Other type of hospital: 22 (8.84%), Psychiatric hospital: 33 (13.25%), Missing values: 3 (1%)	0.0031	202
	Did you have day-time or part-time treatment for mental problems?	1	No: 190 (89%), Yes: 23 (11%)	No: 183 (73.49%), Yes: 63 (25.3%), Missing values: 3 (1%)	0.0028	212
	How many contacts for a homecare did you have *in the last 6 months?*	1	Mean: 7.65, SD: 49.34	Mean: 7.73, SD: 51.37	0.0028	213
	Number of hours homecare took over domestic work in past 6 months	0	Mean: 1.89, SD: 11.98	Mean: 1.07, SD: 10.37	-	-
	Number of hours paid help took over domestic work in past 6 months	0	Mean: 3.77, SD: 38.18	Mean: 2.92, SD: 15.35	-	-
	How many contacts did you have with the center for alcohol and drugs in the last six months?	0	Mean: 0.24, SD: 1.78	Mean: 0.55, SD: 4.91	-	-
	Did you use homecare in the last six months?	0	No: 202 (95%), Yes: 11 (5%)	No: 229 (91.97%), Yes: 16 (6.43%), Missing values: 4 (2%)	-	-
Y-BOCS (Goodman et al., 1989a; Goodman et al., 1989b)	Total severity score	1	Mean: 19.96, SD: 6.94	Mean: 19.9, SD: 7.35	0.0077	1
	Total severity score - compulsions	1	Mean: 10.26, SD: 4.28	Mean: 10.33, SD: 4.28	0.0062	17
	Total severity score - obsessions	1	Mean: 9.95, SD: 3.83	Mean: 10.06, SD: 4.09	0.0054	47

The *Italic font* in the variable description indicates questions asked to the respondent. For some of these questions, minor adaptations have been made to the text reported in this table in order to improve their understandability.

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CHAPTER 6

GENERAL DISCUSSION

GENERAL DISCUSSION

In this thesis, we explored the role of affective symptoms in obsessive-compulsive disorder (OCD), focussing in particular on the relation between affective and obsessive-compulsive symptoms. Different presentations of affect, such as disgust, depressive symptoms and anxiety, were studied during an experimentally induced distress response as well as during the long-term course of OCD. After summarizing the main findings of the studies described in this thesis, I will reflect on the role of affective symptoms in OCD and the reciprocal relation between affective and obsessive-compulsive symptoms considering our results within the context of the broader literature.

Main findings per chapter

In **chapter 2**, we examined the role of disgust sensitivity during an experimentally induced distress response using symptom provocation and its relation to the OCD symptom dimension contamination/washing. Using fMRI with visual stimuli with fear-, OCD-specific and neutral content, we compared the brain response in OCD patients with symptoms of the contamination/washing dimension and OCD patients without contamination/washing symptoms, and investigated whether this response was related to a general sensitivity to react with disgust. OCD patients with contamination/washing symptoms reported a higher disgust sensitivity and in these patients disgust sensitivity correlated positively with the reported distress during symptom provocation. The brain response during symptom provocation was similar in OCD patients with and without contamination/washing symptoms. In OCD patients with the contamination/washing dimension this response was at least partially related to disgust sensitivity. Disgust sensitivity correlated in particular with activity in regions involved in emotion regulation (supplementary motor area, dorsomedial prefrontal cortex and the caudate nucleus), processing of an aversive internal state (operculum including the anterior insula) and visual attention and emotional intensity (visual association cortex). Our findings indicate that disgust sensitivity may form a modulating factor, which increases the probability of the occurrence of a distress response and the severity of it by affecting attentional processes and emotion regulation.

In **chapters 3, 4** and **5** we moved the focus from the distress response to the role of affective symptoms during the long-term course of OCD, using data from the Netherlands Obsessive Compulsive Disorder Association (NOCDA) study, a naturalistic prospective multi-center study, which followed 419 OCD patients for 6 years.

In **chapter 3** we described the relation between depressive and obsessive-compulsive symptoms in OCD patients during the natural follow-up of one year. Depressive symptoms were significantly associated with the severity of OCD symptoms one year later, but OCD symptoms were not associated with depressive symptoms one year later. This relation was observed in all patients irrespective of a comorbid major depressive disorder (MDD) and also in patients who were first diagnosed with OCD and developed MDD later in life. However, the association between depression and subsequent obsessive-compulsive symptoms was strongest in patients with MDD, especially when its onset preceded the onset of OCD. These results demonstrate that - in contrast to previous research (Tibi et al., 2017; Anholt et al., 2011) - obsessive-compulsive symptoms did not lead to (an increase in) depressive symptoms, but that depressive symptoms affected the course of OCD, even when the diagnostic criteria of a major depressive disorder were not met.

In **chapter 4** we investigated the role of anxiety during the long-term course of OCD using the data of the NOCDA study from 6 years of follow-up. At baseline, OCD patients with symptoms of the aggressive obsessions/checking and the contamination/washing dimension reported more anxiety than OCD patients without these symptoms. To describe the long-term relation between anxiety and obsessive-compulsive symptoms, we compared three models: 1) a cross-lagged model which assumed that anxiety and obsessive-compulsive symptoms are distinct groups of symptoms which interact directly during the course of OCD, 2) a stable traits model, which assumed that anxiety and obsessive-compulsive symptoms result from two distinct underlying latent factors, which are stable over the time, e.g., a chronic vulnerability to develop anxiety respectively obsessive-compulsive symptoms, and that these latent traits interact, and 3) a common factor model, which assumed that anxiety and obsessive-compulsive symptoms are presentations of a common latent factor. The common factor model fitted poorly and thus was rejected, while both the cross-lagged model and the stable traits model had a good model fit. Based on these results, we concluded that anxiety and obsessive-compulsive symptoms do not result from a shared underlying factor but are distinct concepts in OCD, which interact during the long-term course. However, our results also suggest that additional factors not included into the model play a role. Regarding the question whether the role of anxiety changes during the long-term course of OCD, our results were mixed. We found a cross-sectional correlation between anxiety and obsessive-compulsive symptoms of significant strength at each follow-up assessment, which did not change during the follow up. On the other hand, the cross-lagged model suggested a reciprocal positive association between anxiety and obsessive-compulsive symptoms during the early follow-up, while after four years of follow-up this relation changed into a negative relation between compulsions and anxiety.

The previous chapters showed the involvement of affect during the long-term course of OCD and may point towards a role of affect as a potential predictor. However, multiple factors play a role in the course of OCD (Sharma et Math, 2019) and predictions based on regression analyses of a single or few factors may oversimplify the complexity of OCD. A data-driven approach including several factors may overcome these limitations and facilitates reliable prediction of remission on individual level.

In **chapter 5**, we reported the development of a supervised machine learning algorithm to predict OCD remission after two years. We included predictors which can be easily assessed in the clinical routine, such as severity, onset and course of OCD, comorbid diagnoses, medication use, psychosocial functioning, and affective symptoms (e.g., depression and anxiety) among others. The ranking performance of the predictors included in the algorithm confirmed that various factors play a role in the prediction of remission of OCD, as OCD-related characteristics (e.g., Y-BOCS total score, chronic course) as well as medication use and social factors such as work and involvement in social activities. Affective symptoms were not among the ten most important predictors. The predictive performance of the algorithm was moderate, with a marked variation across different centers which assessed the data. Although this variation limited the generalizability and application of this algorithm, it also reflected the challenge of data-driven research to deal with the heterogeneity of OCD and variations between OCD patients regarding the various predictors, the varying prognosis and the complex relation between both.

The role of affective symptoms in OCD

Obsessive-compulsive symptoms often are accompanied by affective symptoms. They may manifest as a part of the acute distress response, elicited by obsessions and inducing or maintaining compulsions. But they may also occur beyond the acute distress response and affect or interact with the obsessive-compulsive symptoms during the course of OCD.

The intensity and severity as well as the affective expression (i.e., anxiety, disgust, “not just right experiences” (NJRE’s), depressive symptoms) varies widely between individuals with OCD.

A particular relation between distinct affective symptoms and the OCD symptom dimensions has been reported. Patients with symptoms of the contamination/washing dimension have a higher sensitivity to react with disgust to OCD-related stimuli (chapter 2). This is in line with previous research, which found that disgust was particularly related to the contamination/washing dimension (Brady et al., 2021; Fink-Lamotte et al., 2021; Olatunji

et al., 2019; Athey et al., 2015). We also found that OCD patients experiencing aggressive obsessions/checking symptoms and contamination/washing symptoms reported higher levels of anxiety in general (chapter 4). Previous research also reported an association between anxiety and the aggressive obsessions/checking dimension (Cervin et al., 2021; Hartmann et al., 2019; Sulkowski et al., 2008). Although the contamination/washing symptom dimension occasionally is referred to as contamination fear (Fink-Lamotte et al., 2021; Olatunji et al., 2004), anxiety has not previously reported to be associated with this symptom dimension (Sulkowski et al., 2008). NJRE's were observed in OCD patients with checking compulsions (Belloch et al., 2016; van Dis et van Hout, 2016) and symptoms of the symmetry/order dimension (Belloch et al., 2016; Coles et Ravid, 2016). Thus, the occurrence of affective symptoms in OCD can be regarded as a common characteristic of OCD, but the concrete presentation of the affective symptoms is associated with the distinct OCD symptom dimensions. However, OCD patients can experience more than one affective state in general as well as during the distress response (Starcevic et al., 2011), and thus anxiety, disgust and NJRE's are not exclusive for a distinct symptom dimension.

The distress response associated with the compulsive behavior may be regarded as an exaggerated "normal" affective reaction. In particular for the OCD dimension contamination/washing, it has been suggested that the distress response resembles an enhanced "normal" disgust reaction" (Bhikram et al., 2017; Brady et al., 2010). In chapter 2, the role of disgust sensitivity in relation to the distress response was investigated. OCD patients with symptoms of the contamination/washing dimension had a similar neural activation pattern during symptom provocation as OCD patients without these symptoms, while only in participants with contamination/washing symptoms the level of disgust sensitivity was associated with the neural as well as subjective distress response during provocation (chapter 2). These findings contradict the hypothesis of an exaggerated "normal" disgust response, because in that case we would expect a different (or at least partially different) neural response between disgust-related and disgust-unrelated distress during symptom provocation. Although a specific exaggerated affective reaction may not be the "core" of the distress response of a distinct subgroup of OCD patients, the sensitivity to react with specific affective symptoms may influence the subjective experience of it. Our results presented in chapter 2 show that the level of disgust sensitivity was associated with provocation induced activation of brain regions involved in attentional processes and emotion regulation. To our knowledge comparable studies addressing the sensitivity to react with other affective symptoms, such as anxiety, during the acute distress response are lacking. However, aberrant attentional processes (Levy, 2018; Hezel et McNally, 2016) and deficits in emotion regulation (Yap et al., 2018; Paul et al., 2016) have been reported in

OCD patients in general and suggested to play a role in its etiology. Thus, the sensitivity to react with a distinct affective state (e.g., disgust) may not only lead to the occurrence of this affective state in distressing situations but may also affect attentional and emotion regulating processes and may therefore lower the threshold to and the intensity of the distress response.

OCD patients also experience affective symptoms beyond the acute distress response. Often, these symptoms meet the classification criteria of comorbid diagnoses such as major depressive disorder or anxiety disorders (Sharma et al., 2021; Klein Hofmeijer-Sevink et al., 2013; Visnawath et al., 2012; Ruscio et al., 2010; Pinto et al., 2006). Other studies showed that almost all OCD patients reported at least mild depressive symptoms, while only one third to two third of them are diagnosed with depression (Klein Breteler et al., 2021). Also subclinical depressive symptoms and anxiety affect obsessive-compulsive symptoms and are in turn influenced by the obsessive-compulsive symptoms (chapter 3 and 4). In chapter 3, we demonstrated that depressive symptoms affect obsessive-compulsive symptoms even when the diagnostic criteria of a MDD were not met. Thus, instead of describing affective symptoms as present or absent, they can rather be assessed on a continuing scale of severity.

In chapter 4, we studied the long-term relation between anxiety and obsessive-compulsive symptoms in OCD and showed that both are distinct but interacting groups of symptoms. However, the results suggest that also additional factors play a role. These factors may represent other symptoms occurring in OCD, which may interact with both anxiety and obsessive-compulsive symptoms. This may be affective symptoms, such as depressive symptoms or NJRE‘s, or other OCD-related characteristics, such as habit forming (Gillan et al., 2016).

In conclusion, affective symptoms are common in OCD, and occur during as well as beyond the acute distress response related to obsessions and compulsions. The expression of the affect varies between individuals with OCD and is associated with the distinct symptom dimensions. Although affective symptoms are not the “core” of OCD, they are part of the experience of the distress and affect attentional and emotion regulating processes related to the acute distress response. Beyond the acute distress response, affective symptoms interact with obsessive-compulsive symptoms on the long-term, and - together with other factors - affect the obsessive-compulsive symptoms during the course of OCD.

The relation between affective and obsessive-compulsive symptoms in OCD

Affective symptoms and obsessive-compulsive symptoms often co-occur in OCD patients. In this thesis we investigated the long-term relation between both groups of symptoms, in particular the relation between obsessive-compulsive symptoms and depressive symptoms (chapter 3) and anxiety (chapter 4) during the course of OCD.

One theory regarding co-occuring symptoms is that they are distinct presentations of a shared underlying factor (Caspi et al., 2014). Barlow et al. developed a hierarchical model of anxiety and mood disorders with negative affect as a higher order factor to both groups of symptoms (Barlow, 2000). Others suggested that the co-occurence of anxiety, depressive and obsessive-compulsive symptoms may rather reflect the severity of the index disorder than a distinct comorbid diagnosis (Fontenelle et Yücel, 2019; Klein Hofmeijer-Sevink et al., 2018). In chapter 4 of this thesis, we investigated the relation between anxiety and obsessive-compulsive symptoms on the long term, and addressed the question whether these are distinct groups of symptoms. The common factor model, which assumed that both anxiety and obsessive-compulsive disorder shared a common latent factor, had a poor model fit and thus was rejected, while the cross-lagged model and the stable traits model, which both assumed that anxiety and obsessive-compulsive symptoms were distinct groups of symptoms, had a good model fit and thus were regarded as valid descriptions of this relation. These results contradict theories which suggest that anxiety and obsessive-compulsive symptoms are presentations of a common underlying vulnerability or etiology. Although using another methodology, a study investigating the relation between depressive and obsessive-compulsive symptoms concluded that also depressive and obsessive-compulsive symptoms are separate groups of symptoms. In addition, they partially contradicted the hypothesis of negative affect as a common underlying vulnerability (Moore et Howell, 2017).

Distinct groups of symptoms may affect each other cross-sectionally as well as longitudinally. Several studies addressed depressive symptoms or depressive disorder in OCD and mostly found an association with more severe obsessive-compulsive symptoms (Klein Breteler et al., 2021; Altintaş et Taşkintuna, 2018; Demal et al., 1996) and more impairment (Velloso et al., 2018; Storch et al., 2014). Previous research suggested that the depressive symptoms may occur as a consequence of the obsessive-compulsive symptoms. The severity of OCD, the chronicity, impairment and diminished quality of life may ”demoralize” OCD patients and lead to secondary depressive symptoms (Abramowitz et al., 2007; Milanfranchi et al., 1995). In a follow-up study after therapy, Anholt et al. found that the course of depressive symptoms in OCD was completely mediated by obsessive-compul-

sive symptoms while the course of obsessive-compulsive symptoms was only partially mediated by depressive symptoms. They concluded that obsessive-compulsive symptoms drive depressive symptoms but not vice versa (Anholt et al., 2011). However, based on the results of chapter 3, we concluded that depressive symptoms may not be secondary to obsessive-compulsive symptoms but may modulate or maintain obsessive-compulsive symptoms. Tibi et al. further investigated this subject using the same population as studied in chapter 3, the NOCDA participants but analyzed the follow-up after two and four years using structured question modeling with depressive and obsessive-compulsive symptoms as latent variables defined by different questionnaires. They concluded that the model in which obsessive-compulsive symptoms were associated with subsequent depressive symptoms was the preferred model (Tibi et al., 2017). The methodological differences may contribute to the differences in the results, but it is also possible that the effect of depression on obsessive-compulsive symptoms was of shorter duration and that the longer follow-up period of two years lead to different results.

Several publications addressed the immediate effect of anxiety on obsessions and compulsions. In addition, OCD patients reported to engage in compulsive behavior in response to more general anxiety which is not related to obsessions or other obsessive-compulsive symptoms (van Schalkwijk et al., 2016). However, studies which investigate the long-term relation between anxiety and obsessive-compulsive symptoms and its direction are lacking. In chapter 4, we described results on the interaction between anxiety and obsessive-compulsive symptoms in the NOCDA participants during a follow-up period of 6 years.

The stable traits model demonstrated that obsessive-compulsive symptoms and anxiety affect each other. According to this model, the relation between anxiety and obsessive-compulsive symptoms during the follow-up period was primarily characterized by an interaction between the respective latent traits, an anxiety trait and an obsessive-compulsive trait (chapter 4).

The cross-lagged model also showed that obsessive-compulsive symptoms and anxiety interact. It may even suggest an alteration in the long-term relation between anxiety and obsessive-compulsive symptoms, although the interpretation is limited by the broadly varying illness duration at baseline and by the fact that the strength of the regression was rather weak. However, results may cautiously point towards a reciprocal relation between anxiety and obsessive-compulsive symptoms during the early follow-up, where both groups of symptoms enhanced each other. After four years of follow-up, this relation seemed to "flip" and obsessive-compulsive symptoms and in particular the severity of compulsions

were associated with less subsequent anxiety. Probably, compulsions were performed in anticipation of anxiety which prevented its experience, or anxiety indeed had a minor role in chronic OCD. Reviews of neuroimaging studies suggest that the involvement of specific neural structures and networks may shift over time resulting in more habitual behavior (Stein et al., 2019). In addition, previous research demonstrated that in OCD patients persistence in habitual behavior was associated with a longer duration of illness (Chase et al., 2020).

However, the results of chapter 4 are not conclusive on an eventual changes in anxiety during the course of OCD. In contrast to the results of the cross-lagged model, the strength of the cross-sectional correlations between anxiety and obsessive-compulsive symptoms did not change during the follow-up assessments, which may suggest that anxiety remained an important feature of chronic OCD.

Chapter 3 and 4 investigated the long-term relation between obsessive-compulsive symptoms and respectively depressive symptoms and anxiety, but did not address the question whether depressive symptoms or anxiety can predict obsessive-compulsive symptoms. Several studies found evidence for a relation between affective symptoms (e.g., depressive symptoms, anxiety or comorbid affective disorders) and an unpreferable course of OCD (Sharma et al., 2021; Nakajima et al., 2018; Visser et al., 2014; Jacubovski et al., 2013; Ferrão et al., 2006). However, OCD is a multifactorial disorder and various predictors have been suggested, for example OCD-related characteristics such as the age of onset (Sharma et al., 2014), duration of OCD (Sharma et al., 2014), or severity of obsessive-compulsive symptoms (Sharma et al., 2014), but also comorbid disorders (Jacubovski et al., 2013), life events and psychotrauma (van Oudheusden et al., 2017), or low social functioning (Skoog et Skoog, 1999). Systematic reviews reveal inconclusive results and specific factors with superior prediction still are lacking (Hazari et al., 2016; Keeley et al., 2008; Knopp et al., 2013). In chapter 5, we developed a tool to predict OCD remission after 2 years. Multiple potential predictors were entered into a machine learning algorithm. The feature ranking of the algorithm confirmed that various predictors play a role in OCD, including anxiety and depressive symptoms, although they were not part of the ten most important features. However, with other machine learning techniques, the automatic feature retainment and feature ranking would be different and thus the feature importance cannot be generalized beyond this specific algorithm. Still, these results remind us that the course of OCD is predicted by a complex interplay of multiple factors, and that limitation to the investigation to only some of them forms a simplification of the nature of OCD.

In conclusion, affective symptoms, such as anxiety and depressive symptoms, and obsessive-compulsive symptoms are distinct groups of symptoms, which interact with each other during the long-term course of OCD. The relation between both groups of symptoms may change during the course of OCD.

Strengths and limitations

In this thesis, we addressed the research question from different points of view using diverse methodological approaches to investigate the relation between specific affective symptoms and obsessive-compulsive symptoms during symptom provocation as well as during the long-term course. Despite the advantages of the applied methods, some limitations have to be addressed.

We used data from a large, naturalistic prospective multi-center study which included 419 OCD patients and followed them for 6 years (chapter 3, 4 and 5). As expected due to the long duration of the study period, not all participants completed all assessments, which may have affected the results. However, still a large number of participants could be included into the statistical analyses. The design of the NOCDA study allowed for drop-out in the calculation of the number of participants (Schuurmans et al., 2012). In addition, the statistical methods used in the studies of the present thesis addressed this limitation, for example by using full information maximum likelihood estimation for data missing at random.

The design of a natural follow-up study allowed to study the natural course of different groups of symptoms and their interaction, which contributes to the high generalizability of the results. However, the group of participants was very heterogeneous and the period between the first onset of OCD and the inclusion into the NOCDA study varied widely between the participants, with a range of 0 to 64 years. This variation in the illness duration prior to the NOCDA assessments may have contributed to the inconclusive results on the question whether the role of anxiety changed during the long-term course of OCD.

Many participants had at least some kind of treatment during the 6 years of follow-up, varying from supportive contacts with caregivers to cognitive behavioral therapy or pharmacotherapy. Unfortunately, the treatment interventions during the study period were not systematically assessed, and therefor we cannot rule out that this may have confounded the results.

The follow-up assessments were accomplished with intervals of two years with in addition a limited assessment after the first year. This design allowed to study affective and obses-

sive-compulsive symptoms during the long-term course of OCD with an acceptable burden and assessment frequency for the participants. However, the questionnaires addressed only the obsessive-compulsive and affective symptoms during the last week. Episodic variations of obsessive-compulsive and affective symptoms during the two years interval were not assessed and thus shorter episodes of deterioration or improvement were not captured.

The relation between symptom dimensions and affective symptoms has been studied in chapter 2 and 4. Symptom dimensions were assessed at baseline using a validated categorial measure, the Y-BOCS symptom checklist. About 75% participants had symptoms of more than one symptom dimension and thus met more than one category. In fact, the co-occurrence of symptom dimensions is the rule rather than the exception in OCD patients and including only OCD patients with symptoms of one symptom dimension would limit the generalizability of the results. Thus, for these analyses, we divided the group of participants and compared OCD patients with and without symptoms of a distinct symptom dimension. A more sophisticated approach would have been a dimensional assessment with subsequent regression analyses, which may be subject to future studies.

Despite these limitations, also some strengths may be highlighted. The follow-up period in the longitudinal studies was exceptionally long and thus gives new insights in the course of OCD over the years. We used data from a naturalistic multi-center longitudinal study, which is exceptional regarding the large number of participants. The only exclusion criterion was insufficient knowledge of the Dutch language to perform the assessments. Thus, a representative and heterogenous group of OCD patients with varying severity and duration of OCD was included, which allows a generalization of our results to other treatment seeking OCD patients.

Suggestions for further research

In this thesis, we studied anxiety, disgust and depressive symptoms in the context of OCD. However, also other affective symptoms may play a role, such as NJRE's or positive emotions. About half of the OCD patients reported the experience of NJRE's (Starcevic et al., 2011). Validated measures to assess NJRE's have been developed and can be used to investigate their role in OCD in general and their relation to obsessive-compulsive symptoms (Melli et al., 2019; Coles et al., 2003). A cross-sectional relation between NJRE's and obsessive-compulsive symptoms has been found (Coles et Ravid, 2016), but to our knowledge, no studies have yet addressed this question longitudinally during the course of OCD. NJRE's are in particular related to the symmetry/order dimension and checking

behavior (Belloch et al., 2016; Coles et Ravid, 2016; van Dis et van den Hout, 2016). In these symptom dimensions, the sensitivity to experience NJRE's may be related to the acute distress response, as was disgust sensitivity in OCD patients with contamination/ washing symptoms (chapter 2). A replication of the study using a dimensional approach for the assessment of the symptom dimensions and including also measures of the sensitivity or propensity to react with other affective states, e.g., NJRE's or anxiety, would allow to make comparisons across symptom dimensions and to further investigate the probable modulating role of these vulnerabilities on the distress response.

Several studies address negative affective states, while research on the role of positive affect in OCD is limited. Positive affect has been described in OCD patients in anticipation of the compulsive act (Fontenelle et al., 2015), and the expectation of positive affect has been shown to be associated with the chronicity and severity of obsessive-compulsive symptoms (Ferreira et al., 2017). Thus, positive affect - or at least its expectation - may function as reward and have an enhancing or maintaining effect on compulsions. Another study found a negative correlation between the severity of OCD and positive affect in OCD patients (Landmann et al., 2020). OCD patients probably experience less positive affect, because they tend to dampen it and enjoy positive experiences less (Eisner et al., 2009). Positive affect has previously been linked to resilience in other mental disorders (Harpøth et al., 2021; Hoorelbeeke et al., 2019; Robinson et al., 2014). More research on positive affect and its possible effect on obsessive-compulsive symptoms may open the way to interventions, which can have a role in the treatment or prevention of OCD by increasing aspects as happiness, contentment or savoring. A recent study, which investigated positive affect and obsessive-compulsive symptoms after mindfulness-based therapy in OCD patients, found no additional effect of mindfullness in addition to cognitive behavioral therapy (Landmann et al., 2020), but a replication with an improved methodology (e.g., sufficient statistical power) may further elucidate this question.

In chapter 4, we studied the long-term relation between anxiety and obsessive-compulsive symptoms during six years of follow-up. The role of anxiety during the acute distress response and the potential functional relation between obsessions, anxiety and compulsions was not the subject of this thesis but may be addressed in future research. Many theoretical considerations are published on this issue and the learning theory is the fundament of exposure with response prevention, which is an effective treatment for OCD (Reid et al., 2021). Nevertheless, experimental or observational studies on this subject are rare, maybe due to methodological challenges. Assessment of obsessions, compulsions and affective states in the daily life at different moments during the day, for

example using experience sampling methods, overcomes limitations such as memory bias due to retrospective evaluation. In addition, momentary assessment captures short-term fluctuations of symptoms, in contrast to traditional questionnaires which measure symptoms equalized over a time-period of several days to weeks. With a short questionnaire applied several times per day during a period of a week, naturally occurring obsessive-compulsive and affective symptoms are registered and short-term relations between the symptoms can be investigated. However, the participation in a study using experience sampling methods can be challenging for OCD patients. Interruption of compulsive behavior to fill in the questionnaire may be difficult for some participants and the assessment itself can possibly trigger compulsive behavior. Nonetheless, several studies in varying groups of patients reported a good acceptability of experience sampling methods (e.g., Vachon et al., 2019; van Os et al., 2017) and previous studies in OCD patients using this method have proven its feasibility in this group (Landmann et al., 2020; Gloster et al., 2008).

The role of anxiety may decrease during the long-term course of OCD. Clinical observations report that OCD patients with very chronic and long-lasting symptoms seem to experience less anxiety but nevertheless continue to perform compulsions. The present thesis (chapter 4) could not clearly answer this question due to methodological limitations. To that end, it would be interesting to follow a cohort of OCD patients in the early stage of the disease and periodically assess anxiety, habit and obsessive-compulsive symptoms, both on the short-term in daily life as well as during the long-term course of the disease.

In the past years, the previously assumed central role of the affective distress response as the “motor” of OCD driving compulsive behavior has been challenged by the growing evidence of the role of habit in OCD. According to the habit-theory, an imbalance between goal-directed behavior and habit forming, in favor of the latter, leads to compulsivity (Gillan et al., 2016). On the first view, both approaches seem to exclude each other: whether compulsions are performed to diminish affective distress, e.g., anxiety, or they are performed habitually. However, the findings of several neuroimaging studies integrate both points of view by demonstrating the involvement of multiple parallel cortico-striatal-thalamo-cortico (CSTC) circuits associated with parallel processes such as habitual behavior, executive functions (e.g., response inhibition), reward learning, and emotional processing, including emotion regulation (Den Ouden et al., 2022; Shephard et al., 2021; Thorsen et al., 2018; van den Heuvel et al., 2016). Anxiety and habit may even interact or affect each other. Affective symptoms, such as negative affect, may enhance habit forming or diminish cognitive top-down control. Anxiety for example have been shown to affect executive control (Kalanthroff et al., 2015) and stress to enhance habit forming (Schwabe et Wolf, 2009).

Disruption of habitual behavior may on the other hand provoke anxiety. A simultaneous assessment of anxiety and habit and an investigation of their interaction, momentary as well as during the course of the disease, would lead to a better understanding of the nature of OCD and an integration of different etiological theories.

Clinical implications

This thesis demonstrated that depressive symptoms and anxiety affect obsessive-compulsive symptoms and play a role in the prognosis of OCD among other factors. They therefore should be routinely assessed in OCD patients. Treatment planning and evaluation in OCD often is based on OCD-specific assessment, e.g., the presentation and severity of obsessive-compulsive symptoms, as well as the presence or absence of comorbid diagnoses. However, the results of chapter 3 imply that depressive symptoms affect subsequent obsessive-compulsive symptoms even in the absence of MDD. Thus, treatment should not address diagnoses but symptoms. Obsessive-compulsive and affective symptoms share transdiagnostic characteristics, such as maladaptive beliefs (Miegel et al., 2019), repetitive thoughts (Wahl et al., 2019), avoidance or withdrawal behavior (Blakey et al., 2019) or impairment in emotion regulation (Sloan et al., 2017), which may provoke or maintain these symptoms. A treatment approach targeting shared characteristics may help to improve the mental health care for OCD patients.

The results of this thesis are in line with previous research which emphasize the heterogeneity of OCD (e.g., Shephard et al., 2021; Strom et al., 2021; Olatunji et al., 2017). The presentation of affective symptoms differs between symptom dimensions, as shown in chapter 2 and 4. Also the relation between affective symptoms and obsessive compulsive symptoms varies between individuals with OCD, depending on its presentation and probably course and duration of OCD. Previous research found evidence that the outcome of current treatment of OCD, i.e., therapy with exposure with response prevention, cognitive therapy and pharmacotherapy with serotonergic antidepressants, may vary between different groups of OCD patients (Thorsen et al., 2018; Hazari et al., 2016). A thorough assessment of OCD-related, but also other symptoms regarding emotion, cognition or behavior, may result in a personal symptom profile of the individual OCD patient, and may lead to a more individually-tailored and effective treatment.

Concluding remarks

Affective symptoms play a role in OCD, irrespective of eventual causality. Their occurrence and intensity differ between individuals with OCD and probably during the long-term course of the illness. Affective and obsessive-compulsive symptoms are distinct groups

of symptoms, which interact. Within the complex interplay of different factors involved in the etiology and maintenance of OCD, affective symptoms contribute to the occurrence and presentation of the acute distress response. During the long-term course, they affect the severity and course of the obsessive-compulsive symptoms. Although they are not a "core" mechanism in the etiology, they are of importance for the experience and prognosis of OCD.

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ADDENDUM

SUMMARY

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CURRICULUM VITAE

SUMMARY

The aim of this thesis was to investigate the role of affective symptoms and the relation between affective and obsessive-compulsive symptoms in OCD, during an experimentally provoked acute distress response, as well as during the long-term course of OCD.

Chapter 1 forms the introduction into the topic of the thesis. It gives an overview over the characteristics and etiology of OCD. Findings from the literature on affective symptoms occurring in OCD, such as anxiety, fear, disgust, "not just right experiences" and depressive symptoms, are reviewed. I discuss the role of affective symptoms in OCD and how they are related to obsessive-compulsive symptoms. This chapter finishes with an outline of the thesis.

In **chapter 2** the role of disgust during the acute distress response elicited by experimental symptom provocation is described. We investigated the relation between the sensitivity to react with disgust and the neural response to symptom provocation, and compared them between OCD patients with and without contamination/washing symptoms. During functional MRI scanning, participants were confronted with pictures, which may provoke fear- or obsessive-compulsive symptoms, as well as neutral pictures. The amount of distress per picture was assessed, and the brain activation was compared between pictures with high versus low reported distress. OCD patients with contamination/washing symptoms reported a higher disgust sensitivity, which correlated with the reported distress during symptom provocation. The neural activation did not differ between both groups of OCD patients. However, only in OCD patients with contamination/washing symptoms, the sensitivity to react with disgust was related to the neural activation in regions associated with emotional processing, attention and emotion regulation, and may thus affect the experience and occurrence of the distress response in this group of OCD patients.

Chapter 3 and **chapter 4** focus on the long-term relation between affective and obsessive-compulsive symptoms using the data from the NOCDA study, a longitudinal naturalistic cohort study which follows OCD patients for six years.

In **chapter 3**, we report results on a study addressing the relation between depressive and obsessive-compulsive symptoms during the follow-up of one year. Depressive symptoms were associated with subsequent obsessive-compulsive symptoms. Although the regression was strongest in OCD patients with a comorbid major depressive disorder, in particular when the onset of the depression preceded the onset of OCD, it was also

significant in OCD patients without the diagnosis of a major depressive disorder. This is in contrast with the assumption that depressive symptoms in OCD improve along with the obsessive-compulsive symptoms. Thus, we should assess depressive symptoms in OCD patients, even in the absence of a comorbid depressive disorder.

In **chapter 4**, we investigated the long-term relation between anxiety and obsessive-compulsive symptoms during a follow-up period of 6 years. To that aim, we compared three different models. The first model (cross-lagged model) assumed that anxiety and obsessive-compulsive symptoms are distinct groups of symptoms, which interact longitudinally during the follow-up period. The second model (stable traits model) supposed that anxiety and obsessive-compulsive symptoms are related to each other by two distinct underlying latent stable traits, an anxiety and an obsessive-compulsive trait, which determine the severity of anxiety and obsessive-compulsive symptoms at different points during the course of OCD. The third model (common factor model) hypothesized that anxiety and obsessive-compulsive symptoms both result from a common underlying latent factor, and that changes in this factor lead to changes in anxiety as well as obsessive-compulsive symptoms. The common factor model had a bad model fit and was rejected, while the cross-lagged model and the stable traits model had a good model fit. We concluded, that anxiety and obsessive-compulsive symptoms are distinct groups of symptoms which interact during the long-term course of OCD, either directly or by interactions of two respective underlying stable traits.

In this chapter we also aimed to investigate whether the strength of the relation between anxiety and obsessive-compulsive symptoms changes during the course of OCD. Unfortunately, our results were ambiguous due to methodological limitations. Future research with improved methods may further elucidate this question.

In **Chapter 5**, we report on the development of an algorithm to predict the remission of OCD after two years using supervised machine learning techniques. Various features were included in the algorithm, as for example the severity of obsessive-compulsive symptoms, anxiety and depression, but also comorbid diagnoses, pharmacotherapy, negative life events and trauma, and social factors such as marital status, work and social activities. The algorithm was trained and tested using the NOCDA-data from OCD patients from seven centers in the Netherlands. The predictive performance of the algorithm in the pooled data set was moderate, but when the algorithm was tested separately in the distinct centers of the NOCDA study, it varied widely. This variation may be due to specific drifts/shifts, which often are observed during the use of algorithms, and stresses the importance of a

thorough testing in different, independent populations before the algorithm safely can be applied. In addition, our results demonstrate the heterogeneity of OCD and that multiple varying factors are involved in the prediction of its course.

In **chapter 6**, I discuss the main findings of the thesis focusing on the role of affective symptoms in OCD and the relation between affective and obsessive-compulsive symptoms. I also address limitations and strengths of the studies, and give suggestions for further research and clinical implications.

In conclusion, affective symptoms play a role in OCD. Their presentation as well as the occurrence and intensity differ between individuals with OCD and may change during the course of the disease. With regard to the long-term relation, affective and obsessive-compulsive symptoms are best described as distinct groups of symptoms which interact. Affective symptoms affect obsessive-compulsive symptoms during the acute distress response as well as during the long-term course of OCD.

SAMENVATTING

In dit proefschrift staan de resultaten beschreven van het onderzoek naar de rol van affectieve symptomen bij mensen met een obsessieve-compulsieve stoornis, oftewel dwangstoornis. We hebben gekeken naar de relatie tussen affectieve en obsessieve-compulsieve symptomen, zowel tijdens acuut opgewekte spanning bij experimentele symptoomprovocatie, als ook op de lange termijn gedurende het beloop van de dwangstoornis.

Hoofdstuk 1 leidt het thema van dit proefschrift in. Het geeft een overzicht van de kenmerken van de dwangstoornis en vat de literatuur over affectieve symptomen bij een dwangstoornis, zoals angst, vrees, walging, het "gevoel, dat het niet klopt" en depressieve symptomen, samen. Er wordt ingegaan op de rol van affectieve symptomen bij mensen met een dwangstoornis en op de relatie tussen affectieve symptomen en dwangsymptomen. Dit hoofdstuk eindigt met een schets van de inhoud van dit proefschrift.

In **hoofdstuk 2** beschrijven we de rol van walging tijdens de acuut opgewekte spanning ten gevolge van een symptoomprovocatie taak. We focussen hierbij op de relatie tussen de individuele neiging om met walging te reageren op bepaalde situaties in het dagelijkse leven en de hersenactiviteit tijdens symptoomprovocatie, en het mogelijke verband tussen deze relatie en smetvrees. Tijdens de symptoomprovocatie werden de deelnemers, terwijl ze een functioneel MRI onderzoek ondergingen, geconfronteerd met foto's die dwangsymptomen of angst kunnen uitlokken, als ook met neutrale foto's, en gaven ze aan hoeveel spanning ze bij elke foto ervoeren. De hersenactiviteit werd vergeleken tussen foto's met een hoge versus een lage mate van ongemak. Tijdens dit experiment verschilde de hersenactiviteit van dwangpatiënten met en zonder smetvrees niet. Dwangpatiënten mét smetvrees gaven wel een hogere walgingsneiging aan, en deze correleerde met het ervaren ongemak tijdens symptoomprovocatie. De neiging om met walging te reageren was in deze groep gerelateerd aan de activatie van hersengebieden, die in verband gebracht worden met emotieverwerking, aandacht en emotieregulatie. Dit was niet het geval bij patiënten met een dwangstoornis, die geen smetvrees hadden. Mogelijk beïnvloedt de neiging om met walging te reageren via deze weg de ervaring en het optreden van spanning bij mensen met smetvrees.

In **hoofdstuk 3** en **hoofdstuk 4** onderzochten we de lange-termijn relatie tussen affectieve en obsessieve-compulsieve symptomen. Hierbij maakten we gebruik van data van de NOCDA-studie, een longitudinale naturalistische cohort studie, waarbij mensen, die een dwangstoornis hebben of hadden, zes jaar opgevolgd werden.

In **hoofdstuk 3** worden de resultaten gepresenteerd van een studie over de relatie tussen depressieve en obsessieve-compulsieve symptomen over een jaar van natuurlijk beloop. Depressieve symptomen aan het begin van de studie hielden verband met dwangsymptomen een jaar later, waarbij meer ernstige depressieve klachten gevolgd werden door meer ernstige dwangklachten, maar niet andersom. Hoewel deze relatie het sterkst was bij dwangpatiënten met een comorbide depressieve stoornis, vooral wanneer de depressieve stoornis als eerste optrad, was dit verband ook significant bij dwangpatiënten zonder een depressie. Dat spreekt tegen de aanname, dat depressieve klachten mee opklaren, wanneer de dwangklachten verminderen. Daarom adviseren we om bij mensen met een dwangstoornis aandacht te hebben voor depressieve klachten, ook wanneer er geen sprake is van een comorbide depressie.

Hoofdstuk 4 beschrijft een onderzoek naar de lange-termijn relatie tussen angst en obsessieve-compulsieve symptomen gedurende een periode van zes jaar. Daarvoor vergeleken we drie verschillende modellen. Het eerste model *(cross-lagged model)* gaat ervan uit, dat angst en dwangsymptomen twee aparte symptoomgroepen zijn, die elkaar gedurende het beloop beïnvloeden. Het tweede model *(stable traits model)* veronderstelt, dat angst en dwangsymptomen met elkaar interageren via twee onderliggende onveranderlijke kenmerken, een angst- en een obsessieve-compulsieve *trait*, die de ernst van de angst en dwangsymptomen op verschillende momenten tijdens het beloop beïnvloeden. Het derde model *(common factor model)* stelt, dat angst en obsessieve-compulsieve symptomen beide uit een gedeelde overkoepelende factor voortkomen, die de angst en dwangsymptomen gedurende het beloop bepaalt. Uit de statistische analyses van de modellen bleek, dat het *common factor model* niet passend was, terwijl zowel het cross-lagged model als ook het stable traits model een passende weergave zijn van de statistische lange-termijn samenhang tussen angst en obsessieve-compulsieve klachten. We concluderen daaruit, dat angst en dwangklachten twee verschillende symptoomgroepen zijn, die elkaar wederzijds beïnvloeden gedurende het lange-termijn beloop van de dwangstoornis, direct of middels een interactie tussen twee onderliggende stabiele *traits*.

Er werd tevens gepoogd om te onderzoeken of de sterkte van de relatie tussen angst en obsessieve-compulsieve symptomen verandert gedurende het lange-termijn beloop. Helaas waren de resultaten van deze analyses niet eenduidig, wat mogelijk een gevolg was van beperkingen van de gebruikte methodiek. Toekomstige onderzoeken met andere methodes zullen hierover hopelijk meer helderheid geven.

In **hoofdstuk 5** beschrijven we de ontwikkeling van een algoritme om de remissie van een dwangstoornis na twee jaar te voorspellen. Hierbij is gebruik gemaakt van de techniek "*supervised machine learning*". Een groot aantal verschillende factoren zijn opgenomen in het algoritme, bij voorbeeld de ernst van de obsessieve-compulsieve symptomen, angst en depressie, maar ook comorbide diagnoses, medicatiegebruik, negatieve ervaringen en trauma, en sociale factoren zoals burgerlijke staat en deelname aan werk en verenigingsleven. Voor de trainings- en testprocedures is gebruik gemaakt van de NOCDA-data, die in zeven verschillende behandelcentra in Nederland verzameld zijn. Het voorspellende vermogen van het algoritme was matig, wanneer alle centra samen genomen worden. Wanneer het algoritme echter apart in elk centrum getest werd, zagen we een grote variatie in het voorspellende vermogen. Dit kan een gevolg zijn van bepaalde processen (*drifts/ shifts*) die vaak optreden bij het gebruik van algoritmes, en maakt duidelijk, hoe belangrijk het is om een algoritme in meerdere, onafhankelijke populaties te testen alvorens hem toe te passen. Daarnaast onderstrepen de resultaten van deze studie, dat een grote hoeveelheid aan diverse factoren een rol speelt in het voorspellen van het beloop van de dwangstoornis, en dat deze individueel verschillen.

In **hoofdstuk 6** worden de belangrijkste bevindingen van het proefschrift besproken, waarbij de focus ligt op de rol van affectieve symptomen bij de dwangstoornis en de relatie tussen affectieve symptomen en obsessieve-compulsieve symptomen. Ook beperkingen en sterke punten van de studies worden genoemd en ideeën geopperd voor verder onderzoek en advies voor de klinische praktijk.

Samenvattend concluderen we, dat affectieve symptomen een rol spelen bij de dwangstoornis, waarbij de presentatie en vorm van het affect, maar ook het optreden en de intensiteit hiervan sterk individueel verschillen en mogelijk ook veranderen gedurende het beloop van deze ziekte. Affectieve symptomen en dwangsymptomen moeten beschouwd worden als twee aparte symptoomgroepen, die met elkaar interageren. Affectieve symptomen beïnvloeden obsessieve-compulsieve symptomen zowel tijdens het ervaren van acuut opgewekte spanning als ook gedurende het beloop van de dwangstoornis op de lange termijn.

IMPACT PARAGRAPH

Just graduated, I started as a young doctor at the Academic Anxiety Center in Maastricht, where I met patients with OCD. I was impressed by the impairment and burden of this disease, for the patients as well as for the people around them, and by the complex compulsive rituals, which they cannot stop, although they knew that the thoughts and worries which caused these behaviors were unreasonable and sometimes even bizar. What keeps them going on with the compulsive behavior? Anxiety and the reward of the rapid relief after compulsions, I learned from the behavioral therapists. I saw, how the severity of the symptoms and impairment due to the OCD diminished after treatment using exposure with response prevention, and I had little doubt that OCD was an anxiety disorder. However, the DSM-5 was in development and with it rose the discussion if OCD better fits within a new category of obsessive-compulsive and related disorders. Research stressed the importance of habits in compulsive behavior, and the focus seemed to change from the role of anxiety to the role of habitual behavior. What is the relevance of anxiety or affective symptoms in general within this approach to the etiology of OCD? Are they still of significance in the diagnosis and treatment of OCD? The wish to investigate these questions resulted in a PhD-trajectory and the aim of this thesis: What is the role of affective symptoms in OCD and how do they relate to obsessive-compulsive symptoms?

In this thesis, we demonstrate that affective symptoms have a role in OCD and that they affect obsessive-compulsive symptoms. We found that obsessive-compulsive symptoms and anxiety are distinct groups of symptoms, which can be considered as an argument for a specific obsessive-compulsive category. But does this categorization of psychiatric diagnoses really help to better understand the nature of the distinct disorders? In fact, many patients suffering from mental health problems experience several co-occuring symptoms, which often are diagnosed as comorbidities. In addition, most psychiatric symptoms, such as anxiety or depressive mood, are not exclusively associated with specific disorders but occur transdiagnostically. The borders between distinct diagnostic categories are not clear-cut but very diffuse. Although a structured overview and generally-shared definition is helpful in the clinical and scientific communication, clinicians and researchers should not forget that several factors not included in the diagnostic criteria play a role in the experience and course of psychiatric illness, as the results of this thesis demonstrate with regard to OCD.

Another risk of the concept of distinct categories of comorbid diagnoses is that symptoms not fulfilling the diagnostic criteria of a specific psychiatric illness may be ignored. Results

of this thesis demonstrate that even subclinical co-occuring depressive symptoms affect obsessive-compulsive symptoms. Thus, we recommend to routinely assess them and consider them in treatment planning. However, further research on treatment approaches addressing both groups of symptoms, e.g., by targeting transdiagnostic mechanisms, and their efficacy is needed.

The results of this thesis underline that OCD is a heterogeneous disorder. The presentation of the obsessive-compulsive symptoms as well as the affective symptoms varies between individuals with OCD, and the relation between affective and obsessive-compulsive symptoms differs between OCD patients depending on the symptom profile and probably also on the duration of OCD. This asks for a personalized treatment planning instead of a "one-size-fits-all" protocol. Such a personalized approach requires a thorough assessment of all aspects of affect, cognition and behavior, leading to a more holistic explanation of the mental problems and the relation of the distinct symptoms. When the patient and mental health care worker agree on such an individual theory of the mental problems, approaches for treatment can be chosen. During the training of medical students, future psychiatrists and other mental health care workers, I try to emphasize that such a diagnostic explanation is more important than the diagnostic classification.

The development of predictive algorithms, such as described in this thesis, may form a tool for individual treatment planning in the future. While the developed algorithm predicted the remission or persistence of OCD with moderate accuracy, future algorithms may help to differentiate between treatment options by predicting outcome of different treatments. However, as described in chapter 5, several methodological challenges still have to be solved before such an algorithm can be safely applied in clinical practice. In addition, there may be several ethical concerns that accompany the broad application of algorithms in mental health care. An algorithm may unjustly suggest high certainty of the prediction, which may lead to an over-reliance on the prognosis. We could also ask the question if predictions are always helpful. In particular negative outcome, such as the prognosis of chronicity or deterioration, may induce feelings of despair and demoralization and thus become a self-fulfilling prophecy. Maybe, sometimes it is better not to know. In addition, we do not know, how the inclusion of algorithms in the clinical practice affects decision making by the mental health care workers and patients. Whom to trust, the prediction of the algorithm or the experience of the doctor, especially when both oppose each other?

When reflecting on the results of this thesis, I remembered a conversation with a peer worker with OCD. He explained to me that according to his experience the focus on

reducing obsessive-compulsive symptoms is too restrictive and only partially effective, for the sole decrease of OCD symptoms leaves an emptiness, which has to be filled. Instead, the increase of positive feelings and experiences and meaningful and satisfying activities diminish the room for obsessive-compulsive symptoms and thus help to improve OCD. The feature ranking of the developed algorithm underlines the importance of such factors by acknowledging the involvement in organizations or sports club, working hours or a paid job as top-ten predictors.

Unfortunately, I have to admit that this thesis also focussed on negative factors and left out factors which may be related to resilience. Thus, I leave the investigation of this very relevant subject to future research.

DANKWOORD

Nu ik aan het echt allerlaatste hoofdstuk van mijn proefschrift begin, dringt het langzaam tot me door, dat - na zo veel jaren - het einde van dit mooie en soms ook moeizame traject in zicht is. Ik wil daarom graag een moment nemen voor terugblik en vooral ook dankbaarheid voor de weg, die ik mocht afleggen, en voor alle mensen, die me op deze weg begeleid hebben.

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CURRICULUM VITAE

Judith Rickelt was born on March 9, 1982 in Stralsund, Germany. She completed high school at the Gymnasium Grimmen in 2000. From 2000-2007 she studied medicine at the Ernst-Moritz-Arndt Universität Greifswald, Germany. During her study, she did an internship at the Academic Anxiety Center in Maastricht, later PsyQ Anxiety disorders, Mondriaan, where she started working after her graduation as Medical Doctor. In 2010 she started her training to become a psychiatrist and worked as a resident at Mondriaan in Heerlen and Maastricht, Orbis Medical Center in Sittard and GGzE in Eindhoven. Since 2013 she works as a psychiatrist at GGzE, Eindhoven, where she was granted to do research. She participated in a PhD-trajectory for a day a week, besides her clinical work at a forensic psychiatric clinic (De Woenselse Poort, 2013-2016) and since 2016 at Opsy, a treatment center for patients with psychiatric problems and intellectual disability.