The Emotional Brain in Obsessive-Compulsive Disorder

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Scientific environment

The work of this thesis has been carried out at the OCD-team at Haukeland University Hospital, Bergen, Norway; the Departments of Psychiatry and of Anatomy and Neurosciences at Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam Neuroscience, The Netherlands, and the Department of Clinical Psychology at the University of Bergen, Norway. My main supervisor has been professor Odile A. van den Heuvel, MD PhD (associated with the OCD-team in Bergen and Amsterdam UMC/Amsterdam Neuroscience in Amsterdam, The Netherlands), while professor Bjarne Hansen, PhD and professor Gerd Kvale, PhD (both affiliated with the Department of Clinical Psychology and the OCD-team) have been my co-supervisors. I have been enrolled at the International Graduate School in Integrated Neuroscience (IGSIN) at the University of Bergen during my PhD.

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Abstract

Background

Obsessive-compulsive disorder (OCD) is characterized by distressing obsessions and time-consuming compulsions. The disorder affects 1-3% and can be highly impairing to daily functioning and detrimental to the quality of life. Cognitive behavioral therapy is an effective treatment for 50-75% of people with OCD, leaving a considerable minority who do not benefit from the best available treatments we have today. Neuroimaging has related the disorder to the function and structure of cortico-striato-thalamo-cortical and fronto-limbic circuits. A better understanding of these circuits might contribute to a better understanding of the disorder, how current treatments change the brain, and how we can help non-responders with better treatments in the future. This is likely particularly true for fronto-limbic and affective circuits, given their role in the formation, maintenance, and extinction of fear as well as motivating behavior. The aim of this dissertation was, first, to investigate how OCD is related to brain activation during emotional processing of aversive stimuli. Secondly, we wanted to examine if unaffected siblings of OCD patients showed similar anxiety, brain activation, and connectivity during emotion provocation and regulation as their OCD-affected siblings compared to unrelated healthy controls. Lastly, we wanted to investigate if the resting-state network structure changes in OCD patients directly after the Bergen 4-Day Treatment (B4DT), a concentrated and exposure-based psychological therapy.

Methods

Paper I was a meta-analysis of 25 functional neuroimaging studies comparing OCD patients and healthy controls during emotion processing, when participants were exposed to aversive or neutral stimuli. In Paper II we used functional magnetic resonance imaging (fMRI) to investigate distress, brain activation, and fronto-limbic connectivity during emotion provocation and regulation of neutral, fear-related, and OCD-related stimuli in 43 unmedicated OCD patients, 19 unaffected siblings, and 38 healthy controls. In Paper III we used resting-state fMRI to study the network

structure of 28 OCD patients (21 unmedicated) and 19 healthy controls the day before and three days after B4DT. We examined static and dynamic graph metrics at the global, subnetwork, and regional levels, as well as between-subnetwork connectivity.

Results

In Paper I, we found that OCD patients showed more activation than healthy controls in the orbitofrontal cortex (OFC), extending into the subgenual anterior cingulate cortex (sgACC) and ventromedial prefrontal cortex (vmPFC), bilateral amygdala (extending into the right putamen), left inferior occipital cortex, and right middle temporal gyrus during aversive versus neutral stimuli. Meta-regressions showed that medication status and comorbidity moderated amygdala, occipital and ventromedial prefrontal cortex hyperactivation, while symptom severity moderated hyperactivation in medial frontal prefrontal and superior parietal regions. In Paper II we showed that unaffected siblings resembled healthy controls in task-related distress, less amygdala activation/altered timing than OCD patients during emotion provocation. During OCD-related emotion regulation siblings showed no significant difference in dmPFC activation versus either OCD patients or healthy controls, but showed more temporo-occipital activation and dmPFC-amygdala connectivity compared to healthy controls. In Paper III we found that unmedicated OCD patients showed more frontoparietal-limbic connectivity before treatment than healthy controls. This, along with sgACC flexibility, was reduced in OCD patients directly after B4DT.

Conclusions

OCD patients show hyperactivation of the amygdala and related structures, but this characteristic is not directly shared with unaffected siblings during provocation or regulation of emotional information. However, siblings seem to show compensatory activation and connectivity in other areas. The rapid changes in frontoparietal-limbic connectivity and subgenual ACC flexibility suggests that concentrated treatment leads to a more independent and stable network state. OCD is related to subtle alterations in limbic activation and fronto-limbic connectivity during both emotional

tasks and resting-state, which seems to vary with comorbidity and is sensitive to treatment.

Sammendrag

Bakgrunn

Tvangslidelse (obsessive-compulsive disorder, OCD) er definert som angstvekkende tvangstanker og tidkrevende tvangshandlinger. Lidelsen rammer omtrent 1-3% av befolkningen og kan være svært hemmende i daglig fungering og livskvalitet. Kognitiv atferdsterapi er en effektiv behandling for 50-70% av personer med OCD, mens en betydelig minoritet ikke opplever bedring av de beste behandlingene vi har i dag. Hjerneavbildning har relatert lidelsen til endret fungering og struktur i kortiko-striato-thalamo-kortikale og fronto-limbiske hjernebaner. En bedre forståelse av disse banene kan gi en bedre forståelse av lidelsen, hvordan behandling påvirker hjernen, og hvordan vi kan hjelpe dem som ikke responderer med mer skreddersydd behandling i fremtiden. Dette er antakeligvis særlig relevant for fronto-limbiske og affektive hjernebaner, gitt disses rolle i dannelsen, opprettholdelsen og ekstinksjon av frykt, så vel som å motivere atferd. Målet med denne avhandlingen var, for det første, å undersøke hvordan OCD er knyttet til hjerneaktivering under emosjonell prosessering av aversive stimuli. For det andre ville vi undersøke om friske søsken av OCD-pasienter viste liknende ubehag, hjerneaktivering og konnektivitet under emosjonsprovokasjon og -regulering som sine søsken med OCD, sammenlignet med friske kontrollpersoner uten OCD-pasienter i familien. Til slutt ville vi undersøke om hjernens funksjonelle nettverksstruktur under hvile endres hos OCD-pasienter umiddelbart etter Bergen 4-Day Treatment (B4DT), en konsentrert og eksponeringsbasert behandling.

Metode

Artikkel I var en meta-analyse av 25 funksjonelle hjerneavbildningsstudier som sammenlignet OCD-pasienter og friske kontrollpersoner under emosjonsprosessering, når deltakerne ble eksponert for aversive eller nøytrale stimuli. I Artikkel II brukte vi funksjonell magnetresonnanstomografi (fMRI) for å undersøke ubehag, hjerneaktivering og fronto-limbisk konnektivitet under emosjonsprovokasjon og regulering av nøytrale, frykt-relaterte og OCD-relaterte stimuli hos 43 umedisinerte

OCD-pasienter, 19 friske søsken og 38 friske kontrollpersoner. Artikkel III brukte vi fMRI for å undersøke den funksjonelle nettverksstrukturen til 28 OCD-pasienter (21 umedisinerte) og 19 friske kontrollpersoner dagen før og tre dager etter B4DT. Vi undersøkte statiske og dynamiske grafeteoretiske beregninger på globalt, subnettverk og regionalt nivå, i tillegg til å undersøke koblingene mellom subnettverk.

Resultater

I Artikkel I fant vi at OCD-pasienter viste mer aktivering enn friske kontrollpersoner i orbitofrontal korteks (OFC), som strakk seg inn i subgenual anterior cingulate korteks (sgACC) og ventromedial prefrontal korteks (vmPFC), bilateral amygdala (som også strakk seg inn i høyre putamen), venstre inferior occipital korteks, og høyre medial temporal gyrus under aversive versus nøytrale stimuli. Meta-regresjoner viste at medisinbruk og komorbiditet modererte hyperaktiviteten i amygdala, occipital og ventromedial prefrontal korteks, mens symptomtrykk modererte hyperaktivering i mediale frontale og øvre parietale regioner. I Artikkel II viste vi at friske søsken lignet på friske kontrollpersoner i oppgaverelatert stress, lavere amygdalaaktivering/endret timing sammenlignet med OCD-pasienter under emosjonprovokasjon. Under OCD-relatert emosjonsregulering viste søsken ingen signifikante forskjeller i dmPFC-aktivering fra verken OCD-pasienter eller friske kontrollpersoner, men viste mer temporo-occipital aktivering og dmPFC-amygdala-konnektivitet enn friske kontrollpersoner. I Artikkel III fant vi at umedisinerte OCD-pasienter viste mer frontoparietal-limbisk konnektivitet før behandling enn friske kontrollpersoner. Dette ble, i tillegg til fleksibilitet i sgACC, redusert hos pasienter umiddelbart etter B4DT.

Konklusjoner

OCD-pasienter viser hyperaktivering i amygdala og tilknyttede strukturer, men dette kjennetegnet deles ikke med friske søsken under provokasjon eller regulering av emosjonelle stimuli. Søsken ser imidlertid ut til å vise kompensatorisk aktivering og konnektivitet i andre områder. De raske endringene i frontoparietal-limbisk konnektivitet og fleksibilitet i subgenual ACC foreslår at konsentrert behandling fører

til en mer uavhengig og stabil nettverkstilstand. OCD er knyttet til subtile endringer i limbisk aktivering og fronto-limbisk konnektivitet under både emosjonelle oppgaver og under hvile, og dette ser ut til både å variere med komorbiditet og være følsomt for behandling.

Abbreviations

ACC	Anterior cingulate cortex
B4DT	Bergen 4-Day Treatment
CBT	Cognitive behavioral therapy
CSTC	Cortico-striato-thalamo-cortical circuits
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
ERP	Exposure and response prevention
fMRI	Functional magnetic resonance imaging
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
PET	Positron emission tomography
SCID	Structured Clinical Interview
SSRI	Selective serotonin reuptake inhibitors
vmPFC	Ventromedial prefrontal cortex
Y-BOCS	Yale Brown Obsessive Compulsive Scale

List of publications

Thorsen, A. L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., & van den Heuvel, O. A. (2018). Emotional processing in obsessive-compulsive disorder: A systematic review and meta-analysis of 25 functional neuroimaging studies. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3(6),* 563-571. doi:10.1016/j.bpsc.2018.01.009

Thorsen, A. L., de Wit, S. J., de Vries, F. E., Cath, D. C., Veltman, D. J., van der Werf, Y. D., Mataix-Cols, D., Hansen, B., Kvale, G., & van den Heuvel, O. A. (2019). Emotion regulation in obsessive-compulsive disorder, unaffected siblings, and unrelated healthy control participants. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 4(4)*, 352-360. doi:10.1016/j.bpsc.2018.03.007

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Kong, X. et al. (in press). Mapping cortical and subcortical asymmetry in obsessive compulsive disorder: Findings from the ENIGMA consortium. *Biological Psychiatry*. doi:10.1016/j.biopsych.2019.04.022

Contents

1. Introduction

1.1 Obsessive-compulsive disorder

1.1.1 Diagnostic criteria, insight and functional impairment

Obsessive-compulsive disorder (OCD) is defined by the following diagnostic criteria: to experience either obsessions, compulsions or both. Obsessions are defined as recurrent and persistent thoughts, urges or impulses that are experienced as intrusive and anxiety provoking. Examples of obsessions are thoughts of being contaminated or catching a disease, being afraid of causing harm to others or oneself, an urge for symmetry to reduce the chance of a catastrophe. Compulsions are defined as repetitive mental or physical behaviors that are performed to prevent or neutralize obsessions or reduce anxiety. Compulsions are often not realistically linked to preventing the feared outcome of obsessions or are clearly excessive (American Psychiatric Association, 2013; Stein et al., 2016; World Health Organization, 1992). Symptoms must be time consuming (minimum one hour per day) or cause significant distress and impairment in personal, work or other aspects of daily life. Furthermore, these symptoms cannot be better explained by drugs or medication use, or other physical or mental conditions (American Psychiatric Association, 2013; Stein et al., 2016; World Health Organization, 1992).

Most patients with OCD realize that their obsessions are unrealistic or exaggerated and that their compulsions are excessive, at least when they are calm and outside of situations that trigger their fears (Foa et al., 1995). Approximately 15-30% have poor or absent insight, and these patients may show higher symptom severity, more functional impairment, and worse treatment outcomes (Alonso et al., 2008; Jakubovski et al., 2011; Visser et al., 2017). However, even patients with good insight often struggle with disregarding obsessions or stopping compulsions once triggered, and insight can increase during treatment (Alonso et al., 2008; Visser et al., 2015). This suggests that insight might be a dynamic state rather than a fixed trait, and is likely influenced by factors such as the present situation, comorbidity, and if

the patient has received adequate treatment (Alonso et al., 2008; Jakubovski et al., 2011; Visser et al., 2017; Visser et al., 2015).

OCD is often highly disabling in family, social, work life and overall quality of life (Huppert, Simpson, Nissenson, Liebowitz, & Foa, 2009). Results from Swedish national registries suggest that OCD patients have 17 times higher risk of receiving disability pension and three times higher risk of up to three months sickness absence after adjusting for factors such as socioeconomic status and somatic problems (Perez-Vigil, Mittendorfer-Rutz, Helgesson, Fernandez de la Cruz, & Mataix-Cols, 2018). There are likely many pathways to disability in OCD, including symptoms interfering directly with work and personal life, reduced cognitive capacity, worse educational attainment, and more fatigue (Markarian et al., 2010). The negative impact of OCD also extends to family members, who also show worse quality of life (Cicek, Cicek, Kayhan, Uguz, & Kaya, 2013). Importantly, disability and quality of life often improve after effective treatment (Diefenbach, Abramowitz, Norberg, & Tolin, 2007; Hollander, Stein, Fineberg, Marteau, & Legault, 2010), which shows how treatment can be not only immensely important for the individual, but also their relatives and the society they live in.

1.1.2 Symptom dimensions and subtypes

The content of the obsessions and compulsions can vary widely from one person to the next (Mataix-Cols, Rosario-Campos, & Leckman, 2005; Thorsen, Kvale, Hansen, & van den Heuvel, 2018). The heterogeneity of OCD symptoms may complicate accurate differential diagnosis and make it more difficult to investigate the genetic, cognitive, and neural correlates of the disorder. A common approach to reduce this heterogeneity is to categorize symptoms using the Yale Brown Obsessive Compulsive Scale (Y-BOCS) Symptom Checklist, which is a standardized list of 58 different obsessive and compulsive symptoms (Goodman et al., 1989). Other options are to use interviews or questionnaires that specifically ask about different symptoms, such as the dimensional Y-BOCS (DY-BOCS, Rosario-Campos et al., 2006) or the Obsessive Compulsive Inventory (OCI-R, Foa et al., 2002).

Factor analyses have suggested that OCD symptoms can be reduced into approximately four dimensions: contamination and washing, symmetry and ordering, sexual, religious and aggressive symptoms, and hoarding and saving (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008; Mataix-Cols et al., 2005). Hoarding has since been classified as a separate disorder since these symptoms are more separate than other symptom clusters, often more ego-syntonic, and they tend to show worse treatment response (American Psychiatric Association, 2013; Mataix-Cols et al., 2010). The symptom dimensions are relatively stable over time and complete shifts are rare (Fullana et al., 2009; Mataix-Cols et al., 2002). A debate in the literature has been if different symptoms should be regarded as distinct subtypes (where patients are placed into the best fitting category) or co-occurring dimensions (where patients score higher or lower on several axes (McKay et al., 2004)). A dimensional model has been suggested to more accurately reflect the disorder since patients often report several kinds of symptoms, but not necessarily with the same severity (Mataix-Cols et al., 2005). Symptom dimensions have been related to individual differences in dysfunctional beliefs and cognitive biases (Brakoulias et al., 2014; Wheaton, Abramowitz, Berman, Riemann, & Hale, 2010), neuropsychological performance (Hashimoto et al., 2011; Leopold & Backenstrass, 2015), and vulnerability to genetic and environmental risk factors (Iervolino, Rijsdijk, Cherkas, Fullana, & Mataix-Cols, 2011; van Grootheest, Boomsma, Hettema, & Kendler, 2008). However, studies into symptom dimensions are often limited by inconsistent definitions and findings, and little research has investigated the mechanisms underlying different symptom presentations (Thorsen, Kvale, et al., 2018) .

1.1.3 Prevalence, onset, course and comorbidity

The prevalence of OCD was estimated to be around 1-3% in the National Comorbidity Survey Replication study of a representative US sample (Ruscio, Stein, Chiu, & Kessler, 2010), and Norwegian studies of populations from Oslo and Sogn og Fjordane have found a somewhat smaller prevalence of around 1% (Kringlen, Torgersen, & Cramer, 2001, 2006). It should be noted that there are several challenges with setting an accurate OCD diagnosis in both epidemiological studies

and clinical practice. Patients may underreport symptoms due to shame and stigma related to their symptoms, such as being afraid of being a pedophile or hurting others (Bruce, Ching, & Williams, 2018; Simonds & Thorpe, 2003) and delay or avoid seeking help (Torres et al., 2006). Patients with low insight or egosyntonic OCD often do not perceive their symptoms as exaggerated or excessive, but as external problems (Belloch, Del Valle, Morillo, Carrio, & Cabedo, 2009). There is also some overlap in diagnostic criteria with other disorders, such as bodily checking in hypochondriasis and worrying in GAD, which may require careful differential diagnosis (Leckman et al., 2010).

The mean age of OCD onset in the United States was approximately 19.5 years, and males tend to develop the disorder earlier than females, and in patients with a lifetime OCD diagnosis approximately 80% of males and 60% females had already developed their first symptoms by the age of 25 (Ruscio et al., 2010). Evidence from a Dutch study of 377 adult OCD patients suggests that early onset is correlated with higher symptom severity (Anholt et al., 2014). Naturalistic longitudinal studies show that OCD is often a chronic disorder, and only a minority appear to recover naturally over time (Marcks, Weisberg, Dyck, & Keller, 2011; Skoog & Skoog, 1999; Visser, van Oppen, van Megen, Eikelenboom, & van Balkom, 2014). However, these studies often do not measure if patients received treatment and whether the treatment was of high quality or not.

Patients with OCD often have other disorders as well, though OCD is often the developed first (Ruscio et al., 2010). More comorbid disorders have also been related to early onset of OCD (Ruscio et al., 2010). The National Comorbidity Survey Replication study estimated that approximately 75% have a comorbid anxiety disorder, 63% have a comorbid mood disorder, and 56% have a comorbid oppositional-defiant or attention-deficit/hyperactivity disorder. Considerable comorbidity is also reported in international clinical studies (Brakoulias et al., 2017; Hofmeijer-Sevink et al., 2013), though it is difficult to directly compare rates between studies due to methodological differences. OCD patients and their family members also show elevated prevalence of obsessive-compulsive spectrum and other

disorders, such as BDD, Tourette and tic disorder, and trichotillomania (Bienvenu et al., 2012; Phillips et al., 2010).

1.1.4 Risk factors for developing OCD

OCD is more common in some families than others, which may suggest both genetic and environmental risk factors (Pauls, Abramovitch, Rauch, & Geller, 2014). Twin and population-based studies suggest that it is a partly heritable disorder, where genetic factors account for approximately 50% of the risk for developing the disorder (Mataix-Cols et al., 2013; Pauls, 2010; van Grootheest, Cath, Beekman, & Boomsma, 2005), where genetic factors may account for more risk in early onset cases (Davis et al., 2013). Family studies have found that the risk of developing OCD increases with being more closely related, with the highest risk seen in parents, siblings and direct children of someone with OCD. This risk steadily decreases as the amount of shared genetic variance decreases, as seen in half siblings, uncles and aunts, or nephews and nieces (Mataix-Cols et al., 2013). Potential environmental risk factors for OCD include pre- and perinatal events (birth weight, delivery, smoke exposure during pregnancy). A recent systematic review suggested that stressful or traumatic life experiences have also been linked to a higher risk of having OCD (Brander, Rydell, et al., 2016). There have been largely inconsistent findings for other factors, such as socioeconomic status, parental rearing style, birth seasons and order, infections, and household crowding (Brander, Perez-Vigil, Larsson, & Mataix-Cols, 2016). Many studies of genetic and environmental risk factors share important limitations, such as few replications, potential recall biases for childhood factors, and inconsistent measures across studies (Brander, Perez-Vigil, et al., 2016).

Current genetic studies have not found any markers that are significantly related to having OCD at the whole genome level (Mattheisen et al., 2015; Stewart et al., 2013), but promising findings have been found in polymorphisms related to glutamate and serotonin transmission (International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS), 2018; Taylor, 2013). The lack of clear group-level genetic risk factors likely reflect that OCD is a multifactorial and heterogenous disorder and that

very large sample sizes with more precise phenotyping is needed to uncover genetic effects (Burton et al., 2018; Katerberg et al., 2010).

The risk for developing OCD is partly heritable, but how it is transmitted within families is not well understood (Mataix-Cols et al., 2013). One method for finding familial risk factors is to compare OCD patients, their unaffected family members, and unrelated people who don't have the disorder. This could reveal heritable aspects where OCD patients and their family members are similar to each other but different from unrelated people, which is called an endophenotype (Gottesman & Gould, 2003). Criteria for a formal endophenotype also requires that it is related to the disorder in the population, heritable, present even if the person recovers from the disorder, and stronger in afflicted persons within families (Gottesman & Gould, 2003). Robust endophenotypes could be useful to discover mechanisms for familial risk of developing a disorder, and more precisely guide genetic and neuroimaging studies. OCD patients and their relatives have been compared across a variety of metrics (Taylor, 2012). Some studies have found partial endophenotypes in dysfunctional beliefs and cognitive biases, such as beliefs about responsibility for hindering dangers and overestimating situations as threatening (Albert et al., 2015; Rector, Cassin, Richter, & Burroughs, 2009). OCD patients and their relatives also show shared worse performance during tasks requiring cognitive flexibility or response inhibition relative to healthy controls (Chamberlain et al., 2007; Rajender et al., 2011). These factors may explain some of the familial risk for developing OCD, but are likely not sufficient to understand why some family members develop OCD and others do not, which could indicate resiliency to mental disorders. Later sections will describe how potential endophenotypes have been investigated using neuroimaging.

1.2 Evidence-based treatments for OCD

1.2.1 Psychological and pharmacological treatments

Treatment guidelines recommend cognitive behavioral therapy (CBT) (including exposure and response prevention (ERP)) as the first-line treatment for OCD

(National Institute for Health and Care Excellence, 2015). Meta-analyses suggesting that approximately 50% recover after treatment (Öst, Havnen, Hansen, & Kvale, 2015; Skapinakis et al., 2016). Therapist-directed CBT/ERP has been shown to be effective when provided to individuals, in groups, over telephone or the internet, and when delivered weekly and intensively (Öst et al., 2015; Patel et al., 2018; Vogel et al., 2014; Wootton, 2016). Dropout rates are often around 15-20% (Ong, Clyde, Bluett, Levin, & Twohig, 2016; Öst et al., 2015). Effectiveness studies also show that ERP is effective when provided in real-life clinical practice (Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000; Hans & Hiller, 2013; B. Hansen, Kvale, Hagen, Havnen, & Ost, 2018; Kvale et al., 2018). Lastly, various forms of CBT (including ERP, cognitive therapy and metacognitive therapy) all seem to be effective and contain overlapping elements of psychoeducation, exposure, cognitive restructuring, and stopping compulsions and avoidance behaviors (Papageorgiou et al., 2018).

Selective serotonin reuptake inhibitors (SSRI) are the other recommended first-line treatment for OCD (National Institute for Health and Care Excellence, 2015). A recent meta-analysis found that SSRIs lead to a mean improvement of 3.5 points on the Y-BOCS relative to placebo, with no significant differences between different types of SSRIs (Skapinakis et al., 2016). High quality studies and meta-analyses comparing ERP and SSRIs have shown that ERP is more effective, has fewer side effects, and less dropout than SSRIs treatment alone (Öst et al., 2015; Skapinakis et al., 2016). ERP has also been shown to be superior to augmenting SSRIs with risperidone (an antipsychotic medication which is commonly used to augment pharmacotherapy for patients not responding to SSRIs alone, McLean et al., 2015; Simpson et al., 2013).

There is an international shortage of therapists with adequate experience and competency in ERP (McKay, 2018; Shafran et al., 2009). Furthermore, many therapists often report that they don’t have enough time to implement proper therapist-directed exposure sessions in clinical practice, that they are afraid to treat patients with ERP due to concerns of inducing high anxiety levels, or that arousal reduction strategies are needed to manage anxiety during exposure (Deacon et al.,

2013; Pittig, Kotter, & Hoyer, 2019). ERP is therefore often not provided at all or provided sub-optimally in clinical practice. Considerable effort is needed to provide therapists with adequate training and supervision, make sure that they provide high quality treatment, and that results in clinical practice are systematically evaluated (Kvale & Hansen, 2014; Waller & Turner, 2016).

After effective treatments have been developed, an important goal is to improve outcomes and reduce drop-out through personalized treatment (Schneider, Arch, & Wolitzky-Taylor, 2015). Both CBT/ERP and pharmacotherapy in clinical practice already involves some tailoring to the individual, for example by identifying individual triggers, compulsions, and exposure tasks, or by adjusting drug dosages throughout treatment for adequate symptom reduction and tolerable side-effects, but there are not an evidence-based procedures for systematically tailoring using individual patient characteristics (Hirschtritt, Bloch, & Mathews, 2017). A prerequisite for better personalization is uncover factors explaining individual variation in treatment attrition and outcome. There is a wealth of studies aimed at identifying such pre-treatment using demographic, clinical or biological factors. These include age, gender, symptom severity, comorbidity, medication use, cognitive biases (Steketee, Siev, Yovel, Lit, & Wilhelm, 2018), symptom dimensions (Thorsen, Kvale, et al., 2018; Williams et al., 2014), functional and structural neuroimaging (Fullana & Simpson, 2016), and genetic variants (Qin et al., 2016). However, none of these factors have been adequately replicated as predictors of treatment response (Knopp, Knowles, Bee, Lovell, & Bower, 2013; Schneider et al., 2015).

The most consistent predictor of outcome after CBT/ERP seem to be patient compliance, or how much the patient invests in therapy, follows its principles, and stops engaging in compulsions or anxiety reduction both during and between therapy sessions (Abramowitz, Franklin, Zoellner, & DiBernardo, 2002; De Araujo, Ito, & Marks, 1996; Tolin, Maltby, Diefenbach, Hannan, & Worhunsky, 2004; Wheaton, Galfalvy, et al., 2016). The task dimension of working alliance, which is how much the patient and therapist agree on what they should do in therapy, may be a possible mediator of the relationship between compliance and outcome (Hagen et al., 2016;

Wheaton, Huppert, Foa, & Simpson, 2016). Lastly, more willingness to experience anxiety, obsessions and bodily sensations have also been related to more and faster symptom reduction during ERP (Reid et al., 2017).

1.2.2 Bergen 4-Day Treatment

The Bergen 4-Day Treatment (B4DT) is a concentrated format for ERP which has been developed by Gerd Kvale and Bjarne Hansen at the OCD-team at Haukeland University Hospital in Bergen, Norway. It includes separate stages of psychoeducation and treatment planning, ca. 16 hours of ERP, and relapse prevention. The difference is that these stages are concentrated into four consecutive days, where patients vary between individual treatment with at least one certified therapist per patients and being together with both therapists and other patients in a group setting. B4DT also includes three weeks of self-exposure, where patients both perform planned ERP exercises and practice translating the treatment principles into their daily lives.

B4DT was developed for patients with severe OCD who are entitled to public mental health, and patients are not excluded based on comorbidity or severity of the disorders. Patients who are ordinarily not offered B4DT include those with another disorder that required priority (such as schizophrenia spectrum disorder), or has severe suicidal ideation, ongoing substance abuse, too low Body Mass Index (BMI) to start treatment for OCD, ERP treatment is not offered until these issues are dealt with. Also, patients with mental retardation, are typically not offered the B4DT.

The initial results as well as systematic replications of adult OCD patients found that approximately 90% of patients responded one week after treatment, where approximately 75% were classified as recovered using the Y-BOCS (Havnen, Hansen, Öst, & Kvale, 2017; Havnen, Hansen, Öst, & Kvale, 2014). Similar results have also been shown and replicated for adolescent patients (Riise, Kvale, Öst, Skjold, & Hansen, 2018; Riise et al., 2016). These improvements were durable after three months, six months, one year, and three to four years of follow-up, with no significant changes between the post-treatment and follow-up time points (B. Hansen,

Hagen, Ost, Solem, & Kvale, 2018; B. Hansen, Kvale, et al., 2018; Havnen et al., 2017; Havnen et al., 2014). Significant improvements were also seen for comorbid symptoms of depressive and anxiety, quality of life, and ability to work and function in daily life (B. Hansen, Hagen, et al., 2018; Havnen et al., 2017; Havnen et al., 2014). The effective transportability of B4DT has also been shown in new clinics in both Norway and Iceland (Davíðsdóttir et al., 2019; Kvale et al., 2018; Launes et al., 2019), and clinics in Sweden and the US are currently being trained to deliver the treatment.

1.3 Neurobiology of OCD

1.3.1 A brief history of functional neuroimaging in OCD

Before the advent of functional neuroimaging, OCD was primarily studied using neuropsychological, electrophysiological, psychosurgical methods, and lesion case reports (Khanna, 1988; Turner, Beidel, & Nathan, 1985). Already in the 1980's, a hypothesis was that OCD was related to the function of orbitofrontal and limbic structures (Khanna, 1988; Turner et al., 1985). OCD was among the first mental disorders to receive focus from functional neuroimaging when Baxter et al. (1987) used positron emission tomography (PET) to study which parts of the brain used most glucose (and were thus most active) in OCD patients during resting conditions. They found that these patients showed higher metabolism of glucose in the right orbitofrontal cortex (OFC) and bilateral caudate nucleus than healthy controls. The same group of researchers were also the first to show that treatment could change the brain, and found reduced glucose metabolism in the right caudate nucleus after behavioral therapy and fluoxetine for 18 OCD patients (Baxter et al., 1992). The effect of behavioral therapy was replicated in a later study with nine additional patients (Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996). These and other early studies emphasized the role of cortico-striato-thalamo-cortical (CSTC) circuits, which are involved in many sensorimotor, cognitive and emotional processes (Alexander, DeLong, & Strick, 1986; Draganski et al., 2008; LeDoux & Pine, 2016). The CSTC circuits involve excitatory glutaminergic and inhibitory GABAergic pathways that

bridge together cortical areas, such as the OFC and ACC, with the basal ganglia (striatum, putamen, globus pallidus, substantia nigra, subthalamic nucleus) and the thalamus. These connections form loops and allow for integrated information processing. An early central hypothesis was that OCD patients show an imbalance between excitatory direct pathways and inhibitory indirect CSTC pathways, resulting in a positive feedback loop and a self-reinforcing cycle of obsessions and compulsions (Graybiel & Rauch, 2000). An explosion of studies using structural and functional neuroimaging led to the gradual development of newer models with more complex relationship between different brain circuits. Mataix-Cols and van den Heuvel (2006) conceptualized OCD as an imbalance between a hyperactive ventral circuit for emotional processing and motivation and a hypoactive dorsal circuit for cognitive control. Here, obsessions were thought to be related to less cognitive control and effective emotion regulation, in combination with more emotional reactivity to threatening stimuli. This model was later expanded as subsequent research found that 1) cognitive and emotional functions recruit not only dorsal or ventral circuits; 2) OCD patients showed widespread abnormal function and structure, including parietal, visual, cerebellar regions (Menzies, Chamberlain, et al., 2008); and 3) OCD patients show aberrant communication between brain circuits (Harrison et al., 2009). This, along with a renewed focus on the role of fear processing and conditioning, lead Milad and Rauch (2012) to suggest the involvement of affective, dorsal cognitive and ventral cognitive circuits in OCD.

In recent years, OCD has been extensively investigated using a variety of neuroimaging methods, including magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) for gray and white matter volumes and integrity (Boedhoe et al., 2018; Boedhoe et al., 2017; de Wit et al., 2014; Norman et al., 2016; Radua et al., 2014), magnetic resonance spectroscopy (MRS) for neurotransmitter metabolites (S. Fan et al., 2017; Tadayonnejad et al., 2018; Whiteside, Port, Deacon, & Abramowitz, 2006; Yucel et al., 2007), resting-state fMRI for connectivity between brain regions (de Vries et al., 2017; Gursel, Avram, Sorg, Brandl, & Koch, 2018; Harrison et al., 2013), and a range of cognitive and emotional paradigms during functional MRI or

PET (Chamberlain et al., 2008; de Vries et al., 2014; de Wit et al., 2012; de Wit et al., 2015; Milad et al., 2013; Norman et al., 2019; Vaghi et al., 2017; O. A. van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005). These studies made it clear that a sole focus on the core CSTC regions was insufficient for describing the pathophysiology of OCD.

In an effort to integrate both classical and recent findings in OCD, a contemporary model was recently proposed by O. A. van den Heuvel et al. (2016). This model suggested that OCD can be related to abnormalities in affective, dorsal and ventral cognitive, sensorimotor, and fronto-limbic circuits (Table 1). The affective circuit is thought to be involved in the emotional response to triggering stimuli, reward processing, and motivating compulsive and avoidance behaviors. This is related to hyperactivation in the ventromedial prefrontal cortex (vmPFC), subgenual ACC (sgACC), nucleus accumbens and thalamus, as well the amygdala and hippocampal complex (O. A. van den Heuvel et al., 2016; O. A. van den Heuvel, Veltman, Groenewegen, Witter, et al., 2005). This is further supported by a fronto-limbic circuit which is involved during emotional conditioning and extinction, and encompasses the vmPFC along with the amygdala and hippocampal complex (Apergis-Schoute et al., 2017; Milad et al., 2013). The ventral cognitive circuit governs flexible behavioral preparation and execution, for example by starting and stopping in response to stimuli. This recruits the inferior frontal gyrus (IFG), anterior putamen, and pre-supplementary motor area (pre-SMA) (de Wit et al., 2012; Marsh et al., 2014; van Velzen, Vriend, de Wit, & van den Heuvel, 2014). The dorsal cognitive circuit is related to top-down control during cognitive tasks, such as planning and working memory. This recruits areas such as the dorsolateral prefrontal cortex (dlPFC) and caudate nucleus (de Vries et al., 2014; Heinzel et al., 2018; O. A. van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005). Lastly, the sensorimotor circuit is recruited during execution of well learned behaviors, such as habitual actions. This relies on the premotor cortex and posterior putamen (Gillan et al., 2015).

Table 1 *Affected brain circuits in OCD*

Circuit	**Function(s)**	**Core areas**	**Task(s)**	**Clinical relevance**
Fronto-limbic	Fear conditioning and extinction	vmPFC, amygdala, hippocampus	Symptom provocation and fear conditioning	Conditioning and extinction of feared stimuli
Affective	Goal-directed motivational learning	OFC, nucleus accumbens, amygdala	Reward tasks and symptom provocation	Exaggerated emotional and behavioral response to triggering stimuli, interference during cognitive tasks
Ventral cognitive	Motor preparation, response inhibition	IFG, anterior putamen, parietal cortex	Stop signal task, Go-no go	Cognitive control over compulsive behavior
Dorsal cognitive	Planning, working memory, emotion regulation	dlPFC, dmPFC, caudate nucleus, parietal cortex	Tower of London, N-back, emotion regulation	Dysfunction in executive function
Sensorimotor	Motor execution, stimulus-response learning	Premotor cortex, posterior putamen	Habit formation, motor sequencing	Habitual use of compulsions and avoidance

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1.3.2 Functional connectome during resting-state

The brain is not only a set of distinct regions, but has complex connections that carry information across regions and circuits. These connections are often referred to as the connectome of the brain (Bassett & Sporns, 2017; Bullmore & Sporns, 2009). Studies mapping the connectome has seen an immense growth in the last two decades, and large-scale projects have shown the intrinsic organization of the brain (Seeley et al., 2007; Yeo et al., 2011). This research has revealed some subnetworks that are activated during cognitive or emotional processes and others that are activated during wakeful rest, where resting-state fMRI can be used to measure the intrinsic organization of both (Fox et al., 2005; Hugdahl, Raichle, Mitra, & Specht, 2015). Based on fMRI of 1,000 healthy participants during resting-state, Yeo et al. (2011) categorized seven visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal and default-mode subnetworks, which were separable into 17 subnetworks at an even finer scale. These subnetworks likely serve specific roles: the frontoparietal subnetwork is activated during executive tasks (Dosenbach et al., 2007; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015). The default-mode subnetwork supports self-referential and emotional processes (Raichle, 2015). The dorsal and ventral attention subnetworks are recruited when noticing, interpreting and allocating cognitive resources to a stimulus, where the ventral attention is especially active in the early detection of unexpected and arousing stimuli (Vossel, Geng, & Fink, 2014; Vuilleumier, 2005). The limbic subnetwork is involved in emotional processing and contributes to emotionally guided decision making, such as approach and avoidance behavior (LeDoux & Pine, 2016; Pessoa, 2017). The somatomotor subnetwork is recruited during the execution of motor actions, and relies on the premotor cortex, posterior insula, and basal ganglia (Choi, Yeo, & Buckner, 2012; Draganski et al., 2008; Yeo et al., 2011). Lastly, the visual subnetwork is recruited during perceptual tasks (Wandell, Dumoulin, & Brewer, 2007), and its activation is also modulated by emotional and cognitive demands (Pessoa & Adolphs, 2010; Vuilleumier, 2005).

It should be noted that the resting-state subnetworks reported by Yeo et al. (2011) reflect the organization of the brain in healthy adults, while the model of CSTC and

fronto-limbic circuits by O. A. van den Heuvel et al. (2016) describe the altered subnetworks in OCD and not a general framework of brain organization. For clarification, the attention and frontoparietal subnetworks in Yeo et al. (2011) are closely aligned to the respective ventral cognitive and dorsal circuits in O. A. van den Heuvel et al. (2016), while the limbic subnetwork in Yeo et al. (2011) partly corresponds with the limbic and affective circuits in O. A. van den Heuvel et al. (2016).

An important contribution to characterizing the connectome was the application of graph theory, which uses mathematical models to study relations between interconnected objects (Bullmore & Sporns, 2009). Graph theory allows for investigating the topology of a network through defining nodes (e.g. brain regions or neurons) and connecting edges (e.g. structural or functional connections between brain regions). Many graph theoretical measures have been developed. For example for assessing how efficiently a network is organized, defining important hubs, and for finding local neighborhoods whose nodes are tightly interconnected (Rubinov & Sporns, 2010). Recently, dynamic graph measures have also been developed, which allow for a better understanding of how brain networks evolve and change according to external or internal demands (Avena-Koenigsberger, Misic, & Sporns, 2017). Dynamic measures have also been used to detect distinctive mental states and the circuitry involved in switches between them (Allen et al., 2014).

The connectome develops and changes across the lifespan, showing remarkable plasticity in both structural and functional connections (Collin & van den Heuvel, 2013; Kaiser, 2017). In early childhood this is characterized by massive developments of connections, followed by a period of pruning and formation of more efficient connections and hub regions (Collin & van den Heuvel, 2013). During adolescence and puberty, the connectome becomes more individualized and distinctive, similar to a fingerprint. Girls are earlier to develop a distinctive connectome, while boys catch up around the age of 16 (Kaufmann et al., 2017). Kaufmann et al. (2017) also found that having more symptoms of depression, attention deficit disorder or schizophrenia was related to a slower development of

distinctiveness, which was also evident in the default mode, motor, and frontoparietal subnetworks. This supports adolescence as an important period of brain development, where slower maturation is related to mental health problems across diagnostic categories. In adulthood the brain is typically organized so that information can both efficiently reach across the brain through key hub regions as well as be processed in locally segregated clusters (Collin & van den Heuvel, 2013). In late adulthood and old age the connectome becomes less efficient (Cao et al., 2014), accompanied by loss of gray matter volume and integrity of white matter tracts (Douaud et al., 2014; Westlye et al., 2010). This recent body of work has provided a better understanding of how brain networks develop. It is now important to understand how developing and recovering from OCD is related to the brain through various developmental stages. This could also help in disentangling the causes and consequences of OCD, and guide treatment development in early-onset cases.

Resting-state connectivity and graph theoretical measures may help relate connectome abnormalities to OCD and other mental disorders (Braun et al., 2018; Menon, 2011). OCD patients have been reported to show both stronger and weaker connections within the default-mode subnetwork (Beucke et al., 2014; J. Fan, M. Zhong, J. Gan, et al., 2017; Hou et al., 2013; E. R. Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). This may reflect the impact of emotional processing and vigilance on self-referential processing, supported by greater connectivity with the limbic and ventral attention networks (Beucke et al., 2014; de Vries et al., 2017; J. Fan, M. Zhong, J. Gan, et al., 2017; Hou et al., 2013; E. R. Stern et al., 2012). Abnormal connectivity with the limbic and ventral attention subnetwork has also been found for the executive frontoparietal subnetwork (Gursel et al., 2018). Recent studies have further found that the global efficiency, or how economically brain regions are connected, seems to be lower in OCD patients than healthy controls (Jung et al., 2017; D. J. Shin et al., 2014; Z. Zhang, Telesford, Giusti, Lim, & Bassett, 2016). OCD patients may also have less differentiated subnetworks (functional modules), suggesting more cross-talk between them (Gottlich, Kramer, Kordon, Hohagen, & Zurowski, 2014; D. J. Shin et al., 2014). Both stronger and weaker connections between neighboring nodes (clustering coefficient) in CSTC circuits has also been

reported, which may suggest that the aberrant activation in these structures is also influenced by their connections with each other (Beucke et al., 2013; Hou et al., 2014; Jung et al., 2017; Moreira et al., 2017). These findings suggest that the neurobiology of OCD is not limited to single regions or circuits, but is related to how circuits communicate with each other.

1.3.3 Emotions, cognition, and their interaction

The hallmark of OCD is the loop between experiencing intrusive obsessions, getting anxious, and trying to manage the anxiety through compulsive rituals, which maintains a self-reinforcing cycle (American Psychiatric Association, 2013). Much research has tried to probe what happens in the brain when patients experience obsessions and become anxious. The most relevant and common paradigm in task-based fMRI or PET studies is symptom provocation through visual stimuli, for example by showing aversive (e.g. a dirty toilet) and neutral (e.g. a forest) pictures, and comparing the levels of distress, brain activation, or psychophysiological correlates of the two conditions. Early on, such studies often found more activation in the OFC and ACC, among other areas, during emotional provocation relative to healthy controls (Adler et al., 2000; Breiter et al., 1996; Nakao et al., 2005). The amygdala is often a key region looked for in such studies due to its theoretical importance in the detection of salient stimuli, fear processing, and behavioral motivation (Etkin & Wager, 2007). However, though some found more activation in the amygdala in OCD patients compared to controls (Breiter et al., 1996; O. A. van den Heuvel et al., 2004), others found less amygdala activation in patients (Cannistraro et al., 2004). This was also reflected in a meta-analysis of emotion provocation studies, which did not find abnormal amygdala activation, but instead greater activation in the OFC, ACC, dlPFC, precuneus, and left superior temporal gyrus in OCD compared to healthy controls (Rotge et al., 2008). This lead some authors to suggest that “fear/anxiety-related brain regions … do not appear to mediate the core OCD symptomatology” (L. M. Shin & Liberzon, 2010, p. 180). This was further considered in the debate on whether OCD should continue to be grouped among anxiety disorders in the DSM-5 or if it should be classified together with obsessive-compulsive and related disorders (Stein et al., 2010).

Less research has focused on the initiation of compulsive or avoidance behavior directly. A novel exception was done by Banca et al. (2015) in 15 OCD patients and 15 healthy controls, using live streamed video of therapists disorganizing patients home or touched the patient with a dirty item during scanning. The patients could stop the provocation at any time, which allowed for modeling the buildup and release of activation related to avoidance and presumably compulsive behavior. The results showed that patients showed a gradual increase right in the seconds before stopping the provocation, a peak during stopping, and a gradual decrease in the seconds afterwards. This suggests that the putamen is involved in the regulation of avoidance and compulsive behavior, shedding some light on the functional role of its altered activation and structure in OCD patients (Banca et al., 2015).

The search for which regions are activated during emotion provocation in OCD, and what this meant for how to understand the disorder, is limited by several factors. Symptom dimensions may be differentially related to brain activation, which could obscure group differences between heterogenous patients and healthy controls (Mataix-Cols et al., 2004). SSRIs have substantial effects on amygdala recruitment, even in low doses in healthy controls (Outhred et al., 2013). Finally, the idiosyncratic nature of OCD may make it difficult to find personalized and aversive enough stimuli that can be used in an MRI scanner (Baioui, Pilgramm, Merz, et al., 2013; Simon, Kaufmann, Musch, Kischkel, & Kathmann, 2010).

Recent research has investigated the role of emotion regulation in OCD (de Wit et al., 2015), which involves changing emotional responses through processes such as shifting attention, changing the meaning of an event through cognitive reappraisal, or suppressing the expression of an emotion (Ochsner, Silvers, & Buhle, 2012). Some emotion regulation strategies are more automatic (e.g. holding one's breath or avoiding looking at distressing stimuli), while others require substantial effortful control (e.g. deliberately exposing oneself to a stimulus while willfully refraining from compulsive rituals) (Ochsner et al., 2012). The use of reappraisal strategies are often found to be linked to better outcomes in terms of well-being, more positive emotions, and less negative emotions in comparison to suppression or attention

shifting strategies (John & Gross, 2004). Emotion regulation recruits a widespread frontoparietal subnetwork, including the pre-SMA, dACC, dorsomedial prefrontal cortex (dmPFC), dlPFC, IFG and middle temporal gyrus and parietal lobule/supramarginal gyrus, and downregulates amygdala activation (Buhle et al., 2014; Frank et al., 2014). Cognitive reappraisal has been found to most consistently recruit the entire network, while distancing and suppression strategies are more limited to the parietal lobule/supramarginal cortex (Morawetz, Bode, Derntl, & Heekeren, 2017; Ochsner et al., 2012).

Difficulties with emotion regulation, and less successful use of cognitive reappraisal, has been associated with more mental health problems across diagnostic categories (Aldao, Nolen-Hoeksema, & Schweizer, 2010). The use of cognitive reappraisal may also be a transdiagnostic marker of treatment response, as the use of cognitive reappraisal seems to improve after treatment for anxiety, mood, substance abuse, and personality disorders (Sloan et al., 2017). In OCD patients and selected student samples, more use of suppression has been related to both more distress caused by obsessions and higher symptom severity (Goldberg et al., 2016; Najmi, Riemann, & Wegner, 2009), whereas more use of cognitive reappraisal strategies has been related to lower symptom severity (Goldberg et al., 2016). OCD symptom severity has also been linked to more fear of both negative and positive emotions (Fernandez de la Cruz et al., 2013; M. R. Stern, Nota, Heimberg, Holaway, & Coles, 2014). This is line with the cognitive-behavioral model of OCD, which posits that the disorder is maintained by attempts to take control over or ruminate over thoughts and emotions, rather than treating them as normal, non-threatening mental events (Foa & McLean, 2016). Some studies have suggested that symptom dimensions have specific correlates with emotion regulation strategies (Berman, Shaw, & Wilhelm, 2018; Smith, Wetterneck, Hart, Short, & Björgvinsson, 2012), while others have found similar relations across symptom presentations (Fergus & Bardeen, 2014).

The first fMRI study of emotion regulation in OCD used an emotion regulation task where fear-related, OCD-related and neutral stimuli were presented and participants were asked to either passively view them or actively downregulate their emotions

using cognitive reappraisal (de Wit et al., 2015). The study included 43 OCD patients and 38 healthy controls. During symptom provocation OCD patients showed more distress during the appraisal of fear and OCD-related stimuli, as well as greater activation and altered shape of the BOLD response in the amygdala compared to healthy controls. During emotion regulation, patients showed less activation in the left dlPFC and parietal cortex for fear-related regulation and more activation in the dmPFC during OCD-related regulation. OCD patients also showed less dmPFC-amygdala connectivity during emotion regulation. These findings suggest that OCD patients show altered recruitment of emotion regulation related regions, as well as less cognitive control over limbic circuitry (de Wit et al., 2015). Interestingly, symptom severity was negatively related to recruitment of the dmPFC during OCD-related, which could suggest that more dmPFC recruitment is a compensatory factor (de Wit et al., 2015).

Meta-analyses have shown that OCD patients show small to moderate deficits in general executive function, response inhibition, working memory, planning, and reversal learning (Abramovitch, Abramowitz, & Mittelman, 2013; Snyder, Kaiser, Warren, & Heller, 2015). This is also reflected in altered activation of the dorsal cognitive circuit during planning, response inhibition and working memory, as well as hyperactivation of premotor cortex during response inhibition (de Vries et al., 2014; de Wit et al., 2012; Norman et al., 2016; O. A. van den Heuvel, Veltman, Groenewegen, Cath, et al., 2005). The difference between OCD patients and controls are also often larger in more difficult task conditions (de Vries et al., 2014; Heinzel et al., 2018; Vaghi et al., 2017). However, some authors argue that neuropsychological impairment is not a primary cause or maintaining factor in OCD (Abramovitch, Mittelman, Tankersley, Abramowitz, & Schweiger, 2015; Snyder et al., 2015). For one, the difference in neuropsychological performance between OCD patients and healthy controls are smaller than what is typically characterized as clinically relevant, and many OCD patients don't show performance outside the norm (Abramovitch et al., 2015). Neuropsychological studies in OCD have also been criticized for methodological limitations in representative recruitment, group matching, and insufficient focus on the contribution of different patient characteristics (such as

medication, symptom dimensions, disease onset and duration, and comorbidity, Abramovitch et al., 2015). Furthermore, some studies have found increases in cognitive performance after treatment (Bolton, Raven, Madronal-Luque, & Marks, 2000; Katrin Kuelz et al., 2006), but these findings are inconsistent (Bannon, Gonsalvez, Croft, & Boyce, 2006; Vandborg et al., 2012).

Abramovitch, Dar, Hermesh, and Schweiger (2012) proposed that worse neuropsychological performance in OCD is explained by the "executive overload model", where worse task performance is an epiphenomenon of obsessions and anxiety, and not a primary neuropsychological deficit. A recent study also suggested that OCD patients may perform worse due stereotype threat. This suggests that internalized negative beliefs about performing worse due to their disorder may actually lead to worse task performance by itself (Moritz, Spirandelli, Happach, Lion, & Berna, 2018). Neuroimaging studies provide some support for the "executive overload model", as worse task performance has been related to more state distress and amygdala activation during planning in both OCD, panic disorder, and hypochondriasis (O. A. van den Heuvel et al., 2011). Further support comes from fMRI studies of task-related functional connectivity, where OCD patients show abnormal coupling between the amygdala and dorsal or ventral cognitive circuits, particularly in patients with the worst task performance (de Vries et al., 2014; Heinzel et al., 2018; van Velzen et al., 2015). Together, these lines of research suggest that there are many factors influencing cognitive performance in OCD, and that longitudinal studies are needed to uncover the relation between state and trait-related factors.

The partly heritable nature of OCD has motivated researchers to investigate if brain function and structure could account for the familial risk of developing OCD, and perhaps even guide future genetic studies (Gottesman & Gould, 2003). This led to findings that both OCD patients and their family members are similar to each other and different from unrelated healthy controls in the neural correlates of multiple cognitive functions. For example, both OCD patients and their siblings show altered activation relative to unrelated healthy controls in frontoparietal areas during reversal

learning (Chamberlain et al., 2008), working memory (de Vries et al., 2014), response inhibition (de Wit et al., 2012), planning (Vaghi et al., 2017), as well as more error-related negativity during response inhibition (Riesel, Endrass, Kaufmann, & Kathmann, 2011). Shared abnormalities have also been found in the volume and thickness of several brain regions (Menzies, Williams, et al., 2008; Shaw et al., 2015). Despite this considerable interest there are several outstanding issues before declaring any findings as reliable endophenotypes. There is limited evidence that these abnormalities are driven by genetic and not environmental influences, are present even if the patient recovers from OCD, and that they are causally related to developing OCD. Finally, it is unknown which abnormalities represent deficits and which abnormalities represent compensatory mechanisms. Further research is therefore needed to help understand why unaffected family members show similar brain structure, activation and connectivity as OCD patients, but without having any symptoms or reduced cognitive capacity. Indeed, one study suggest that altered activation during working memory is compensatory as both siblings and the OCD patients who performed the task most efficiently showed the most abnormal activation relative to healthy controls (de Vries et al., 2014).

1.3.4 Treatment effects on the brain

As treatments can have dramatic treatment effects on symptom severity in OCD, they could also be used to investigate how the brain changes when patients recover from the disorder. Treatment studies are therefore important in better understanding how OCD is related to the brain. In addition, combining treatment and neuroimaging can potentially reveal more about how effective treatments work, or better understand why some patients respond quickly while others don't benefit from treatment. Finally, it could also disentangle which aspects are stable risk or compensatory factors, and which are more state-related markers of current OCD symptoms.

As previously mentioned, Baxter et al. (1992) was the first to show that psychological treatment was associated with reduced and normalized resting-state regional glucose metabolism in 18 OCD patients. Current studies using CBT/ERP have since used various imaging modalities, including structural and functional MRI, as well as MRS,

PET and electroencephalogram EEG (systematically reviewed by Brooks & Stein, 2015; Thorsen et al., 2015). Investigators have assessed treatment effects during resting-state (e.g. Feusner et al., 2015; Moody et al., 2017; Saxena et al., 2009), cognitive (e.g. Freyer et al., 2011; Nakao et al., 2005), and emotional conditions (e.g. Baioui, Pilgramm, Kagerer, et al., 2013; Morgieve et al., 2014). These studies vary across many dimensions, such as the efficacy of the treatment, targeted brain processes or regions, and length of treatment/follow-up period.

Studies using emotional provocation paradigms have most consistently reported reduced ACC, OFC, and caudate activation after treatment (Baioui, Pilgramm, Kagerer, et al., 2013; Morgieve et al., 2014; Schiepek et al., 2013). There are also findings of reduced occipital, hippocampal, thalamic and insula activation during symptom provocation or Stroop tasks (Nabeyama et al., 2008; Nakao et al., 2005; Schiepek et al., 2013). In one of the largest and most comprehensive studies, Morgieve et al. (2014) measured activation to both standard and individualized symptom provocation paradigms at four time points; before, during, and after treatment, as well as six months after treatment. They reported a gradual decrease in symptom severity during treatment and stable improvement between the end of therapy and follow-up. Using a region-of-interest approach, they found a significant decrease in dACC and left OFC activation during personalized symptom provocation. This study also indicated that changes in the brain correlate with symptom improvement, which supports an earlier finding from a small study that the largest changes in the brain were found following therapy sessions with the most clinical change (Schiepek et al., 2013). Morgieve et al. (2014) also saw a large decrease in activation between the end of therapy and six-month follow-up. Together, these findings suggest that changes in the brain track the patients progress in therapy (indicative of direct or short-term treatment effects), but also that some changes in the brain can happen after a period of normalized behavior (indicative of long-term recovery).

Studies of executive function have reported increases in dlPFC, parietal cortex and cerebellar activation during Stroop task after treatment in adult patients (Nabeyama et

al., 2008; Nakao et al., 2005). Decreased ACC, OFC, putamen and hippocampal activation have also been found during Stroop and reversal learning tasks (Freyer et al., 2011; Nabeyama et al., 2008; Nakao et al., 2005). Increases in dlPFC, ACC and parietal areas have been reported in studies of pediatric patients using Flanker and planning tasks after CBT/ERP (Huyser, Veltman, Wolters, de Haan, & Boer, 2010, 2011). Treatment studies have not used functional neuroimaging to investigate other relevant tasks, such as classical fear conditioning, extinction learning, emotional Stroop, or working memory tasks. Other tasks, such as planning, has only been used in pediatric and not adult samples after treatment. There are very few studies on structural changes after treatment for OCD. Hoexter et al. (2012) investigated regional brain volumes using T1-weighted voxel-based morphometry in 26 adult OCD patients, of which half were randomized to CBT/ERP and the other half to fluoxetine, as well as 36 healthy controls. They found smaller volumes in the left putamen, OFC and left ACC in patients before treatment, and a small increase in left putamen volume after treatment in patients treated with fluoxetine. Recently, Zhong et al. (2019) performed the first CBT/ERP treatment study using DTI in 56 patients. They found increased fractional anisotropy in orbitofrontal, inferior frontal, temporal pole, and cerebellar regions, as well as decreased anisotropy in the right putamen after treatment.

The few treatment studies using SSRI in OCD have used resting-state (D. J. Shin et al., 2014), symptom provocation (Hendler et al., 2003), and motor tasks (Lazaro et al., 2008) using PET, fMRI, and single-photon emission computed tomography, as well as structural neuroimaging (reviewed by Quide, Witteveen, El-Hage, Veltman, & Olff, 2012). Some studies have reported decreased caudate nucleus metabolism after SSRI (Baxter et al., 1992; E. S. Hansen, Hasselbalch, Law, & Bolwig, 2002). Other studies, using MRI, have reported decreased amygdala and temporal volumes in adolescent patients (Gilbert et al., 2000; Szeszko et al., 2004). A recent crossover study using intravenous citalopram during symptom provocation in eight OCD patients and eight healthy controls found that citalopram resulted in less OFC activation, which correlated with reductions in state anxiety (Bhikram et al., 2016). There are no large-scale studies comparing if CBT/ERP and SSRIs (the most

commonly used treatments for OCD) differ in their effects on the brain, and the few available studies are underpowered to reliably detect moderate or small differences between treatments (Apostolova et al., 2010; Baxter et al., 1992; Hoexter et al., 2012; Nakao et al., 2005).

Pre-treatment neuroimaging characteristics in patients have also been used to predict treatment efficacy with some success (reviewed by Fullana & Simpson, 2016; Thorsen, Kvale, et al., 2018). For instance, Olatunji et al. (2014) reported that more pre-treatment amygdala activation and less dlPFC activation (among other regions) during symptom provocation was related to a better outcome after exposure therapy in 12 patients. Structural data from 74 patients further suggested that a thinner left ACC was related to better outcome (Fullana et al., 2017). Using resting-state fMRI and machine learning, Reggente et al. (2018) found that functional connectivity patterns within DMN and visual networks explained 67% of the variance in outcome in 42 patients after intensive CBT/ERP. However, an important limitation of current predictor studies is the low rate of replicability, few comparable studies, and no clear estimate of their predictive validity. These factors, along with the considerable cost of an (f)MRI scan, likely limit the current clinical utility of existing studies (Fullana & Simpson, 2016; Thorsen, Kvale, et al., 2018).

The current field of treatment studies is limited considerably by several factors. First, most have small sample sizes (earlier studies often had around 10 patients), which markedly increases the risk for both false positive and negative findings (Button et al., 2013). This problem has been somewhat improved in recent years, with newer studies having around 30-50 patients (e.g. Moody et al., 2017; Zhong et al., 2019). Second, there are few studies that are similar enough to directly compare, and very few systematic replications. This sheds considerable doubt on how replicable the findings are. Third, some studies show only moderate symptom improvement after treatment, have considerable attrition or number of patients still showing moderate or mild OCD after treatment, or report little information on the actual treatment (Baioui, Pilgramm, Kagerer, et al., 2013; Olatunji et al., 2014; Zhong et al., 2019). Fourth, many experimental tasks used in case-control or endophenotype studies have not yet

been evaluated in treatment studies (e.g. de Vries et al., 2014; de Wit et al., 2012). This makes it difficult to determine which behavioral aspects of OCD and their neurobiological correlates are state- or trait-related, or what happens to putative compensatory factors when patients have recovered. Fifth, there are few studies using a waitlist controlled or repeated baseline design to separate treatment effects from natural variation in brain characteristics (Moody et al., 2017). This issue is further compounded by the moderate and varying test-retest reliability of task- and resting-state fMRI, which may introduce additional noise in the estimation of any treatment effects (Braun et al., 2012; Plichta et al., 2012). Lastly, most studies only measure the brain before and directly after treatment, and few measure changes during treatment or long-term changes.

In summary, studies combining psychological treatment and neuroimaging have found that the brain changes after treatment in OCD (Thorsen et al., 2015). These changes largely occur in affective and cognitive brain circuits that have been implicated in the pathophysiology of OCD in case-control studies, though there are some findings of changes outside these classical areas. This suggests that the brain is plastic and sensitive to symptom improvement in symptoms. However, the field is limited by small studies, poor replicability, lack of longitudinal studies differentiating between short- and long-term changes over time, and limited understanding of how more or less activation in the brain relates to real life behavior, emotions and thoughts (Thorsen et al., 2015).

1.4 Present thesis

This thesis investigated the role of limbic circuits, emotion processing, and effects of concentrated psychological treatment in OCD from several perspectives. In Paper I we performed a meta-analysis of studies using functional neuroimaging to compare correlates of emotional processing in OCD and healthy controls, and investigated if variability in study and sample characteristics influence the reported findings.

In Paper II we used an emotion regulation task to investigate if provoked distress and associated brain activation and connectivity is an endophenotype for OCD. This was done by expanding the analyses of a previous comparison of 43 unmedicated OCD patients and 38 healthy controls (de Wit et al., 2015) by adding 19 unaffected siblings. Here, we used the results of Paper I to guide the selection of key regions during emotion provocation.

In Paper III we investigated if the B4DT leads to short-term changes in brain topology and network function during resting-state fMRI. This was done by analyzing key graph theoretical measures acquired the day before treatment and after one week (i.e. three days after the end of treatment) in 28 OCD patients and 19 age, gender and education-matched healthy controls. In this study we investigated both the brain as a whole as well as specific subnetworks and regions, and investigated both the static network structure and how connections dynamically vary during a scan session.

2. Methods and Results

2.1 Paper I

2.1.1 Research question

The goal of Paper I was to investigate if and where OCD patients show abnormal brain activation during emotional processing compared to healthy controls.

2.1.2 Participants

Paper I included summary information from 25 studies and a total of 571 OCD patients and 564 healthy controls.

2.1.3 Measures

The primary measure of Paper I was statistical parametric maps of between-group differences in activation during the presentation of emotional contrasted with neutral stimuli (representing group by task interaction effects). We also gathered information about mean symptom severity (Y-BOCS), percentage of medicated patients, comorbidity with depressive and anxiety disorders, mean age, mean percentage of male patients, and mean illness duration.

2.1.4 Preprocessing and statistical analyses

Statistical analysis was performed using ES-SDM, a whole-brain meta-analytic program. We first extracted the coordinates and t-value of the foci from each study, which were then transformed into MNI space. The contrasts of studies using more than one emotional condition (e.g. OCD-relevant and general fear stimuli) were combined. The location and strength of the between-group difference was then smoothed using an anisotropic Gaussian kernel, which was masked with a gray matter template. This produced estimated statistical parametric map per study. These maps were then entered into a random-effect meta-analysis weighted by the number of OCD patients and healthy controls, between- and within-study heterogeneity. Non-parametric permutation tests were then used to estimate regions of between-group differences in activation during emotional processing. The statistical threshold was set at $p < .005$, peak voxel $Z < 1$, and minimum cluster extent of 10 voxels. This is

comparable to voxel-level $p < .05$ corrected for the family-wise error rate. We also analyzed the moderating role of mean symptom severity (Y-BOCS), percentage of medicated patients, percentage of patients with comorbid depressive or anxiety disorders, mean age, mean percentage of male patients, and mean illness duration using meta-regression analyses which were thresholded at a stricter $p < .0005$.

2.1.5 Ethics

Paper I only included published results of studies with ethical review board approval, and therefore requires no additional effort or risk from participating researchers or participants. The paper is therefore not subject to ethical review board approval and ensures that the original studies are useful for science beyond their original publication.

2.1.6 Results

We found that OCD patients showed more activation in the right OFC (extending into the sgACC and vmPFC), bilateral amygdala (extending into the right putamen), left inferior occipital cortex, and right middle temporal gyrus than healthy controls when viewing emotional versus neutral stimuli. This shows that the exaggerated emotional processing of aversive stimuli in OCD patients involves a distributed network of structures.

The meta-regressions showed that studies with more medicated patients reported less hyperactivation in the right amygdala and left occipital cortex in OCD patients. Studies with patients with higher Y-BOCS scores showed more hyperactivation in the sgACC, medial PFC, and precuneus in OCD patients. Finally, studies with more patients with depressive/anxious comorbidity showed more hyperactivation in the right insula (extending to the putamen and amygdala) and less hyperactivation in the left amygdala and right vmPFC in OCD patients. Furthermore, studies with more patients with longer illness durations showed more hyperactivation of the right putamen and less hyperactivation of the left temporal pole and OFC in OCD patients.

2.2 Paper II

2.2.1 Research question

The goal of this paper was to investigate if unaffected siblings of OCD patients show similar distress, brain activation and functional connectivity during emotion provocation and regulation as patients, relative to healthy controls without a family history of OCD.

2.2.2 Participants and measures

The study included 43 unmedicated patients with OCD, 19 unaffected siblings of these patients, and 38 unrelated healthy controls. A diagnosis of OCD and comorbid disorders was done using the Structural Clinical Interview for DSM-IV (SCID, First, Spitzer, Gibbon, & Williams, 2002). Symptom severity of OCD was determined using the Y-BOCS, depressive symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS, Montgomery & Asberg, 1979), and use of reappraisal and suppression as emotion regulation strategies was measured using the Emotion Regulation Questionnaire (ERQ, Gross & John, 2003).

2.2.3 Experimental design of emotion regulation task

All participants performed an emotion regulation task, which has been extensively used to probe brain regions involved in various forms of emotion regulation in both healthy participants and participants with mental disorders (de Wit et al., 2015; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009; Ochsner et al., 2004; Rive et al., 2013). The task involves the appraisal of emotionally neutral pictures, OCD-related aversive pictures (such as dirty toilets, door handles, water taps, or asymmetric objects), or general fear-related pictures (such as spiders, bears or guns). The participants were either instructed to attend the picture naturally or intentionally try to reduce its emotional relevance using cognitive reappraisal techniques. During the task the participants were first given the instruction to either “attend” or “regulate” and where then show a picture for 10 seconds. They were then asked to rate their distress using a visual analogue scale.

2.2.4 Preprocessing and statistical analyses

Group differences in demographic characteristics, symptoms of OCD and depression, ERQ, and distress during emotion provocation and regulation were analyzed using chi-square or t-tests. Changes in distress during emotion provocation and regulation were analyzed using repeated-measures ANOVA. Tukey or Games-Howell corrections were used to adjust for multiple comparisons.

Group comparisons of activation during emotion provocation and regulation were performed in SPM12. Participant-specific maps of BOLD signal, and its two derivatives, during provocation (fear attend/regulate > neutral attend, OCD attend/regulate > neutral attend) were included in separate second-level, random effects ANOVAs. Three by three ANOVAs for fear and OCD-related provocation included group (OCD patients, siblings, HC) as a between-subject factor and HRF (canonical, temporal, dispersion) as a within-subject factor. The interaction between groups and picture type was modelled in a separate 3 X 2 X 3 ANOVA with group as a between-subject factor and HRF and picture type (fear, OCD-related) as within-subject factors. Separate one-way ANOVAS were used for emotion regulation and regulation-related function connectivity.

In Paper II we primarily focused our analyses to regions of the brain where OCD patients have previously been shown to differ from healthy controls during emotion processing or cognitive reappraisal. We therefore formed our hypotheses on emotion provocation on significant regions from our meta-analysis comparing OCD patients and healthy controls in Paper I (Thorsen, Hagland, et al., 2018). At that time no meta-analysis of the neural correlates of emotion regulation in OCD had been published, so we based our hypotheses on cognitive reappraisal on significant regions from the two largest meta-analysis of healthy controls (Buhle et al., 2014; Frank et al., 2014). We then investigated these specific regions using small volume correction (Worsley et al., 1996), and adjusted the p-values of comparisons between the groups using SISA-Bonferroni corrections (http://www.quantitativeskills.com/sisa/calculations/bonhlp.htm; Perneger, 1998).

2.2.5 Ethics

The study was approved by the ethical approval board of the VU University Medical Center (Amsterdam, the Netherlands) and all participants provided written informed consent. The participants were not placed at risk by the procedure and had the right to withdraw at any time without giving a reason. In accordance with the ethical approvals, all data were deidentified prior to being available to the Norwegian PhD student and there was no way of identifying the participants. The PhD student was also formally associated with VUMC when working with the data.

2.2.6 Results

We found that unaffected siblings of OCD patients reported similar levels of distress as unrelated healthy controls during emotion provocation and regulation, and significantly less distress than OCD patients. This suggests that they did not appraise the aversive stimuli as threatening.

During emotion provocation no significant differences was found between the three groups for fear-related stimuli. For OCD-related stimuli OCD patients showed significantly altered activation in the right amygdala/hippocampus compared to healthy controls, which was mainly driven by differences in timing and shape of the BOLD response. Siblings were intermediate and not significantly different from either group during OCD-related emotion provocation.

During emotion regulation no significant differences was found between the three groups for fear-related stimuli, similar to emotion provocation. During OCD-related regulation siblings showed significantly higher activation in the left temporo-occipital cortex compared to both OCD patients and healthy controls. OCD patients showed significantly higher dmPFC activation compared to healthy controls, where siblings were intermediate and not significantly different from either. Exploratory analyses of functional connectivity between the dmPFC and amygdala showed that siblings showed distinctly higher co-activation of these structures during regulation of OCD-related stimuli, which was significantly greater than OCD patients.

2.3 Paper III

2.3.1 Research question

The goal of Paper III was to investigate if OCD patients and healthy controls differed in the topology and organization of resting-state brain networks, and if these networks change immediately after B4DT. Following a preregistered analysis plan we investigated these questions both in the entire sample and in a subsample of unmedicated OCD patients.

2.3.2 Participants

This study included 34 patients with OCD who were offered B4DT at the OCD-team at Haukeland University Hospital (Bergen, Norway). All patients received the treatment as part of ordinary public mental health care. The patients were interviewed using the MINI (Sheehan et al., 1997) and Y-BOCS (Goodman et al., 1989) by a trained local clinical psychologist at the OCD-team as part of standard procedure and were also interviewed using the SCID (First et al., 2002) and Y-BOCS by a trained external psychologist who was not part of the treatment. We also recruited a sample of demographically matched healthy controls with no current or lifetime history of any mental disorder.

2.3.3 Measures

Both OCD patients and healthy controls were assessed using the SCID for lifetime and current mental disorders before the first fMRI session. Patients were interviewed by trained independent raters who were not part of the treatment and healthy controls were interviewed by the first author. Both before the first fMRI session and after one week, OCD symptom severity was measured using the Y-BOCS, and both OCD patients and healthy controls provided self-report ratings of OC symptom severity using the OCI-R (Foa et al., 2002), depressive symptoms using the Patient Health Questionnaire 9 (PHQ-9, Kroenke, Spitzer, & Williams, 2001) and anxiety symptoms using the Generalized Anxiety Disorder 7 (GAD-7, Spitzer, Kroenke, Williams, & Lowe, 2006).

2.3.4 fMRI preprocessing

FMRIB's Software Library version 5.0.10 (FSL; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) was used to preprocess the fMRI data. The EPI volumes were motion corrected (with 6 regressors) and spatially smoothed (with a 5 mm kernel). Participants were excluded if they showed movement exceeding a relative mean RMS of 0.2 mm or showed more than 20 volumes with RMS above 0.25 mm (Ciric et al., 2017). Additional movement correction was subsequently performed using ICA-AROMA (Pruim, Mennes, Buitelaar, & Beckmann, 2015). Nuisance signals in white matter and cerebrospinal fluid were removed using linear regression and the data were high-pass filtered (with 100 seconds cut-off). The functional images were linearly registered to the anatomical T1-weighted images, and the anatomical image was then parcellated into 226 nodes. Two hundred and ten cortical, as well as four bilateral dorsolateral and ventromedial putamen nodes, were defined based on the Brainnetome Atlas (Fan et al., 2016) and warped to the functional image. The bilateral thalamus, caudate nucleus, pallidum, hippocampus, amygdala, and nucleus accumbens were individually segmented using FSL FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011). We also applied a mask to the functional images to account for signal dropout near boundaries between air and tissue during scanning, which excluded voxels with signal intensities in the lowest quartile. Nodes with less than four remaining voxels with adequate signal were discarded. Time-series were then extracted from each node, and Morlet wavelet coherence (Grinsted, Moore, & Jevrejeva, 2004) in the frequency range of 0.06 to 0.125Hz (Z. Zhang et al., 2016) was used to calculate the coherence between each pair of nodes to construct a weighted connectivity matrix per subject and per time point.

2.3.5 Graph theoretical measures

Based on these connectivity matrices we calculated the static measures using in-house scripts and the Brain Connectivity Toolbox (version 2017-15-01; Rubinov & Sporns, 2010).

For dynamic measures we used a sliding window approach over 136 windows to assess variation during scanning (window size 25 TRs, each window was shifted 1

TR) (Hutchison et al., 2013). Dynamic measures were then calculated using the toolbox by Sizemore and Bassett (2017). Analyses were performed in MATLAB R2017a (MathWorks, Inc, Natick, MA, USA). We did not perform any threshold of the connectivity matrices in order to maximize the information contained therein and to avoid using arbitrary sparsity levels (Knock et al., 2009). For subnetwork analyses we assigned all nodes to the visual network, somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network, frontoparietal network (FPN), or default mode network (DMN) based on a previously validated parcellation from 1000 healthy controls (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Choi et al., 2012; Yeo et al., 2011).

We investigated the following graph measures (See Figure 1 for illustration and Rubinov & Sporns, 2010; Sizemore & Bassett, 2017 for details): Efficiency, which measures functional integration or how easily information can cross from one side of the network to the other, is defined as the inverse mean path length. Modularity refers to the degree to which the network can be divided into functionally different communities, which maximize the strength of within-module connections and minimize the strength of between-module connections. The clustering coefficient measures if a node's neighbors are also neighbors of each other which, indicates the level of functional segregation. It is calculated as the fraction of neighbors that are connected to each other divided by the neighbors that could have been connected. Betweenness centrality is the ratio of shortest paths through the network that cross through a given node, and indicates its importance for efficient network communication. Strength is the total weight of connections to a node, and reflects how strongly it is connected to rest of the network. We also calculated and compared the groups' total functional connectivity strength, as unbalanced connectivity may bias group comparisons of other graph measures (M. P. van den Heuvel et al., 2017). For the dynamic graph variables, we measured: Variation in efficiency and clustering coefficient during a scan. Flexibility refers to how often a node changes which the module it belongs to. Promiscuity is similar to flexibility but also requires that the node switches between different modules, not just back and forth between a few.

Finally, we assessed the temporal correlation coefficient, which is how stable the connections between a node's neighbors are during a scan (similar to the clustering coefficient). At the global and subnetwork levels we assessed efficiency, clustering coefficient and dynamic variation in these measures (i.e., temporal correlation coefficient, flexibility, promiscuity), as well as between-subnetwork connectivity. At the regional level we assessed node strength, clustering coefficient (and dynamic variation in these measures), betweenness centrality, temporal correlation coefficient, flexibility and promiscuity.

2.3.6 Statistical analyses

ANOVAs and t-tests were used for clinical measures, and within-group Cohen's d were calculated for changes over time (Morris & DeShon, 2002). Group differences in graph measures were tested using permutated Wilcoxon-Mann–Whitney tests in the coin package in R (version 3.5.0), while main effects of time, group and group × time interactions were performed using the nparLD package (Noguchi, Gel, Brunner, & Konietschke, 2012). NparLD applies a non-parametric rank-based model, which yields valid estimates in small sample sizes and data with ties. P-values were calculated using a modified F-statistic that has been shown to perform well in small sample sizes (Brunner & Puri, 2001). Within-group changes over time were calculated using Wilcoxon signed-rank. P-values for Wilcoxon-Mann–Whitney and Wilcoxon signed-rank tests were calculated based on 10,000 Monte Carlo resamples using the coin package. The relation between Y-BOCS, graph measures, and changes in these variables over time was tested using Kendall's tau correlations. We used the false discovery rate (FDR; Benjamini & Hochberg, 1995) to correct for multiple comparisons per graph metric and type of statistical test. We report results of between-group and longitudinal analyses if they were significant after FDR-correction ($q < .05$), except when otherwise specified. P-values of Wilcoxon signed-ranks were not adjusted for FDR but were only performed when time or group × time effects were significant. Partial eta squared (η^2_p) was calculated for time, group and group × time effects using the modified F-statistic (Lakens, 2013). We calculated the r effect size for Wilcoxon-Mann–Whitney and Wilcoxon signed-rank tests (Rosenthal, 1991), which can be regarded as small when ≥ 0.10, medium ≥ 0.30 and

large ≥ 0.50 (J. Cohen, 1988). A positive r for Wilcoxon-Mann–Whitney tests indicates that the value was greater in OCD patients than healthy controls. For Wilcoxon signed-rank tests a positive r indicates an increase over time.

2.3.7 Ethics

The study was approved by the Norwegian Regional Ethics Committee South-East (2015/936), and all participants provided signed informed consent. The participants were not placed at risk by participating in the study and had the right to withdraw at any time without giving a reason.

2.3.8 Results

The treatment was highly effective, and 17 (61%) OCD patients were in remission, an additional 7 (25%) responded, while only 4 (14%) showed no clinically significant change after one week. There were no significant differences in changes in clinical measures between medicated and unmedicated patients. Healthy controls showed no significant changes in OCI-R, PHQ-9, or GAD-7 scores after one week.

We first compared the entire sample of 34 OCD patients (25 unmedicated and 9 medicated) and 28 healthy controls before treatment, and found no significant group differences after correction for multiple comparisons in static or dynamic measures at baseline. After excluding medicated patients from the analyses the only difference, at an uncorrected threshold, was that unmedicated OCD patients showed more connectivity between the FPN and limbic subnetwork compared to healthy controls (r = 0.30, p = .03), which was no longer significant after treatment (r = -0.15, p = .36).

We then compared the longitudinal changes in 28 OCD patients (21 unmedicated and 7 medicated) and 19 healthy controls. This showed no significant differences between the groups (group × time effect), but common changes (main effect of time) at global and subnetwork but not local levels. Specifically, we observed changes over time in global efficiency, clustering coefficient, temporal correlation coefficient, total functional connectivity at the global level. At the subnetwork level we observed changes in connectivity between the SMN and VAN, efficiency in the SMN, VAN, and dynamic variation in SMN efficiency. We also found changes in SMN, VAN,

DMN and limbic clustering coefficient. Follow-up tests showed that these effects were mainly driven by increases in healthy controls after one week, while OCD patients showed no significant changes.

We then compared the longitudinal changes after excluding medicated patients from the analyses we found significant group differences (group×time effects) in the change in FPN-limbic connectivity and flexibility in the right sgACC, which were both driven by significant decreases in OCD patients (both $p = .03$, r connectivity = -0.44, r flexibility = -0.52), while healthy controls showed no significant changes.

We found no significant correlations between pre-treatment Y-BOCS, and graph measures nor between changes in symptom severity and graph measures. Comorbid anxiety disorders and onset of OCD were not significantly related to change in FPN-limbic connectivity or sgACC flexibility. When comparing changes in right sgACC flexibility in depressed and non-depressed OCD patients we found a significant group × time effect ($F(1,19) = 6.11$, $\eta^2_p = 0.26$, $p = .01$), which was driven by a larger decrease in depressed ($r = -0.89$, $p = .02$) than non-depressed patients ($r = -0.23$, $p = .41$).

3. Discussion

The present thesis has investigated emotional processing, regulation, and resting-state connectivity in OCD using meta-analytical, endophenotype, and longitudinal treatment designs. All three papers have included limbic regions, and the results have implications for how to understand limbic involvement in the disorder.

The following section will discuss how the findings of the present thesis relate and contribute to our understanding of OCD. First, it will focus on emotional processing and regulation. Secondly, it will focus on the plasticity and stability of resting-state brain network features after treatment. Thirdly, it will consider methodological concerns of the thesis and general literature. Lastly, it will consider both clinical implications of our findings as well as the neurobiological implications of clinical research.

3.1 Findings of Papers I, II and III

3.1.1 Limbic involvement in OCD

The role of the fronto-limbic circuit has been the focus of many studies in OCD, but with inconsistent findings and methodologies (Adler et al., 2000; Breiter et al., 1996; Cannistraro et al., 2004; Simon et al., 2010; O. A. van den Heuvel et al., 2004). Inconsistent findings regarding the involvement of limbic structures in OCD, showing both hyper- and hypoactivation of the amygdala, has even been used as an argument by for OCD to be classified as an obsessive-compulsive spectrum disorder, instead of an anxiety disorder (L. M. Shin & Liberzon, 2010; Stein et al., 2010). The previous meta-analysis on this topic had some important weaknesses that limited its usefulness, such as not including all relevant studies, including studies without a healthy control group, and not investigating the role of medication or comorbidity (Rotge et al., 2008). The purpose of meta-analysis in Paper I was to investigate which regions are related to hyper- or hypoactivation during emotional processing in OCD, and identify factors that have contributed to the inconsistent findings in the literature.

The results of Paper I challenge previous assertions that OCD is unrelated or negatively related to limbic activation on the group level, and instead suggest that group differences are subtle and sensitive to patient characteristics (Outhred et al., 2013; Thorsen, Hagland, et al., 2018; O. A. van den Heuvel et al., 2016). Classical models of the detection, evaluation and motivation of action after exposure to aversive stimuli propose a fast "low" road projecting from the visual cortex to the amygdala through the thalamus as well as a slower "high" road through cortical visual areas. Whether the "high" or "low" road "wins" and generates behavior is thought to be mediated by the affective value, need for conscious evaluation, and situational factors (LeDoux & Pine, 2016; Pessoa & Adolphs, 2010; Vuilleumier, 2005). Recent models have further suggested many pathways between the visual cortex and amygdala, which also include parietal, temporal, and orbitofrontal cortices (Pessoa & Adolphs, 2010; Vuilleumier, 2005). In that context, our findings of amygdala, OFC, occipital and middle temporal hyperactivation indicates that OCD patients recruit the visual pathways to larger degree when processing relevant, aversive stimuli. This is largely encompassed by the affective circuit in the model by O. A. van den Heuvel et al. (2016). The putamen is thought to be involved in the preparation and execution of behaviors to neutralize or avoid threats, such as compulsions (Banca et al., 2015; O. A. van den Heuvel et al., 2016), and the finding of putamen hyperactivation may reflect the readiness and planning of compulsive or avoidance behavior.

In summary, Paper I provides an updated view of the neural circuity of emotional processing in OCD, and highlights important moderating factors. This can provide a point of reference for future studies and analyses. However, we were not able to answer further important questions, such as how the implicated regions connect to each other. Future studies should aim to also investigate task-related functional connectivity during emotion processing to determine the nature and direction of regions in the affective and fronto-limbic circuits. It is also important to better understand the timing and neural correlates of the involved psychological processes, including noticing, processing emotionally, and deciding on a behavioral response to disorder-relevant stimuli.

3.1.2 Emotion processing and regulation as a risk or protective factor

After having investigated the neural correlates of emotion processing in OCD in Paper I, we intended to investigate if emotion processing and regulation was an endophenotype that could help explain the familial risk of OCD in Paper II. This investigation extended the previous work of de Wit et al. (2015), which compared distress, activation and connectivity during an emotional regulation task in unmediated OCD patients and healthy controls. In Paper II we added 19 unaffected siblings of the OCD group. We found that the siblings showed low distress levels during provocation (lower than patients and similar to healthy controls), suggesting that only patients were excessively distressed by the fear and OCD-related stimuli (Thorsen et al., 2019). The siblings showed no significant difference in right amygdala activation during OCD-related provocation, relative to patients or healthy controls, while OCD patients showed an altered shape and timing of the BOLD response in this area. Patients showed greater recruitment of the dmPFC during regulation of OCD-related stimuli relative to healthy controls, but there was no significant difference between siblings and patients or controls after correcting for multiple comparisons. Interestingly, only siblings showed hyperactivation of the left temporo-occipital cortex during regulation of OCD-related stimuli. Siblings alone also showed greater dmPFC-amygdala connectivity compared to OCD patients during regulation of OCD-related stimuli (Thorsen et al., 2019).

Our findings indicate that distress and activation during emotion provocation and regulation is not a good endophenotype of OCD. However, the greater temporo-occipital activation and dmPFC-amygdala connectivity during OCD-related regulation was specific to the sibling group. Previous research has indicated that neighboring areas on the border of the temporal and parietal cortex is activated more during distancing than cognitive reappraisal (Morawetz et al., 2017; Ochsner et al., 2012), which could indicate that siblings rely more on this strategy. The finding that siblings and OCD patients showed opposite effects in dmPFC-amygdala connectivity during OCD-related regulation could also indicate a compensatory role, where the regulatory dmPFC is even more strongly connected in siblings that partly share the

environmental and genetic risk of OCD and yet do not develop the disorder. However, the behavioral role of this finding is unclear since the siblings showed low distress ratings for all conditions and the specific use of emotion regulation strategy was not recorded. In summary, more activation in the fronto-limbic circuit during provocation, less dlPFC activation during fear-related regulation and more dmPFC activation during OCD-related regulation seem to be characterize patients but not siblings. This suggests that emotion provocation and regulation does not mediate the familial risk of OCD (Thorsen et al., 2019).

Despite substantial efforts, there are currently no findings that meet all formal criteria for an endophenotype in OCD (Gottesman & Gould, 2003; Taylor, 2012). Endophenotype studies in the same sample found more frontoparietal activation during working memory and more pre-SMA activation during response inhibition in both OCD patients and siblings versus healthy controls, with evidence from clinical and behavioral variables suggesting that both may be compensatory (de Vries et al., 2014; de Wit et al., 2012). Its noteworthy that this was not found during emotion processing or regulation, which may indicate that these functions are more state-related to having the disorder. Unfortunately, the subtle differences found between unaffected family members of OCD patients relative to healthy controls in the field has not been systematically replicated, and most current studies have not been designed to disentangle genetic and environmental effects. The finding with the strongest evidence for being a possible endophenotype may be greater error-related negativity as measured with EEG during Flanker tasks. Evidence has suggested that this is shared by OCD patients and their unaffected first-degree relatives but not unrelated healthy controls in both adults and adolescents (Carrasco et al., 2013; Riesel et al., 2011), is largely shared across different symptom dimensions (Riesel, Kathmann, & Endrass, 2014), and remains unaffected by effective CBT/ERP (Riesel, Endrass, Auerbach, & Kathmann, 2015). However, more error-related negativity seem to present in many disorders, and could reflect a general vulnerability to psychopathology (Olvet & Hajcak, 2008; Riesel, 2019; Riesel et al., 2019).

3.1.3 Changes in functional network structure as an early marker of treatment response

Paper III measured functional connectivity during resting-state fMRI the day before the B4DT in 34 OCD patients and 28 healthy controls, and 28 patients and 19 healthy controls were rescanned after one week (i.e. three days after the end of treatment in patients). We then used several graph theoretical metrics to describe the functional connectome at the global, subnetwork and regional level. This included dynamic metric that capture variation in the network structure during the scanning session (Bassett & Sporns, 2017; Sizemore & Bassett, 2017), which no studies have previously investigated in OCD. We found that OCD patients showed more connectivity between the FPN and limbic subnetworks compared to healthy controls at an uncorrected threshold. This was only seen when medicated patients were excluded from the analysis. We also found longitudinal changes after one week, where OCD patients showed reductions in FPN-limbic connectivity and sgACC flexibility while healthy controls showed no changes in these measures. This indicates that symptom improvement directly after concentrated exposure therapy is related to less crosstalk between subnetworks involved in executive and emotional processing, extending earlier pretreatment findings of abnormal fronto-limbic connectivity during resting-state (de Vries et al., 2017; Harrison et al., 2013) and task-related fMRI (de Vries et al., 2014; de Wit et al., 2015; van Velzen et al., 2015). However, our results do not answer if the decrease in between-subnetwork connectivity is driven by changes within one or both subnetworks nor if the connectivity is bidirectional, top-down or bottom-up. Future analyses using effective resting-state connectivity might answer this question. Previous studies using such techniques have shown links from the vmPFC to the amygdala and dorsal striatum during symptom provocation (Banca et al., 2015) and from the OFC to the nucleus accumbens at rest (Abe et al., 2015). In comparison, connections from the dlPFC to the OFC and IFG to amygdala have been found during emotional working memory and stop signal tasks, respectively (Han et al., 2016; van Velzen et al., 2015). This suggests that the direction of connectivity is modulated by task demands. It is possible that activation of task-related regions (i.e. cognitive circuits) are correlated

with limbic activation. For instance, when OCD patients experience that their performance is not good enough they may also try harder at the task (more task-related activation) which feeds a cycle of increasing anxiety and maladaptive monitoring (i.e. more limbic activation). This might be particularly observable during more demanding levels of cognitive tasks (de Vries et al., 2014). In comparison, OCD patients may show more activation within limbic circuits during resting-state (Abe et al., 2015; de Vries et al., 2017), reflecting more anxiety and obsessions when there is no cognitive demand (Paper III also found more state anxiety during resting-state in OCD patients before treatment relative to healthy controls). I would therefore expect effective connectivity analyses to show more connectivity from the OFC to other limbic areas (including the amygdala) in OCD patients before treatment, which should normalize after treatment.

The sgACC is a central node in the affective circuit, is connected to striatal and thalamic regions, and is activated during emotional and interoceptive processing (Pauls et al., 2014; Pessoa, 2017). Flexibility measures how often a node switches between which functional module it connects the strongest to. A module is a set of several nodes that have strong connections to each other and weaker connections outside of the module. Our finding of reduced sgACC flexibility directly after B4DT in OCD patients suggests a more stable network after treatment. This might be the result of decreased effort in bridging regions implicated in processes related to obsessions, emotion regulation, and compulsions. However, since participants were resting during scanning, we can't draw firm conclusions about the behavioral or psychological function of changes in connectivity.

Surprisingly, additional changes over time were seen in global, subnetwork, and regional measures in healthy controls for both static and dynamic graph measures. This was particularly seen in the somatomotor subnetwork, including its clustering coefficient and variation in efficiency. Similar findings in global and regional measures have been found in healthy controls of previous treatment studies (Li et al., 2018; D. J. Shin et al., 2014), as well as in a study consisting of many time points in a single person (Poldrack et al., 2015). These changes are currently poorly understood,

and could indicate that OCD patients show less normal increases or variation in network integration and clustering, or that healthy controls react differently to being repeatedly scanned. A complicating factor is that healthy controls showed a trend-significant increase in total functional connectivity (which may influence graph measures, M. P. van den Heuvel et al., 2017), though the groups were not significantly different at either before or after treatment.

We were not able to replicate previous findings of less efficiency or modularity in OCD patients as reported in previous case-control comparisons (Jung et al., 2017; D. J. Shin et al., 2014; T. Zhang et al., 2011), nor changes in global clustering coefficient or modularity after treatment (Feusner et al., 2015; D. J. Shin et al., 2014). This went against our hypotheses, but similar null findings have been reported (T. Zhang et al., 2011). A major impediment to comparing different studies directly is the variation in preprocessing pipeline, measures of functional connectivity, scanning duration, and statistical analyses (Ciric et al., 2017; Murphy & Fox, 2017; Z. Zhang et al., 2016). Variation in use of medication, time between scans, and clinical effectiveness further complicates further between-study comparisons (Beucke et al., 2013; Feusner et al., 2015; Moody et al., 2017). The clinical and methodological variation in the field highlight the need for more collaboration (including harmonization in data acquisition and processing) and systematic replications across research groups and scanners.

Network models to better understand the functional connectome is a promising approach to understand the neural correlates of OCD and plasticity after treatment, but it is still in its infancy. For it to be a truly useful tool we need to know more about the functional connectome in general (Avena-Koenigsberger et al., 2017; Bassett & Sporns, 2017), its relation to behavior (Braun et al., 2015), and reach a consensus of how to acquire, process and analyze resting-state fMRI (Ciric et al., 2017; Murphy & Fox, 2017).

3.2 Methodological considerations

3.2.1 Clinical

OCD is a complicated disorder to study due to its highly heterogenous symptom presentation, long illness duration, high comorbidity rates, and medication usage that can influence clinical and biological measures (Brakoulias et al., 2017; Mataix-Cols et al., 2005; Outhred et al., 2013; Ruscio et al., 2010). Furthermore, it is uncertain how representative patients participating in studies are for the total population of people with OCD. For instance, researchers have highlighted the role of symptom presentation, ethnic and sexual minority status in treatment seeking and inclusion in research (Bruce et al., 2018; Williams & Farris, 2011; Williams, Powers, Yun, & Foa, 2010; Williams, Turkheimer, Schmidt, & Oltmanns, 2005).

Most studies of OCD rely on a trained clinician to measure the severity of the disorders (Goodman et al., 1989), which increases the chance that questions are understood and gives the chance to clarify misunderstandings. However, the overlap between interview and self-report is not perfect (intraclass correlation of .75), and less for the obsessions subscale (Federici et al., 2010). We therefore applied both interviewer and self-report scales in Paper II and III. We also used a trained clinician who was not part of the groups or local treatment team for both baseline and post-treatment measures in Paper III. However, the interviewer was not blinded to time point and had access to additional information about the patient, since blinding the rater would have been most impractical. The study of Paper III was not designed to test the effectiveness of the treatment alone or in comparison to others, but we cannot exclude the possibility of patients or raters under- or overreporting symptoms due to biases or allegiances (Munder, Brutsch, Leonhart, Gerger, & Barth, 2013).

The studies in Paper II and III recruited patients with varying age, gender and education status and carefully matched healthy controls on these variables. Varied patients were also recruited, as reflected in symptom severity, comorbidity rates and the type of symptoms that they presented with. However, some types of patients were excluded, such as those with developmental difficulties (such as autism spectrum

disorders or intellectual disability) or with ongoing manic or psychotic symptoms. The sample in Paper III did not include patients who did not want or were unfit for treatment at the time, for example those with severe self-harm, suicidal intent, untreated somatic illnesses, or with disorders which needed to be addressed first. In summary, this suggests that the findings in Paper II and III might generalize to many types of OCD patients commonly seen in clinical practice, but that caution is warranted when interpreting the findings in relation to patients with pervasive developmental difficulties, those not seeking treatment, and patients with low insight.

There is limited knowledge regarding the role of symptom severity, and if and how higher obsessive-compulsive symptom severity is related to having a more abnormal brain, or if more symptom improvement after treatment is related to more pre-post treatment changes in the brain. The results of single studies and meta-analyses are somewhat inconsistent, and some find no significant relation between symptom severity and brain characteristics (Boedhoe et al., 2018; Boedhoe et al., 2017; de Vries et al., 2014; Figee et al., 2011). This was not the case for the meta-analysis in Paper I, which found that studies including OCD patients with a higher mean Y-BOCS score showed more prefrontal and precuneus hyperactivation in OCD (Thorsen, Hagland, et al., 2018). However, in Paper III there was no significant relation between Y-BOCS scores and graph measures where OCD patients were significantly different from healthy controls, nor between change in Y-BOCS and changes in graph measures after treatment. This could be caused by little variation in the level of symptom improvement, as almost 90% of the patients responded after treatment. More research is needed to determine the relation between symptom severity and the brain in OCD.

Future research could also try to understand why some patients improve fast, some slow, and others not at all. Such studies will require both larger sample sizes and measures that can help us understand why they did not benefit from treatment. For instance, one could expect a difference in how emotional brain networks are organized in patients who are not motivated to perform the most difficult exposure tasks compared to those who perform all exposures but engage in compulsions

afterwards (Aigner et al., 2005; J. Fan, M. Zhong, X. Zhu, et al., 2017). In a supplemental analysis of Paper III, we excluded the four patients who did not show significant change after treatment, and found very similar changes in graph measures.

There are few studies reporting the effects of age on changes in the brain after treatment, while younger age has been linked to more improvement on CBT/ERP, both in adults (Öst et al., 2015) and children (Öst, Riise, Wergeland, Hansen, & Kvale, 2016). However, it should also be noted that age has not emerged as a consistent predictor in systematic reviews (Knopp et al., 2013) or mega-analysis of adult patients (Steketee et al., 2018). A better understanding of how age influences brain plasticity and reorganization would be a valuable contribution to the literature, especially given the large potential for brain development seen in early childhood and puberty (Collin & van den Heuvel, 2013; Kaufmann et al., 2017).

3.2.2 Behavioral

The situations that evoke distress and anxiety in OCD is highly idiosyncratic and can be difficult to elicit in a highly controlled experimental setting. This is relevant for both Papers I and II, which study task-induced emotion provocation. Paper II used generic OCD-related pictures for washing, checking and symmetry dimensions, as the study did not recruit patients with only one type of symptoms. However, stimuli were not personalized since this would have complicated interpreting between-group and between-person analyses. It would also have required considerably more time and effort to make personalized stimuli. However, this also meant that some patients saw stimuli that were not particularly relevant for them, which may have resulted in lower mean distress ratings for OCD than fear-related stimuli (Thorsen et al., 2019). Some studies have also found that using personalized stimuli is associated with stronger BOLD responses in relevant regions (Baioui, Pilgramm, Merz, et al., 2013; Morgieve et al., 2014).

It can be difficult to operationalize even relatively simple psychological functions in an MRI scanner, and even more difficult with a complex construct such as emotion regulation. This issue is further complicated in OCD, where patients often try to

regulate their emotions using strategies that resemble cognitive reappraisal or distraction, but often end up trying to reduce distress by relaxing or reasoning themselves out of obsessive thoughts in a compulsive manner. For instance, the "regulate" condition in the emotion regulation task of paper II instructed participants to "imagine a more positive outcome or interpretation of the portrayed events" or "realize the stimulus is not real-life" (de Wit et al., 2015). This resembles typical strategies used to regulate emotions in real life in both healthy controls and patients (John & Gross, 2004; Ochsner et al., 2004). However, it also resembles the dysfunctional strategies used by patients, as they often attempt to compulsively rationalize, reimagine or distract themselves from obsessions (even though most obsessions are normal in terms of content)(Muris, Merckelbach, & Clavan, 1997; Rachman & de Silva, 1978). This can lead to an increase in distress, obsessional frequency, and low mood (Najmi et al., 2009; Purdon, Rowa, & Antony, 2005). In contrast, ERP and other forms of psychological treatment ask patients to systematically increase their anxiety during exposure, which in turn often leads to a higher tolerance of emotional distress and less need to neutralize or distract oneself from obsessions (Grøtte et al., 2015; Reid et al., 2017).

3.2.3 Neuroimaging

Functional neuroimaging using fMRI has key strengths such as being non-invasive, relatively brief, and allowing multimodal imaging. However, it also has critical limitations that must be taken into account when planning, analyzing and interpreting data (Poldrack et al., 2008). Scanning requires balancing temporal and spatial detail, as the number of slices and voxel sizes often increase as repetition time decreases. This may make it difficult to measure fast processes, such as the communication between visual cortex and amygdala during detection of aversive stimuli (Boubela, Kalcher, Nasel, & Moser, 2014; Vuilleumier, 2005). Imaging brain structures of theoretical importance, such as the amygdala, vmPFC and nucleus accumbens (Figee et al., 2011; O. A. van den Heuvel et al., 2016), can be difficult due to nearby tissue boundaries and other confounding physiological variables (Chen, Dickey, Yoo, Guttmann, & Panych, 2003; Lipp, Murphy, Wise, & Caseras, 2014; Stocker et al., 2006). Paper I only included summary information from published studies where

some likely had better coverage of the brain than others, which we were unable to assess or control for. In paper II and III we assessed brain coverage of all participants, and excluded those with poor coverage or artifacts. In Paper III we also ensured that all segmented brain regions had adequate signal (each region had to have a minimum of four voxels with signal intensity in the upper three quartiles), which led to the exclusion of the bilateral nucleus accumbens and the most ventral area of Brodmann 13 in the right hemisphere.

The test-retest reliability (expressed as the intraclass correlation, which measures the consistency or agreement for a measure taken at two or more time points) of fMRI during cognitive and emotional tasks has been reported as good (.89-.98) and acceptable (.66-.97) on whole-brain and regional levels, respectively (Plichta et al., 2012). However, a recent meta-analysis of 90 task-related studies estimated an intraclass correlation of .39, and estimates between .07 and .49 in two large independent datasets (Elliott et al., 2019). Reliability estimates of .50-.60 has also been reported for common static graph measures, such as global efficiency, during resting-state fMRI (Braun et al., 2012; Termenon, Jaillard, Delon-Martin, & Achard, 2016), though reliability was somewhat less for static graph measures in emotional tasks. Both task- and resting-state reliability was influenced by scanning parameters (such as scan duration) and preprocessing pipeline (Braun et al., 2012; Plichta et al., 2012). A recent study found that dynamic graph metrics is worse than static measures, with intraclass correlations under .10 (C. Zhang, Baum, Adduru, Biswal, & Michael, 2018) These findings illustrate the considerable variability and vulnerability to confounding variables of fMRI. These issues are highly relevant for both cross-sectional and longitudinal treatment studies, and should be considered when doing power analyses or estimating clinically reliable change. We used a preprocessing pipeline to robustly adjust for confounding motion and physiological noise to the best of our abilities, but future research should evaluate how test-reliability can be improved in fMRI.

The choice of processing pipeline is particularly important for Paper III due to the vulnerability of resting-state fMRI to confounding variables and the heterogenous

approaches used in previous studies. Our scan duration of 4 minutes and 48 seconds was likely long enough to get stable static graph measures and is comparable to previous studies (Beucke et al., 2013; Fullana et al., 2017). However, a longer duration would have allowed for more sliding windows for dynamic metrics and possibly even more robust static estimates (Birn et al., 2013). To adjust for confounding motion and physiological noise we used linear regressions including six motion directions followed by ICA-AROMA, which has been shown to detect and remove motion artifacts better than 24 motion parameters (Pruim et al., 2015). We used linear regression to remove nuisance signals in white matter and CSF, which were defined using segmentation of the T1-weighted image (Caballero-Gaudes & Reynolds, 2017). We also chose to use of wavelet coherence in the 0.06 to 0.125Hz range as this has been shown to be reliable, robust to outliers and varying autocorrelation in the BOLD signal, and sensitive to neuropsychiatric disorders (Bassett et al., 2013; Z. Zhang et al., 2016).

One of the largest problems in neuroimaging is low statistical power, which may result in both false negative and positive findings, and increased vulnerability to confounding variables (Button et al., 2013). This issue has received considerable interest, and at least 80% power to detect a prespecified group difference is often seen as a minimum (Jacob Cohen, 1992). Methods to calculate power are available for fMRI, but are often not required by journals and may be difficult to do when the expected group effect is unknown (Mumford & Nichols, 2008). We did not use a formal power analysis to plan the studies of Paper II and III, but both were planned to be among the largest studies at the time that they started including participants. We also publicly preregistered the hypotheses and methods of Paper III at the Open Science Foundation to increase transparency and ensure that all our results could be checked against our initial plan (Munafò et al., 2017).

3.3 Implications for future research

The results of Paper I clearly indicate a role of distributed regions in the affective and fronto-limbic circuits in OCD, including the amygdala, and shows how the relatively

subtle differences between patients and healthy controls can be influenced by comorbidity, medication status, and other clinical characteristics (Thorsen, Hagland, et al., 2018). Only a few cross-disorder comparisons have investigated shared and distinct mechanisms of emotional and cognitive processing in OCD, obsessive-compulsive spectrum disorders and anxiety disorders (Marin et al., 2017; Milad et al., 2013; O. A. van den Heuvel et al., 2011). Given the substantial comorbidity between such disorders, future research should help uncover why some develop these disorders and how treatment can be improved. One method to answer this question would be to use population-based studies to separate vulnerability to a disorder from consequences of having lived with a disorder (including effects of treatment and chronic medication use). Finally, treatment studies with a lifespan perspective may show whether children, adolescents, and adults are similar or different in the neurobiological correlates of recovery.

The results of Paper II further support the role of the fronto-limbic circuit during emotional provocation, as well as altered dmPFC and temporo-occipital activation during OCD-related emotion regulation in unaffected siblings of OCD patients. However, further work is needed to uncover the mechanisms underlining emotion regulation, and how treatment affects the way OCD patients confront and manage their symptoms. These questions cannot be adequately answered by commonly used tasks of today, nor by correlations between brain activation and clinical measures. Rather, the field needs to develop more ecologically valid paradigms that can, for example, show what happens when a patient chooses to avoid or confront an aversive stimulus (Banca et al., 2015). This could involve developing paradigms that are closer to how psychological therapies are actually done, such as the B4DT. For instance, performing ERP during fMRI or mobile EEG (Ladouce, Donaldson, Dudchenko, & Ietswaart, 2016) could allow for imaging the emotional and cognitive processes during exposure.

The implication of sensitivity to artifacts, uncertain reliability, and few consistent findings in the field is that large-scale replication efforts with harmonized data acquisition and analysis is required. The Enhancing NeuroImaging Genetics through

Meta-Analysis (ENIGMA) Consortium is a much needed step in the right direction (Thompson et al., 2014), which pools neuroimaging and genetic data across the world using harmonized data processing. A next step would be to harmonize data collection of clinical, neuroimaging and other measures to give better opportunities for cross-country comparisons. Another step would be to increase the number of replication studies, which can both test the robustness of earlier findings and provide a good use of previously collected data (Dinga et al., 2019; Heinzel et al., 2018). The subtle results found in all three papers of this dissertation highlight the need for more powerful studies in the future, where sample size is preferably informed by power analyses rather than tradition (Mumford & Nichols, 2008). This is further supported by findings from the OCD working group in the ENIGMA consortium, where the difference between patients and controls are very small when sample sizes are very large (Boedhoe et al., 2018; Boedhoe et al., 2017).

Paper III was able to highlight short-term changes in resting-state network communication due the concentrated treatment, which few studies have been able to investigate so far. However, it cannot speak to the eventual long-term effects of psychological treatment on the brain. There are very few studies with measurements at more than two time points, and none that can investigate how the brain changes in relation to a rapid, non-gradual decrease in symptom severity (Morgieve et al., 2014). Future studies should investigate treatment-related changes in both the short- and long-term. The resting-state fMRI data in Paper III has also been collected three months after treatment, and will be analyzed shortly. These analyses can show if the short-term changes are stable over time or if other changes emerge after longer periods of normalized behavior. I would expect that the decrease in frontoparietal-limbic connectivity will still be present after three months in remitted patients, but not in those experiencing relapse. Future work at the Bergen Center for Brain Plasticity will also investigate short- and long-term changes in the brain after B4DT in a larger sample of OCD and anxiety disorder patients, enabling more specific analyses on clinical heterogeneity.

Finally, many studies in the field only use one source of neurobiological information, for instance sMRI or fMRI. This could be expanded by including psychophysiological measures (e.g. skin conductance or heart rate variability) or multimodal imaging to understand the disorder, and changes after treatment, at different timescales and biological levels (Robbins, Vaghi, & Banca, 2019). There are some examples of such studies in the literature and more are underway (Moreira et al., 2017; Tadayonnejad et al., 2018). One of the aims of the future work at the Bergen Center for Brain Plasticity is to combine MRI and other biological measures to a contribute to a more integrated view of the psychobiology of OCD and anxiety disorders. We also aim to combine these measures with genetics and epigenetics to better understand how changes in the body and brain are reflected in DNA and its methylation (Todorov, Mayilvahanan, Ashurov, & Cunha, 2019).

3.4 Clinical implications

Findings of amygdala and affective circuit hyperactivation in Paper I support that the anxiety and distress seen in OCD patients are largely accompanied by exaggerated responses in the circuitries known to play an important role in fear conditioning, extinction learning and emotion regulation (Pessoa, 2017; Pessoa & Adolphs, 2010; Vuilleumier, 2005). Similar findings were seen during emotion regulation in Paper II, where patients showed more or less activation than the other groups in regions previously implicated in meta-analyses of healthy controls (Buhle et al., 2014; Frank et al., 2014). Reduced and normalized frontoparietal-limbic connectivity after B4DT suggest that executive resources receive less interference from limbic activation when patients recover, and provides some indirect support for the executive overload model of cognitive performance in OCD (Abramovitch et al., 2012). This could suggest that task-related fronto-limbic connectivity during executive tasks is also sensitive to improvements in symptom severity (de Vries et al., 2014; van Velzen et al., 2015), This will be tested in future analyses of the Tower of London and Stop Signal Tasks before and after B4DT.

Even though a substantial amount of time and money has been spent to find neurobiological and genetic correlates of OCD, few have had any real impact on the development or innovation of psychological or pharmacological treatments, with the possible exception of psychosurgery, deep brain stimulation and transcranial magnetic stimulation (Karas et al., 2018; Zhou, Wang, Wang, Li, & Kuang, 2017). In comparison, the psychological treatments for OCD have traditionally been rooted in classical learning theories, and more recently, inhibitory learning, emotion regulation, and cognitive frameworks (Barlow, Allen, & Choate, 2004; Craske et al., 2008; Jacoby & Abramowitz, 2016; Wells & Matthews, 1996). I hope that the rapidly developing field combining neuroimaging with new tasks and approaches can help us better understand and treat OCD, and lead to a greater degree of integration between neurobiological and psychological perspectives. Possible advances include using biological markers to predict how to best tailor currently available treatments to the individual patient (Fullana & Simpson, 2016; Reggente et al., 2018), using TMS to augment the effects of CBT/ERP (Carmi et al., 2018), or use recent developments from cognitive neuroscience to modify current treatments (Kredlow, Eichenbaum, & Otto, 2018). However, to gain traction in clinical practice such results must be both robust and accurate, so that patients are not offered ineffective treatments or are rejected from traditional treatments they could have benefitted from. This would require more stringent study designs, sample sizes, and advances in neuroimaging to realize (Button et al., 2013; Elliott et al., 2019; Fullana & Simpson, 2016).

4. Conclusions

The present thesis has three main findings that help understand the neurobiological correlates of having and recovering from OCD: First, OCD patients as a group show more activation during emotional processing in the amygdala and affective circuit than healthy controls, but this is dependent on factors such as comorbidity and medication use. Second, the patterns of activation seen in OCD patients during emotion provocation and regulation are not found to the same degree in unaffected first-degree relatives, but the relatives might have specific factors that may protect them from the familial risk of developing the disorder. Third, rapid reduction in symptom severity during the B4DT leads to changes in network communication after only three days, and indicate a more independent and stable network. However, this finding is also influenced by medication use and comorbidity. Together, the findings suggest that OCD is related to subtle differences in limbic activation and fronto-limbic connectivity, and these seem to state-related and sensitive to treatment.

5. References

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I

Paper I

Archival Report

Biological Psychiatry: CNNI

Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies

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ABSTRACT

BACKGROUND: Patients with obsessive-compulsive disorder (OCD) experience aversive emotions in response to obsessions, motivating avoidance and compulsive behaviors. However, there is considerable ambiguity regarding the brain circuitry involved in emotional processing in OCD, especially whether activation is altered in the amygdala.

METHODS: We conducted a systematic literature review and performed a meta-analysis—seed-based *d* mapping—of 25 whole-brain neuroimaging studies (including 571 patients and 564 healthy control subjects) using functional magnetic resonance imaging or positron emission tomography, comparing brain activation of patients with OCD and healthy control subjects during presentation of emotionally valenced versus neutral stimuli. Meta-regressions were employed to investigate possible moderators.

RESULTS: Patients with OCD, compared with healthy control subjects, showed increased activation in the bilateral amygdala, right putamen, orbitofrontal cortex extending into the anterior cingulate and ventromedial prefrontal cortex, and middle temporal and left inferior occipital cortices during emotional processing. Right amygdala hyperactivation was most pronounced in unmedicated patients. Symptom severity was related to increased activation in the orbitofrontal and anterior cingulate cortices and precuneus. Greater comorbidity with mood and anxiety disorders was associated with higher activation in the right amygdala, putamen, and insula as well as with lower activation in the left amygdala and right ventromedial prefrontal cortex.

CONCLUSIONS: Patients with OCD show increased emotional processing-related activation in limbic, frontal, and temporal regions. Previous mixed evidence regarding the role of the amygdala in OCD has likely been influenced by patient characteristics (such as medication status) and low statistical power.

Keywords: Comorbidity, Emotion, Emotional interference, Medication, Meta-analysis, Symptom provocation

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Patients with obsessive-compulsive disorder (OCD) often experience aversive emotions such as anxiety, fear, and disgust in response to obsessive thoughts, urges, or images. These aversive emotions motivate patients to avoid situations and engage in compulsive behaviors to deal with the provoked distress and to prevent the catastrophic outcomes that they anticipate (1).

The neural substrate of emotional processing in OCD has been investigated for nearly 3 decades using a variety of experimental tasks comparing patients with OCD with healthy control subjects. The central idea in these tasks is to experimentally elicit the negative emotions that patients with OCD experience in daily life, thereby visualizing the brain's activation in the symptom-provoked state. During symptom provocation paradigms, participants view stimuli that resemble situations in daily life that typically elicit anxiety or an urge to ritualize in patients (e.g., potentially contaminated objects or situations where one could harm someone). The resulting brain activation patterns are contrasted with a condition with stimuli that are meant to be neutral (e.g., nature scenes, clean household objects) (2,3). Other studies employ emotional faces (e.g., fearful, disgusted) to induce negative emotions and contrast the resulting brain activations with those of neutral facial expressions (4). Another approach is to have participants perform a cognitive task with emotional interference. In these paradigms, participants perform the cognitive task under both neutral and implicitly symptom-provoked states, for example, by naming the color of disorder-related words (5,6).

However, the results from these studies have been somewhat inconsistent and hard to reconcile, especially regarding the role of the amygdala. The largely unclear role of the amygdala in OCD contrasts with theoretical models that propose a central role of this structure in the processing of emotionally valenced stimuli (7,8). The amygdala is involved in the unconscious and conscious appraisal of visual stimuli in the environment (9), the acquisition and extinction of a learned

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response to potential threat (10), and its interference with prefrontal functioning (9). Its activation varies fast over time, under influence of bottom-up and top-down modulation, from the thalamus and cortical areas, among others (11). Within-individual variation in amygdala responsiveness is dependent on the context (the experimental setting), contributing to inconsistencies from neuroimaging studies. For example, various studies in OCD using emotional facial stimuli showed that activation of the amygdala in response to fearful faces was found to be increased, decreased, or neither increased nor decreased (4,12–14). One plausible reason for these inconsistencies is the typically small sample sizes, which not only decrease the chance of finding a true effect but also increase the risk of false-positive findings (15). Many studies also include patients on selective serotonin reuptake inhibitors, which are known to influence brain activation in regions such as the amygdala and hippocampus (16). Comorbidity with anxiety or mood disorders is another source of heterogeneity that may obscure whether alterations are specific to OCD or shared with other psychiatric disorders (17,18).

Meta-analyses are the gold standard of evaluating quantitative findings and work by combining information from all available studies and thereby reducing random noise from individual studies, allowing filtering out robust effects and establishing the contribution of specific factors to the variability in results. However, to our knowledge, only one meta-analysis focusing on emotional processing in OCD has previously been published (19), based on eight studies using symptom provocation tasks. The authors found increased brain activation in patients with OCD compared with healthy control subjects in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus, hippocampus, superior temporal gyrus, and precuneus. Although important for providing a snapshot of the literature at that time, the previous meta-analysis by Rotge *et al.* (19) had several limitations. The authors were not able to investigate whether contributing factors such as medication usage and comorbidity moderated their findings, and owing to both the limited number of included studies and the meta-analysis software available at that time, they omitted at least one available study (2) and included studies that did not compare patients with healthy control subjects, relying only on within-group contrasts (20–22). The authors also included studies analyzing regions of interest with more lenient significance thresholds, which may have increased the rates for both false-positive and false-negative findings.

The aim of the current meta-analysis was to provide a contemporary quantitative comparison of brain activation during emotional processing in patients with OCD and healthy control subjects, to explore the influence of patient characteristics, and to investigate the consistency of these findings. Based on previous reviews of human and animal research on OCD (8,23,24), we hypothesized that patients with OCD compared with healthy control subjects would show altered activation in limbic (amygdala), striatal (putamen), lateral temporal, and frontal (OFC and dorsal ACC) regions during emotional processing. We also hypothesized that studies with a lower proportion of patients on medication and studies with a higher proportion of patients with comorbid anxiety and mood disorders would show higher limbic (amygdala) activation during emotional processing.

METHODS AND MATERIALS

Study Selection

Paradigms assessing emotional processing were defined as those using both stimuli intended to be neutral and those intended to elicit specific negative emotions such as fear, disgust, and more general distress as well as urges to ritualize. The contrast of interest was the comparison of brain activation during neutral and emotional stimuli for patients with OCD and healthy control subjects (i.e., the group by task interaction). A systematic literature search was conducted of all whole-brain neuroimaging studies of emotional processing in OCD up to July 2017 using the PubMed, Web of Science, ScienceDirect, and Google Scholar databases as well as manual searches of relevant published articles. Corresponding authors of studies with unavailable full texts were asked to provide these. Search words were combinations of "obsessive-compulsive disorder" (or "OCD") and "symptom," "provocation," "emotion," and "neuroimaging" as well as "fMRI" (functional magnetic resonance imaging), "SPECT" (single photon emission computed tomography), and "PET" (positron emission tomography). We defined studies of emotional processing using these specific criteria: 1) included both patients with OCD and healthy control subjects; 2) employed functional neuroimaging such as fMRI, PET, or SPECT; 3) included tasks with both an emotional condition and a neutral condition; 4) reported whole-brain analysis of an emotional versus neutral contrast; and 5) were written in English. Meta-analysis of observational studies in epidemiology guidelines were followed (25). The systematic search and data extraction was conducted by Ph.D. and master students (ALT and PH, respectively) under the direct supervision of two senior authors (JR and OAvdH).

Statistical Analyses

Differences in activation during emotional processing between patients with OCD and healthy control subjects were analyzed using seed-based *d* mapping (SDM; http://www.sdmproject.com), a whole-brain, voxel-based meta-analytic approach (26,27). SDM first estimated, for each study, the group by task interaction statistical parametric map (i.e., where patients show increased or decreased activation compared with healthy control subjects during emotional vs. neutral stimuli). Hedges' *g* in the voxels containing a peak was calculated from the peak's *t* score, and an anisotropic Gaussian kernel was used to estimate Hedges' *g* in the surrounding voxels (28). The estimated statistical parametric maps were then included in a random effects meta-analysis that weighted the contribution from each study by sample size and within- and between-study heterogeneity and that ultimately resulted in a whole-brain map of the reported group differences between patients and control subjects. Standard permutation tests were used to estimate the statistical significance of the SDM *Z* scores. The comparison between patients with OCD and healthy control subjects was thresholded at $p < .005$, which has been shown to be comparable to $p < .05$ corrected for multiple comparisons (22). Following standard criteria, significance thresholds were also set at a minimum peak voxel *Z* score over 1 and a minimum cluster extent of 10 voxels (26,27).

Eight studies included more than one OCD-relevant condition (3,29–35). Prior to the analysis, results from each condition were combined into one single statistical map. This was done to include all relevant contrasts without counting these studies several times and thereby giving these studies an undue influence and violating the statistical assumption of independence.

We first performed the primary analysis assessing differences between patients with OCD and healthy control subjects during emotional processing. We also compared the findings of studies using symptom provocation with pictures versus all other paradigms. We then performed secondary meta-regressions assessing the influence of several factors on the group by task effect. This included each study's mean symptom severity using the mean Yale-Brown Obsessive Compulsive Scale (36), the percentage of medicated patients, and an indicator of anxiety/depression comorbidity per study. Of the included studies, 21 reported rates of comorbidity for both anxiety and mood disorders, but these rates were highly correlated, $r_{18} = .74$, $p < .001$. Therefore, we calculated the indicator for comorbidity using the mean percentages of patients per study who also met criteria for a comorbid anxiety or mood disorder. Finally, the moderating roles of percentage of male subjects and mean illness duration were also investigated. The moderating variables did not significantly correlate and therefore were largely independent. Meta-regressions were thresholded at a stricter level ($p < .0005$) to limit the risk of false positives. A jackknife sensitivity analysis was conducted for the primary group by task meta-analysis to assess the robustness of the main findings by iteratively repeating the analysis and excluding one data set at a time. Publication bias was assessed using Egger's tests and funnel plots for the main meta-analytical findings.

RESULTS

Characteristics of Included Studies

In total, 978 studies were rejected after reading the abstract and title because they did not meet inclusion or exclusion criteria. Full texts of 39 studies were retrieved. Of these, 14 were excluded. The reasons for exclusion were as follows: did not report results at the whole-brain level ($n = 10$) (37–46), did not include healthy control subjects ($n = 3$) (47–49), and reported comparisons between patients with OCD and healthy control subjects after patients were treated using cognitive behavioral therapy ($n = 1$) (50) (see Supplemental Figure S1 for flowchart of selection process). The remaining 25 studies comprising 571 patients with OCD and 564 healthy control subjects were included in the meta-analysis. Each study included a mean of 22.84 patients (SD = 16.78) and 22.56 healthy control subjects (SD = 16.09). The mean age of the patients was 33.44 years (SD = 5.91), and all studies included age-matched healthy control subjects. The mean percentage of male subjects was 54.35% (SD = 12.10). In total, 17 studies (68%) included medicated patients, and only 1 study included pediatric patients with OCD. Two studies did not include information on medication status and therefore were not included in the meta-regression of medication usage. The mean Yale-Brown Obsessive Compulsive Scale score of the included studies was 23.46 (SD = 3.45), indicating that most patients were moderately ill (51). In addition, 13 studies provided the mean duration of illness, which was 12.26 years overall (SD = 4.46). Furthermore, 16 studies included participants from Europe, 6 included participants from North America, and 3 included participants from Asia. Finally, 10 studies used symptom provocation using pictures, 5 used emotional faces, and 10 used various other paradigms (e.g., emotional Stroop, working memory tasks combined with emotional stimuli, symptom provocation tasks using written verbal stimuli instead of pictures) (see Supplemental Table S1 for detailed information).

Comparison Between Patients With OCD and Healthy Control Subjects Across All Studies

Across all paradigms, the main effect of group showed that patients with OCD, compared with control subjects, show significantly increased activation in the right OFC extending into the subgenual ACC (sgACC) and ventromedial prefrontal cortex (vmPFC), right putamen, bilateral amygdala, left inferior occipital gyrus, and right middle temporal gyrus during emotional processing. Healthy control subjects did not show increased activation compared with patients in any region (see Table 1 and Figure 1). Finally, we did not find any significant difference in the patterns of activation between studies using symptom provocation with pictures compared with other paradigms (data not shown).

Table 1. Whole-brain Significant Differences Between Comparison of Patients With OCD and HCs During Emotional Processing

Region	Side	MNI Coordinates (X, Y, Z)	BA	SDM *Z* Score	No. of Voxels	Cluster Breakdown
Patients With OCD > HCs						
OFC	R	6, 40, −16	11	2.093	811	Bilateral OFC, sgACC, vmPFC
Amygdala	L	−20, 0, −20	N/A	1.931	437	Amygdala, parahippocampal gyrus
Amygdala	R	28, −2, −12	N/A	1.882	437	Amygdala, putamen
Inferior occipital gyrus	L	−32, −90, −10	19	1.559	95	Inferior, middle occipital gyrus
Middle temporal gyrus	R	58, −50, 8	21	1.746	85	–

BA, Brodmann area; HCs, healthy control subjects; L, left; MNI, Montreal Neurological Institute; N/A, not applicable; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; R, right; SDM, seed-based *d* mapping; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

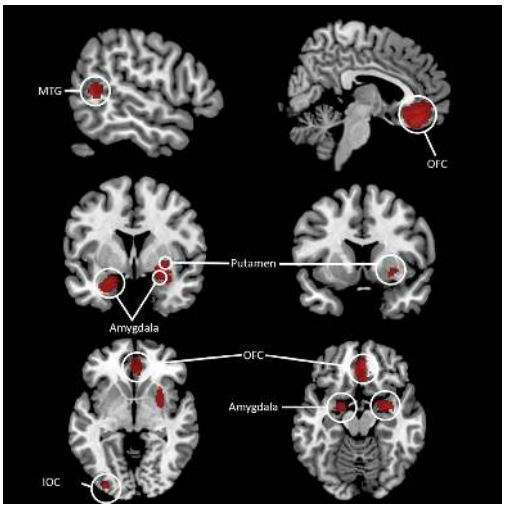

Figure 1. Regions of hyperactivation in patients with obsessive-compulsive disorder compared with healthy control subjects during emotional processing, showing a distributed affective circuit including frontal, limbic, striatal, and ventral visual areas. IOC, inferior occipital cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex.

Meta-regressions of Factors Influencing the Difference Between Patients With OCD and Healthy Control Subjects

The meta-regression analyses (see Table 2 and Figure 2 for details) showed that the percentage of patients per study using psychotropic medication, primarily selective serotonin reuptake inhibitors, correlated negatively with activation in the right amygdala and left inferior occipital gyrus, indicating that the increased limbic and occipital activation during emotional processing in patients compared with control subjects is most pronounced in studies with higher percentages of unmedicated patients.

Studies including patients with higher symptom severity, as measured with the Yale-Brown Obsessive Compulsive Scale, showed significantly increased activation in the right rostral sgACC, the left medial prefrontal cortex, and the right precuneus. Studies with a higher rate of comorbidity with anxiety and mood disorders also found more pronounced activation in the right putamen, amygdala, and insula as well as less pronounced activation in the left amygdala and right vmPFC in patients compared with control subjects.

Studies with more male patients found significantly lower differences in presupplementary motor area activation. Finally, studies with longer mean duration of illness showed increased right putamen activation and decreased left temporal pole and OFC activation in patients versus control subjects.

Sensitivity Analysis and Publication Bias

The whole-brain jackknife sensitivity analysis showed that the main results were replicated in nearly all combinations of studies. Additional findings, however, appeared in some of the combinations. Activation of the left inferior frontal gyrus was found to be significantly increased in patients versus control subjects when one of nine studies was removed (5,6,13,31–34,52,53). The removal of one of three studies also resulted in significantly decreased activation in the bilateral ACC in patients. In addition, the removal of one of two different studies increased activation in the left angular gyrus (54) and right precuneus (13) in patients (see Supplemental Table S2 for detailed information). These jackknife analyses show that the findings of the main meta-analysis were largely robust, while hyperactivation in the left inferior frontal gyrus and hypoactivation in the bilateral ACC in patients may have been underestimated. However, there was no apparent pattern in these studies given that these spanned all functional tasks. In addition, the meta-regressions did not reveal any relations to any of the explored patient characteristics.

Inspections of Egger's intercepts and funnel plots did not indicate significant publication bias in any region from the main results, with the lowest p value on the Egger's test being .175. This indicates that there was a low risk of activation being overestimated because of studies being withheld or not being published.

DISCUSSION

The current study is the largest meta-analysis of emotional processing in OCD to date, encompassing 25 studies using a variety of emotional tasks, including symptom provocation using images or words as well as emotional variants of typical cognitive paradigms such as the emotional Stroop task and working memory tasks with emotional distractors. The results help to integrate a body of research that has often resulted in inconsistent findings that are hard to reconcile, particularly regarding the role of the amygdala in OCD. The main findings were that, compared with healthy control subjects, patients with OCD showed increased activation in the amygdala, OFC extending into the sgACC and vmPFC, putamen, and middle temporal and inferior occipital regions during emotional processing.

The meta-regression analyses showed that the findings in the amygdala are especially sensitive to a number of patient factors such as medication status and comorbidity. In contrast, the group effects in the amygdala were independent of mean symptom severity of the patient samples. Notably, the left and right amygdala showed opposite activation patterns in the meta-regressions for medication usage and comorbidity with anxiety and mood disorders. The right amygdala showed increased activation in studies with higher percentages of unmedicated patients and in studies with more comorbid disorders. By contrast, activation in the left amygdala was less pronounced in studies with more comorbidity. Studies with more male subjects showed lower differences in presupplementary motor area activation. Finally, studies with longer mean duration of illness showed increased differences in right putamen activation and lower differences in the left temporal pole and OFC. Unfortunately, the variance in gender was low, and approximately half of the studies did not report duration of illness, so these effects should be interpreted with caution. These meta-regressions contribute to the understanding of the mixed findings on amygdala involvement in OCD in the

Table 2. Meta-regressions of Factors Influencing the Difference Between Patients With OCD and HCs During Emotional Processing

Region	Side	MNI Coordinates (X, Y, Z)	BA	SDM *Z* Score	No. of Voxels	Cluster Breakdown
Medication Usage: Negative Correlations						
Inferior occipital gyrus	L	−32, −90, −10	19	−2.8702	294	Inferior, middle occipital gyrus
Amygdala	R	24, −6, −18	N/A	−2.685	269	Amygdala, parahippocampal gyrus
Y-BOCS: Positive Correlations						
sgACC	R	4, 34, −8	11	2.113	634	sgACC/rACC
Medial PFC	L	−4, 54, 20	10	1.854	174	–
Precuneus	R	16, −52, 20	17	2.063	84	–
Comorbidity: Positive Correlation						
Insula	R	40, 4, −10	48	1.758	64	Insula, putamen, amygdala
Comorbidity: Negative Correlations						
Amygdala	L	−22, 2, −22	N/A	−1.840	364	Amygdala, parahippocampal gyrus
vmPFC	R	4, 42, −18	11	−1.425	13	–
Gender: Negative Correlation						
Pre-SMA	R	4, 12, 58	6	−2.268	287	–
Illness Duration: Positive Correlation						
Putamen	R	20, 6, −10	N/A	1.614	48	–
Illness Duration: Negative Correlations						
Temporal pole	L	−36, 24, −10	38	−1.464	220	Temporal pole, OFC
OFC	L	−32, 30, −6	47	−1.308	15	–

BA, Brodmann area; HCs, healthy control subjects; L, left; MNI, Montreal Neurological Institute; N/A, not applicable; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; Pre-SMA, presupplementary motor area; PFC, prefrontal cortex; R, right; rACC, rostral anterior cingulate cortex; SDM, seed-based *d* mapping; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

literature, which has been the topic of much discussion (4,12–14,23). They also have implications for future research, showing factors that should be carefully considered in order to accurately measure the response in the limbic areas.

The robustly increased activation in the bilateral amygdala in patients with OCD during emotional processing fits with the proposed role of the amygdala in mediating anxiety, obsessionality, and the urge to ritualize (2,20,41). It also fits the recent findings of limbic interference during cognitive processing in OCD (23,55,56), limbic findings in animal models of OCD (24), and current models of affected frontolimbic and affective cortico-striato-thalamocortical circuits in OCD (23). Furthermore, the findings support that emotional reactivity to stimuli is important in OCD, which may have implications for the focus of psychological treatments (7,57,58).

Endured limbic hyperresponsiveness has been related to dysfunctional top-down control from the dorsal PFC, as shown by diminished frontolimbic functional connectivity during emotion processing (59). However, we were not able to investigate functional connectivity in this meta-analysis, and our results did not show decreased dorsal prefrontal recruitment in patients with OCD during emotional processing. Instead, we found increased activation of the OFC extending into the sgACC/vmPFC, and positive correlations between OCD symptom severity and activation in the same region extending to the rostral ACC. Inspection of the individual studies reporting altered sgACC activation showed that this was driven by increased activation in patients during aversive emotion processing rather than a lack of deactivation when shifting from neutral to aversive stimuli. The OFC plays a pivotal role in emotional decision making and the formation of emotional stimulus–outcome associations (60–62), but much is not known regarding the functional connectivity between cortical and subcortical areas in OCD. One hypothesis might be that both cortical areas (including the OFC/sgACC) and subcortical areas (such as the amygdala) excessively reinforce each other, where prefrontal emotional control does not dampen subcortical emotional responses. This would imply a failure of the top-down emotion regulation often seen in healthy control subjects (63). Limbic hyperactivation may also influence early recruitment of the inferior occipital gyrus, where the ventral visual stream becomes sensitive to disorder-relevant stimuli and relays their detection to the middle temporal cortex, which in turn upregulates activity in the amygdala (64,65). Finally, we also showed increased activation of the posterior putamen, which projects to both limbic and sensorimotor areas (66,67). This likely reflects its involvement in both the processing of aversive emotions and preparation of compulsive behaviors in OCD (23,68). Future research on connectivity patterns during emotional processing in OCD might establish whether a positive feedback loop between cortical and subcortical areas contributes to the maintained anxiety response that patients with OCD experience when they are prevented from performing compulsions.

Comparisons with findings from the largest meta-analysis of voxel-based morphometric studies comparing patients with OCD with healthy control subjects (69) also revealed partial overlap, specifically between altered gray matter volume and increased activation in the OFC, right amygdala, and putamen in patients with OCD.

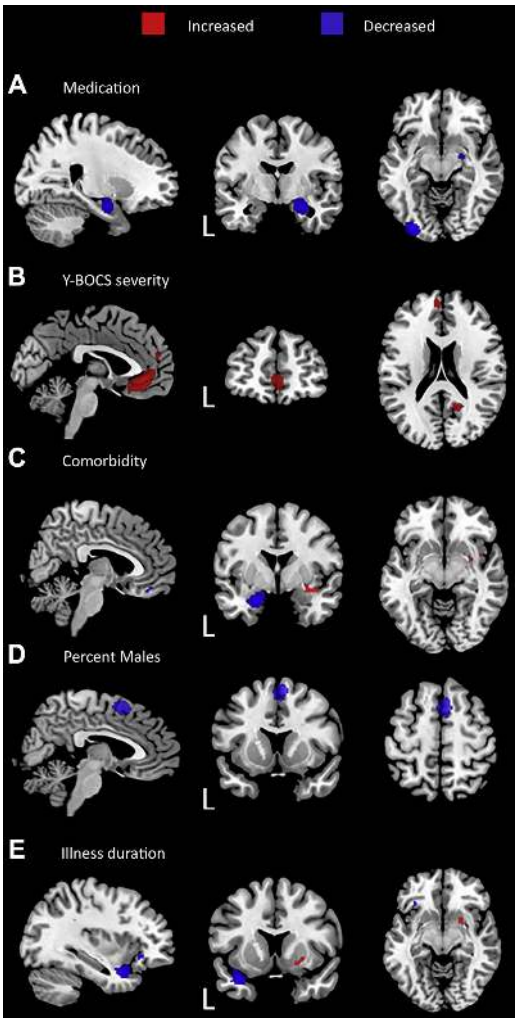

Figure 2. Results of meta-regressions indicating factors that are associated with an increased (red) or decreased (blue) difference between patients with obsessive-compulsive disorder and healthy control subjects. **(A)** Patient samples with more medicated patients showed less hyperactivation in the right amygdala and left cerebellum. **(B)** Increased symptom severity correlated with increased patient hyperactivation in the subgenual/rostral anterior cingulate cortex and medial prefrontal cortex. **(C)** Patient samples with more anxiety and mood disorder comorbidity showed increased activation in the right insula, putamen, and amygdala as well as decreased activation in the left amygdala and right ventromedial prefrontal cortex. **(D)** Patient samples with more male subjects showed less activation in the presupplementary motor area. **(E)** Patient samples with longer mean duration of illness showed increased activation in the right putamen and lower activation in the left temporal pole and orbitofrontal cortex. L, left; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Several studies have investigated whether disorder-specific stimuli elicit different neural responses compared with general aversive stimuli, with mixed results [e.g., (41,45,59)]. For instance, increased activation in the amygdala has been reported during disorder-specific stimuli in some studies (34,59), but not other studies, when compared with general aversive stimuli (45). Unfortunately, we were unable to compare the effects of disorder-specific stimuli with those of general stimuli due to the few studies with comparable paradigms. Because we were unable to differentiate between the provocations of specific symptom dimensions, we assume homogeneity in our analyses, while OCD is a highly heterogeneous disorder not only in its clinical presentation but also in its etiology (70–72). Different symptom dimensions seem to vary in their limbic involvement, being more pronounced in patients with more aggressive, sexual, or religious symptoms and checking rituals (13,73,74).

Abnormal recruitment of the brain circuits during emotional processing in patients with OCD may represent dynamic correlates of the symptom state and not necessarily a static traitlike marker of vulnerability to OCD. Indeed, several studies show that successful treatment with cognitive behavioral therapy or selective serotonin reuptake inhibitors at least partly normalizes patients' provocation-induced response in the OFC, putamen, and parietal cortex (23,75). Less is known about the effect of treatment on the limbic response. It is also possible that brain abnormalities constitute trait or risk factors for the disorder, given that unaffected first-degree relatives of patients with OCD also show increased activation in the OFC during a reversal learning task (76). Longitudinal, genetically informative designs, such as discordant monozygotic twin studies, are needed to shed further light on the origins of the observed emotional processing-related activation patterns in OCD.

The current results show notable differences compared with the findings of the previous smaller meta-analysis (19). For instance, we were not able to replicate the authors' findings of increased activation in the medial PFC, bilateral globus pallidus, right thalamus, left OFC, or left hippocampus in patients compared with healthy control subjects. Because we were able to include nearly three times as many studies as in the previous meta-analysis and selected only those using whole-brain analyses, the current results could be regarded as less sensitive to type I and type II errors.

Our study has some limitations that should be considered. We did not have access to patient-level data that may have provided additional power. Some of the included studies were quite small (the smallest including only 8 patients and 8 control subjects), and smaller studies may have an increased risk of introducing noise. The risk of undue noise was also increased because nearly every study used reported foci at uncorrected *p* values, which heightens the risk of false positives. Studies also varied in their use of statistical packages as well as their use of the Montreal Neurological Institute or Talairach coordinates, including the transformations used to convert between the coordinate systems. Although we used corrections for transforming the foci of each study into Montreal Neurological Institute coordinates using standard SDM procedures, this may have introduced additional noise into our meta-analysis. We chose to include only studies in English, which

may have excluded some studies. However, we are not aware of any relevant high-quality studies in other languages. Finally, although we did not find any significant differences in activation between studies using symptom provocation with pictures compared with all other paradigms, the current literature might not provide adequate power or homogeneity to find smaller differences. This could also be the case for the variables explored using meta-regressions given that the variance was limited in several of the variables. The field is currently lacking studies of emotional processing in pediatric OCD, and our findings may be seen as more generalizable to adult OCD. Studies that directly compare adults with children, or that follow developing children, are needed. The few studies employing each paradigm also meant that there would not have been enough power to adequately analyze them separately. However, a recent meta-analysis of 90 studies of obsessive-compulsive symptom induction in clinical and nonclinical samples showed similar results across a range of induction procedures (77). This provides some support for our nonsignificant comparison between studies using symptom provocation with pictures versus other paradigms.

Conclusions

Compared with healthy control subjects, patients with OCD show increased activation in the frontolimbic circuit, encompassing the amygdala, OFC/sgACC/vmPFC, occipital and middle temporal cortices, and posterior/ventral putamen. Furthermore, the degree to which patients and control subjects differ in their limbic and striatal responses is influenced by medication status, comorbidity, and symptom severity. These findings help to explain some of the inconsistencies in the literature and highlight the importance of well-powered meta- and mega-analyses of neuroimaging data.

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Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis of 25 Functional Neuroimaging Studies

Supplemental Information

Supplemental Table S1

Characteristics of included studies

Study	Imaging modality	Task	N OCD	N HC	Mean age	Males %	Mean Y-BOCS	Medicated %	Comorbid anxiety %	Comorbid depression %	Mean illness duration (years)
(1)	fMRI	Symptom provocation using pictures	29	21	36.55	50.5	27.2	79.31	31.03	41.37	NR
(2)	fMRI	Symptom provocation using pictures	15	15	32	53.33	26	93.33	0	0	NR
(3)	fMRI	Emotional faces and guilt-inducing sentences	13	19	37	76.92	19.3	46.15	NR	NR	NR
(4)	fMRI	Emotional Go/No-Go	9	10	38.33	55.55	23.35	42.11	50	77.77	NR
(5)	fMRI	Emotional Stroop	30	29	32	60	27.8	80	47	23	19
(6)	fMRI	Gender matching of emotional vs. neutral faces	12	17	13.8	58.33	17.8	100	41.7	25	4.20
(7)	fMRI	Emotional vs. neutral faces	10	10	26.8	40	26.3	0	10	0	NR
(8)	fMRI	Emotional face matching	21	21	28.5	47.62	20.7	95.2	23.8	9.5	8.7
(9)	fMRI	Symptom provocation using pictures	43	38	38.4	49.00	21.6	0	41.8	23.2	NR
(10)	fMRI	Symptom provocation using pictures	15	12	31.7	73.3	23.8	100	0	0	NR

Study	Imaging modality	Task	N OCD	N HC	Mean age	Males %	Mean Y-BOCS	Medicated %	Comorbid anxiety %	Comorbid depression %	Mean illness duration (years)
(11)	fMRI	Working memory task with emotional distractors	20	23	25.5	60	23.9	55	0	15	7.05
(12)	fMRI	Moral dilemmas	73	73	33.1	57.53	22.1	97.26	14	10	11.5
(13)	fMRI	Shame/guilt-related sentences	20	20	31.1	50	15.9	NR	0	0	NR
(14)	fMRI	Emotional vs. neutral faces	17	19	34.9	59	25.53	76.47	23.52	NR	15.73
(15)	fMRI	Symptom provocation using pictures	16	17	35.8	50	24.7	75	56.25	29.41	14.2
(16)	fMRI	Symptom provocation using words	22	19	36.1	36.36	29.9	0	0	0	12.63
(17)	fMRI	Emotional working memory	16	16	31.4	75	25.3	NR	0	0	5.9
(18)	fMRI	Symptom provocation using pictures	14	14	34	50	28	78.57	NR	NR	15.5
(19)	fMRI	Symptom provocation using pictures	8	8	41.8	37.5	25.1	0	NR	NR	NR
(20)	fMRI	Symptom provocation using pictures	15	15	43.3	50	24.9	0	NR	NR	NR
(21)	$H_2{}^{15}O$ -PET	Symptom provocation using pictures	11	10	40.5	72.72	23.8	0	0	0	NR
(22)	fMRI	Emotional Stroop	18	19	33.4	33.33	23.4	0	0	0	NR
(23)	fMRI	Emotional face matching	67	67	33.1	56.72	21.8	97.01	16	9	11.42
(24)	fMRI	Symptom provocation using pictures	42	37	32.5	35.71	17.7	62.3	19.05	32.2	16.23
(25)	fMRI	Olfactory symptom provocation	15	15	34.07	53.33	17.73	93.3	50	64.89	16.8

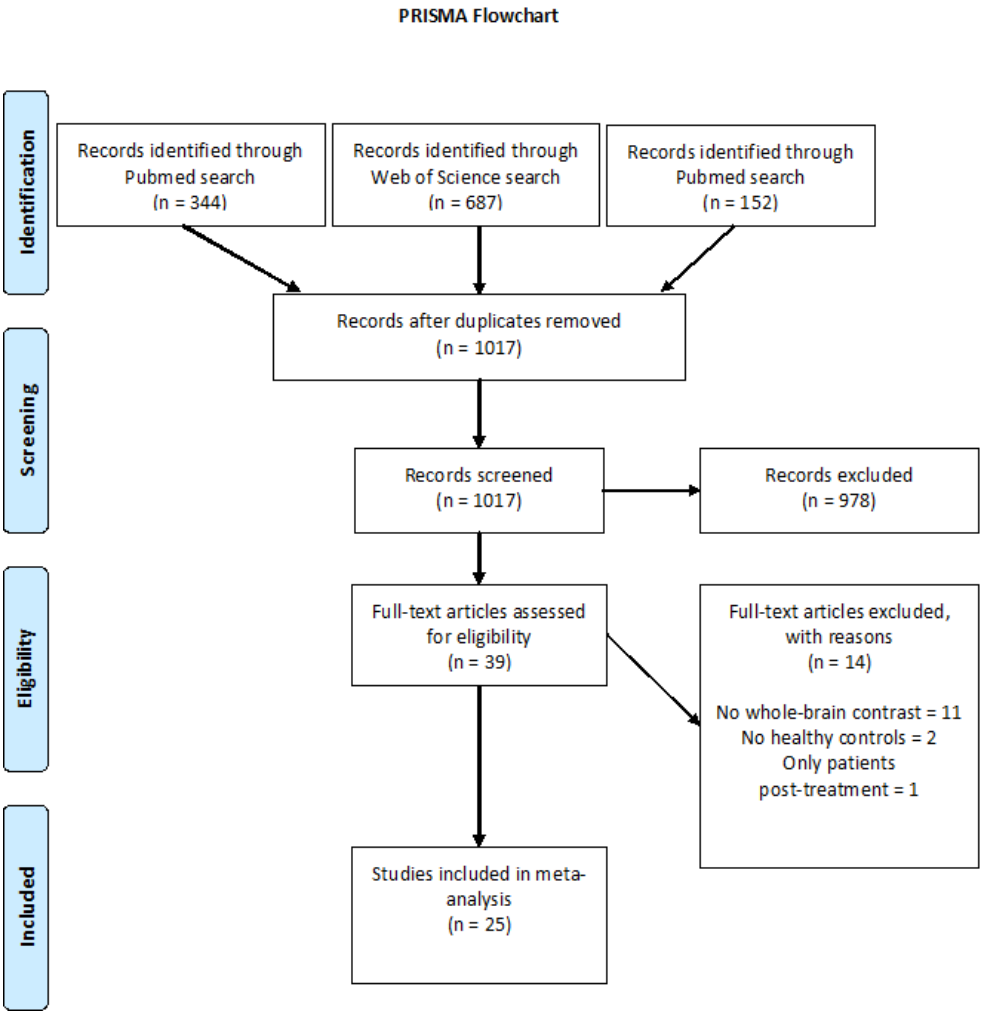
Abbreviations: HC, healthy controls; fMRI, functional magnetic resonance imaging; OCD, obsessive-compulsive disorder; PET, positron emission tomography; NR, not reported; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Supplemental Table S2

Sensitivity of the results to the iterative removal of each study

Removed study	Region negatively influenced by removal	Region positively influenced by removal
(1)	-	L IFG, OCD > HC
(2)	-	L IFG, OCD > HC
(3)	-	-
(4)	-	ACC, HC > OCD
(5)	-	L IFG, OCD > HC
(6)	-	-
(7)	-	-
(8)	-	-
(9)	L amygdala, L IOC, OCD > HC	-
(10)	-	-
(11)	-	-
(12)	R OFC, OCD > HC	R IFG, L angular gyrus, OCD > HC
(13)	-	L IFG, OCD > HC
(14)	-	-
(15)	-	ACC, HC > OCD
(16)	L IOC, OCD > HC	L IFG, OCD > HC
(17)	-	L IFG, OCD > HC
(18)	-	L IFG, OCD > HC
(19)	-	-
(20)	-	-
(21)	R OFC, OCD > HC	-
(22)	-	L IFG, OCD > HC, ACC HC > OCD
(23)	-	L IFG, R precuneus, OCD > HC
(24)	-	-
(25)	-	-

Abbreviations: ACC, anterior cingulate cortex; HC, healthy controls; IFG, inferior frontal gyrus; IOC, inferior occipital cortex; L, left; OCD, obsessive-compulsive disorder patients; R, right.



Supplemental Figure S1

Flowchart of the results of the systematic search, inclusion, and exclusion of studies.

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Paper II

II

Biological Psychiatry: CNNI

Archival Report

Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings, and Unrelated Healthy Control Participants

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ABSTRACT

BACKGROUND: Functional neuroimaging endophenotypes of obsessive-compulsive disorder (OCD) have been suggested during executive tasks. The purpose of this study was to investigate whether behavioral and neural responses during emotion processing and regulation also represent an endophenotype of OCD.

METHODS: Forty-three unmedicated adult OCD patients, 19 of their unaffected siblings, and 38 healthy control participants underwent 3T functional magnetic resonance imaging during an emotion regulation task including neutral, fear-inducing, and OCD-related visual stimuli. Stimuli were processed during natural appraisal and during cognitive reappraisal, and distress ratings were collected after each picture. We performed between-group comparisons on task behavior and brain activation in regions of interest during emotion provocation and regulation.

RESULTS: Siblings reported similar distress as healthy control participants during provocation, and significantly less than patients. There was no significant three-group difference in activation during fear provocation or regulation. Three-group comparisons showed that patients had higher amygdala and dorsomedial prefrontal cortex activation during OCD-related emotion provocation and regulation, respectively, while siblings were intermediate between patients and control participants but not significantly different from either. Siblings showed higher left temporo-occipital activation (compared with both healthy control participants and patients) and higher frontolimbic connectivity (compared with patients) during OCD-related regulation.

CONCLUSIONS: Unaffected siblings do not show the same distress and amygdala activation during emotional provocation as OCD patients. Siblings show distinct activation in a temporo-occipital region, possibly related to compensatory cognitive control. This suggests that emotion regulation is not a strong endophenotype for OCD. When replicated, this contributes to our understanding of familial risk and resilience for OCD.

Keywords: Emotion regulation, Emotional provocation, Endophenotype, Familial risk, fMRI, Obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) is characterized by distressing obsessive thoughts, urges, or images that patients try to manage or neutralize through compulsive behaviors (1). The disorder affects 1% to 3% of the population (1) and has a large impact on social and personal impairment (2,3). OCD is a highly familial disorder (4), with first-degree family members of OCD patients having a nearly fivefold increase in the odds of developing the disorder compared with family members of non-OCD participants (5). Although genetic factors may explain as much as 47% of the variance of the risk for developing OCD (5), the underlying genetic factors are not well known (4).

An endophenotype is defined as a measurable trait along the path between the phenotype of the disorder and the distal genotype (6). Because of the considerable heterogeneity in the symptoms, etiology, and genetic risk markers of OCD, the diagnosis itself is hard to robustly relate to genetic variation (4,7,8). Endophenotypes may provide simpler clues to the genetic basis of a disorder than the disorder itself and contribute to bridging clinical heterogeneity and genetic vulnerability (6). In this context, functional neuroimaging studies on endophenotypes allow for investigating shared behavioral and neural characteristics between OCD patients and their first-degree unaffected family members, in comparison with unrelated healthy control participants (9). Previous functional neuroimaging studies showed that OCD patients and their unaffected relatives show similarities in neural responses during response inhibition (10,11), working memory (12), reversal learning (13), and error monitoring (14). For example, in previous reports on response inhibition and working memory involving the same participants as in the

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current study, OCD patients and their unaffected siblings shared compensatory higher task-related activation in the left presupplementary motor area, as well as altered frontolimbic connectivity, compared with unrelated healthy control participants (10,12,15).

Neural responses during paradigms using emotion provocation with disorder-specific stimuli may provide a more disorder-specific endophenotype for OCD, as deficits in executive functioning are not specific to this disorder (16). When confronted with disorder-specific objects, situations, or thoughts, OCD patients often react with negative emotions such as anxiety, fear, guilt, or disgust, and they often experience an increased urge to ritualize (17,18). In a recent meta-analysis of 25 whole-brain studies contrasting aversive and neutral stimuli, OCD patients showed higher activation than control participants during emotion provocation in the bilateral amygdala, right putamen, orbitofrontal cortex (extending into the subgenual anterior cingulate cortex and ventromedial prefrontal cortex [PFC]), middle temporal cortex, and left inferior occipital cortex (19).

Emotion regulation involves changing emotional responses through active processes such as altering attentional deployment, cognitive reappraisal (reinterpreting the meaning and one's connection to a stimulus), or suppression of the expression or experience of an emotion, and over time these active processes are learned and become more automatic (20). Functional magnetic resonance imaging (fMRI) studies have shown that cognitive reappraisal is associated with higher activation in the dorsomedial and lateral frontal cortices, dorsal anterior cingulate cortex, and parietal and temporal regions (21,22).

Cognitive behavioral models suggest that the catastrophic interpretations of obsessions and the use of compulsions as dysfunctional methods of emotion regulation maintain the disorder (23). Maladaptive emotion regulation strategies, such as suppression, have also been related to increased distress in response to obsessions over time, while acceptance decreases distress (24). In addition, suppression has been related to increased severity of OC symptoms (25). In a previous study we investigated whether unmedicated OCD patients and healthy control participants differed in how successfully they used cognitive reappraisal to regulate distress provoked by fear- and OCD-related pictures, and whether OCD patients show altered activation of emotion regulation–related circuitry using fMRI (26). We showed that distress ratings were higher in OCD patients than in control participants, but that patients were well able to downregulate distress while viewing fear- and OCD-related pictures within the experimental setting. However, this was accompanied by aberrant brain activation in patients versus control participants. OCD patients showed greater emotion provocation-induced amygdala activation and altered timing, while emotion regulation–related activation was lower in the left dorsolateral PFC (dlPFC) and parietal cortex while viewing fear-related pictures, and higher in the dorsomedial PFC (dmPFC) while viewing OCD-related pictures. In addition, patients also showed less functional connectivity between the dmPFC and bilateral amygdala during regulation of fear-related pictures (26). This suggests that OCD patients show frontolimbic and frontoparietal dysfunction during emotion processing, but whether this dysfunction represents a consequence of the disorder or an underlying vulnerability factor remains unanswered.

The aim of the present study was to explore the neural correlates of disorder-specific emotion provocation and regulation as a potential endophenotype of OCD. Extending our previous findings on emotion regulation in OCD, we compared distress ratings and brain activation during emotion provocation and regulation in a group of unaffected siblings, with those of the previously studied OCD patients and healthy control participants (26). Using group comparisons of task-related activation in a priori regions of interest (ROIs), as well as frontolimbic functional connectivity analyses, shared and nonshared activation patterns during emotion provocation and regulation of general fear– and OCD-related stimuli were probed. Based on the previous endophenotype findings in this sample using executive paradigms (10,12,15), we hypothesized that siblings would resemble healthy control participants on the behavioral level (i.e., normal levels of provoked distress) and also show similar amygdala activation during emotion provocation (i.e., less activation compared with OCD patients). During regulation we expected that siblings would resemble OCD patients on the neural level (i.e., decreased activation in dlPFC during fear regulation, increased dmPFC activation during OCD-related regulation, and reduced frontolimbic connectivity compared with healthy control participants).

METHODS AND MATERIALS

Participants

Forty-three patients with a primary diagnosis of OCD, 19 of their unaffected siblings, and 38 healthy control participants were included in the study (see the Supplement for recruitment information). All participants were assessed using the Structured Clinical Interview for DSM-IV (27). The Yale-Brown Obsessive Compulsive Scale (28) and the Obsessive-Compulsive Inventory–Revised (29) were used to assess the severity of OC symptoms. Depressive symptoms were measured using the Montgomery–Åsberg Depression Rating Scale (30). The Emotion Regulation Questionnaire (31) was used to measure reappraisal and suppression as emotion regulation strategies in daily life. Handedness was assessed using the Edinburgh Handedness Inventory (32).

All participants had not used psychotropic medication for at least 4 weeks before inclusion, and had no psychotic symptoms, major physical or neurological illness, or any MRI contraindications. All patients had a primary diagnosis of OCD according to DSM-IV criteria and did not meet criteria for hoarding disorder. Patients experiencing other comorbidities were included as long as OCD was the primary diagnosis. Control participants were excluded if they met criteria for any current DSM-IV diagnosis, while siblings were excluded if they had a lifetime history of OCD. The study was in full compliance with the ethical standards of the local medical ethical review board of VU University Medical Center and with the Helsinki Declaration of 1975, revised in 2008, and all participants provided written informed consent.

The results of the comparison between OCD patients and healthy control participants have been presented previously (26). All subjects also participated in previous endophenotype analyses on response inhibition (10) and working memory (12).

The data for these reports were all collected during the same experiment.

Experimental Task

All participants performed an emotion regulation task [see de Wit *et al.* (26) and the Supplement for detailed procedures] and were presented with neutral, fearful, and OCD-related pictures. The OCD stimuli included those pertinent to washing, checking, and symmetry symptom dimensions, and all the participants watched the same stimuli to capture the symptom heterogeneity of OCD. The participants were instructed to either simply attend to the presented stimulus ("attend" instruction) or use cognitive reappraisal techniques to downregulate negative emotions and cognitions provoked by the stimulus ("regulate" instruction). Stimuli were presented in attend or regulate blocks for each picture type, and each stimulus was followed by having the participants indicate their current level of distress by moving a cursor to either the left (marked "not distressed") or the right ("maximally distressed") along a visual analog scale. Neutral stimuli were presented in the attend condition only.

Statistical Analysis of Behavioral and Clinical Measures

Group comparisons of clinical and demographical variables were analyzed using one-way analyses of variance (ANOVAs), and followed up by post hoc two-sample *t* tests. Categorical variables were analyzed using χ^2 tests. Distress scores during the attend and regulate conditions were analyzed separately for fear- and OCD-related pictures using repeated-measures mixed ANOVAs, with group (OCD patients, siblings, control participants) as the between-subjects factor followed by post hoc *t* tests if the main effects were significant. Within-group tests of changes in distress during provocation and regulation were analyzed with paired-sample *t* tests. Analyses were performed using SPSS statistics version 23 (IBM Corp., Armonk, NY). The statistical threshold was set at $p < .05$, with Tukey or Games-Howell corrections being used for post hoc tests of one-way and repeated-measures ANOVAs.

MRI Acquisition, Processing, and Analysis

Functional gradient echo-planar and structural T1-weighted imaging was performed on a GE Signa HDxt 3.0T MRI scanner (GE Healthcare, Chicago, IL). Functional data were preprocessed and analyzed in SPM8 (Wellcome Trust Centre for Imaging, London, United Kingdom) (see the Supplement for acquisition parameters and preprocessing steps). Intrasubject first-level analyses included nine regressors of interest consisting of the neutral (attend only), general fear, contamination, checking, and symmetry OCD-related pictures during attend and regulate instruction. Regressors of no interest included the time windows where the participants rated their distress (boxcars of 5 seconds), instruction periods (boxcars of 3 seconds), and the participant's six movement parameters. The first-level analyses were different for emotion provocation and emotion regulation to capture the different timings of these respective processes [as we described previously in de Wit *et al.* (26)]. In the emotion provocation analysis, regressors of interest were modeled as 0-second delta functions and convolved with the canonical hemodynamic response function (HRF), and its temporal and dispersion derivatives to model the amplitude of the blood oxygen level–dependent response and variation in its timing and shape. Fear > neutral and OCD > neutral contrast images (collapsed over the attend and regulate instructions) were then computed per participant. In the emotion regulation analysis, activation during emotion regulation was modeled as boxcars of the first 5 seconds of fear and the OCD-related stimuli, and were convolved with the canonical HRF. Contrast images were then computed for fear regulate > attend and OCD regulate > attend. A high-pass filter with a 128-second cutoff was used to remove low-frequency noise. See the Supplement for all additional information on MRI acquisition and modeling.

To test whether unaffected siblings also showed altered functional connectivity between the bilateral amygdala and dmPFC during emotion regulation, which was previously reported for patients versus control participants (26), we used the Generalized Psychophysiological Interaction toolbox (33) (see the Supplement). The dmPFC seed region was set at Montreal Neurological Institute x/y/z of −9/8/64, with a 10-mm sphere, based on the patient-control comparison (26). The WFU PickAtlas (http://fmri.wfubmc.edu/software/pickatlas) was used to determine the bilateral amygdala ROIs for functional connectivity.

Planned group comparisons were performed by entering the first-level contrast images into general linear models using SPM12. Between-group comparisons for emotion provocation were performed using separate 3 × 3 ANOVAs with group (OCD patients, siblings, control participants) as a between-subject factor and HRF (canonical, temporal, dispersion) as a within-subjects factor. A 3 × 2 × 3 ANOVA (group by HRF by picture type [fear- and OCD-related]) was used to test the group by picture type interactions. Group comparisons of emotion regulation and functional connectivity were performed using separate one-way ANOVAs for the two picture types (fear- and OCD-related stimuli), with group as the between-subjects factor. For all group comparisons we first used an *F* contrast to estimate the main effect of group, and the group by instruction interaction where appropriate. Post hoc two-group comparisons were then performed to follow-up significant effects (two-group ANOVAs for the emotion provocation analysis and *t* tests for the emotion regulation analysis).

We used an ROI approach, which was derived from the largest meta-analyses of emotion provocation in OCD compared with healthy control participants (five ROIs) (19), and emotion regulation in healthy control participants (eight ROIs) (21,22), as no published meta-analysis of emotion regulation comparing OCD patients and healthy control participants was available (see Supplemental Table S2 for all ROIs, and the Supplement for more information on ROI definitions, placement, and extraction). The ROIs were placed at the relevant effects of task after initial image thresholding of uncorrected $p < .001$. Statistical significance was set at $p < .05$ familywise error corrected with small volume correction (*p*FWE-SVC) with a 10-mm sphere (*p*FWE-SVC < .05; trends $p < .10$) (34). Results were corrected for the number of ROIs for each contrast using a SISA-Bonferroni correction (see http://www.quantitativeskills.com/sisa/calculations/bonhlp.htm) (35). Separate SISA-Bonferroni corrected *p* values were calculated

per analysis because of differences in provocation related distress and regulation-related reductions in distress between the picture types (see the Supplement for more information).

RESULTS

Demographic and Clinical Characteristics

The groups were demographically matched. Patients scored significantly higher on every clinical measure compared with both siblings and control participants, while siblings and control participants did not significantly differ (see Supplemental Table S1 for all results). For the Emotion Regulation Questionnaire, there was a main effect of group for the use of reappraisal. Post hoc tests showed that patients scored lower than control participants, and siblings scored intermediate (not significantly different from either). Twenty-one OCD patients (49%) had a comorbid DSM-IV diagnosis (details in Supplemental Table S1). One sibling met criteria for specific phobia, which did not interfere with scanning, while no control participants met criteria for any current mental disorder.

Distress Ratings During Emotion Provocation and Regulation

Fear- and OCD-related pictures elicited more distress than neutral pictures for all three groups, regardless of the task instruction (all $p < .05$) (see Table 1 for all behavioral results). There was a significant main effect of group (F contrast: fear, $p < .001$; OCD, $p < .001$), with post hoc tests showing that OCD patients reported more distress in general during both fear- and OCD-related pictures than healthy control participants and siblings, whereas siblings were not significantly different from control participants (t test: fear related, $p = .97$; OCD related, $p = .86$). There was a main effect of regulation across the three groups (F contrast: fear related, $p = .02$; OCD related, $p < .01$). For fear stimuli there was no significant group by instruction interaction ($p = .06$), whereas the interaction analysis was significant for OCD stimuli ($p < .01$). Post hoc two-sample t tests showed that OCD patients reported significantly larger distress reductions during OCD-related regulation compared with both siblings ($t_{43.29} = -3.79$, $p < .01$) and control participants ($t_{75.16} = -2.59$, $p = .01$), whereas siblings were not different from control participants ($t_{55} = 0.57$, $p = .57$).

Within-group paired-sample t tests revealed a regulation effect (higher distress ratings during attend instruction compared with regulation instruction) for OCD patients while viewing both picture types and in healthy control participants for fear-related pictures (all $p \leq .05$). In siblings, there was no regulation effect for fear-related ($p = .43$) or OCD-related ($p = .06$; trend) pictures.

Neural Response During Emotion Provocation in ROIs

The three-group comparison for fear provocation showed no significant differences between the groups (Supplemental Table S3). During OCD-related provocation there was a significant main effect of group in the right amygdala extending into the hippocampus, driven by alterations in the timing and shape of the blood oxygen level–dependent response in OCD patients compared with healthy control participants, whereas siblings were intermediate and not significantly different from either group (Table 2). The group by picture type interaction analysis was trend significant ($p = .02$) (Table 2). This was driven by higher responses in the right amygdala during OCD-related rather than fear-related provocation in patients compared with healthy control participants, as we previously showed (26), whereas the siblings were an intermediate group not different from either group.

Neural Response During Emotion Regulation in ROIs

Three-group comparison showed no significant group differences in activation in any of the ROIs during fear-related emotion regulation. For OCD-related regulation a significant main effect of group was found in the dmPFC and the left temporo-occipital cortex (see Table 3 and Figure 1). On post hoc tests, siblings showed significantly higher activation in the left temporo-occipital cortex compared with healthy control participants and patients. Higher dmPFC activation, as previously found in patients compared with healthy control participants, was also present in siblings compared with control participants, albeit at a trend level.

Functional Connectivity During Emotion Regulation in ROIs

The comparisons of frontolimbic connectivity during fear- and OCD-related regulation did not reveal any significant differences between the three groups (Supplemental Table S6). Exploratory post hoc analyses showed that the previously reported decreased frontolimbic connectivity in patients compared with healthy control participants during fear-related regulation was present for the left (Z score = 3.36, pFWE-SVC = .016) and right amygdala (Z score = 3.30, pFWE-SVC = .019) but that siblings were an intermediate group not significantly different from either group (see Supplemental Figure S1 for group-specific parameter estimates). Specifically, pairwise comparisons of connectivity during OCD-related regulation showed higher dmPFC-amygdala connectivity in siblings compared with patients (Z score = 3.22, pFWE-SVC = .023) and right amygdala (Z score = 3.30, pFWE-SVC = .019), while there were no other significant between-group differences.

DISCUSSION

The present study assessed whether the neural correlates of disorder-specific emotion processing and regulation can serve as a potential endophenotype of OCD. To this aim, we investigated emotion processing during fMRI scanning in unaffected siblings of a large sample of unmedicated OCD patients and in unrelated healthy control participants. We found that siblings resembled control participants in self-reported distress and clinical profile. When assessing brain activation patterns in ROIs during emotion provocation and regulation, we mostly observed that siblings were an intermediate group between patients and control participants. We also found that siblings showed slightly higher dmPFC activation during OCD-related regulation compared with OCD patients and healthy control participants, but this difference was not statistically significant.

Table 1. Group Comparisons of Behavioral Response: Distress During Provocation and Regulation

	OCD Patients (n = 43)			Siblings (n = 19)			HC Participants (n = 38)		
Neural Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	2.04	5.24		0	0		0.74	2.78	
Fear-Related Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	41.44	31.15		16.42	14.58		20.74	26.53	
Regulation	33.74	28.29		14.68	14.20		13.21	15.57	
	t	*df*	*p*	*t*	*df*	*p*	*t*	*df*	*p*
Provocation vs. regulation	2.02	42	.05[a]	0.80	18	.43	2.12	37	.04[a]
	F			*df*			*p*		
Main effect of group	11.28			1, 97			<.01[a]		
Main effect of instruction	5.98			1, 97			.02[a]		
Group × instruction interaction	0.57			2, 97			.57		
	t			*df*			*p*		
Post hoc tests (provocation)									
Siblings vs. OCD	−4.31			59.72			<.01[a]		
Siblings vs. HC participants	−0.66			55			.84		
Post hoc tests (regulation)									
Siblings vs. OCD	−3.53			58.89			<.01[a]		
Siblings vs. HC participants	0.39			55			.97		
OCD-Related Pictures	Mean	SD		Mean	SD		Mean	SD	
Provocation	22.30	17.95		2.75	4.56		4.88	11.93	
Regulation	14.36	9.82		2.26	4.51		3.21	7.05	
	t	*df*	*p*	*t*	*df*	*p*	*t*	*df*	*p*
Provocation vs. regulation	4.08	42	<.001[a]	2.02	18	.06	1.15	37	.26
	F			*df*			*p*		
Main effect of group	25.52			1, 97			<.01[a]		
Main effect of instruction	9.86			1, 97			<.01[a]		
Group × instruction interaction	5.47			2, 97			<.01[a]		
	t			*df*			*p*		
Post hoc tests (provocation)									
Siblings vs. OCD	−6.67			52.56			<.01[a]		
Siblings vs. HC participants	−0.75			55			.84		
Post hoc tests (regulation)									
Siblings vs. OCD	−6.64			59.85			<.01[a]		
Siblings vs. HC participants	−0.62			55			.91		

Responses were rated on a scale of 1 to 100.
HC, healthy control; OCD, obsessive-compulsive disorder.
[a]Significant within- or between-group effect.

We previously compared the same group of patients and control participants directly (26) and observed in OCD patients amygdala hyper-responsiveness during OCD-related emotion provocation, dlPFC hypoactivation and lower dmPFC-amygdala connectivity during fear regulation, and dmPFC hyperactivation during OCD-related emotion regulation. Here, we found that prefrontal and amygdala activation were not significantly different in siblings compared with either OCD patients or control participants during either OCD-related emotion provocation (amygdala) and regulation (dmPFC) or emotion regulation of fear stimuli (dlPFC activation and dmPFC-amygdala connectivity). A sibling-specific finding was increased activation in the temporo-occipital cortex, bordering on the angular gyrus, during OCD-related emotion regulation, in siblings compared with both control participants and patients. Siblings also showed higher dmPFC-amygdala connectivity compared with patients during OCD-related emotion regulation. The difference between the findings in the present report and the earlier report is likely due to methodological differences: 1) the present use of a priori defined ROIs based on meta-analyses, compared with the earlier use of functionally defined ROIs (26), and 2) due to performing a three-group ANOVA in which the dlPFC response in the sibling group is intermediate between patients and control participants. This is also reflected in the Supplemental whole-brain results, showing the same hypoactivation of the dlPFC during fear-related regulation in OCD patients compared with healthy control participants.

Table 2. Group Comparisons of Brain Activation During Emotion Provocation

	BA	Side	K_e	MNI Coordinates x	y	z	*Z*	*p*FWE-SVC
Fear Provocation: Main Effect of Group (ANOVA) (no significant voxels)								
OCD-Related Provocation: Main Effect of Group (ANOVA)								
Amygdala	N/A	R	12	27	−7	−17	3.58	.013[a]
Fear-Related vs. OCD-Related Provocation: Group by Picture Type Interaction (ANOVA)								
Amygdala	N/A	R	5	27	−7	−17	3.45	.020[b]
		K_e		*Z* Score		*p*FWE-SVC		
OCD-Related Provocation: Post Hoc Pairwise Comparisons in Right Amygdala								
Siblings vs. HC participants		NS		NS		NS		
Siblings vs. OCD		NS		NS		NS		
OCD patients vs. HC participants		21		4.22		.001[a]		
Fear-Related vs. OCD-Related Provocation: Post Hoc Pairwise Comparisons in Right Amygdala								
Siblings vs. HC participants		NS		NS		NS		
Siblings vs. OCD patients		NS		NS		NS		
OCD patients vs. HC participants		19		4.12		.001[a]		

ANOVA, analysis of variance; BA, Brodmann area; FWE, familywise error; HC, healthy control; K_e, voxel extent of cluster; MNI, Montreal Neurological Institute; N/A, not applicable; NS, not significant; OCD, obsessive-compulsive disorder; R, right; SVC, small volume correction.
[a]Significant between-group findings.
[b]Trend significant.

One explanation for the current findings is that in OCD, altered emotion processing is more state dependent than the previously reported traitlike cognitive endophenotypes, which were found to be related to altered frontoparietal recruitment, and likely related to a shared genetic vulnerability to the disorder (10,12,15). Previous task-related fMRI studies in first-degree relatives of OCD patients showed altered recruitment of frontal and parietal regions including the presupplementary motor area (10,12), dlPFC (12,13), inferior frontal gyrus (13), parietal cortex (12,13), and precuneus (12) during reversal learning, response inhibition, working memory, and error processing. During resting state, this sample of unaffected siblings (compared with healthy control participants) also showed higher connectivity between the frontoparietal control networks and the rostral anterior cingulate cortex and dmPFC, whereas only patients showed alterations in the frontolimbic circuit (36). Similarly, in this same sample of siblings, frontal-amygdala coupling during executive task we observed to have small or trend-significant aberrations, whereas findings in patients compared with control participants were more robust (12,15). In the present study, exploratory post hoc tests showed that siblings exhibited greater dmPFC-amygdala connectivity during disorder-specific emotion regulation than OCD patients. The increased frontolimbic connectivity in

Table 3. Group Comparisons of Brain Activation During OCD-Related Emotion Regulation

	BA	Side	K_e	MNI Coordinates x	y	z	*Z*	*p*FWE-SVC
Fear Regulation: Main Effect of Group (ANOVA) (no significant voxels)								
OCD-Related Regulation: Main Effect of Group (ANOVA)								
dmPFC	32	Midline	5	0	29	40	3.75	.005[a]
Temporo-occipital cortex	37	L	4	−39	−61	13	3.43	.013[a]
		K_e		*Z* Score		*p*FWE-SVC		
OCD-Related Regulation: Post Hoc Pairwise Comparisons in dmPFC								
Siblings > HC participants		1		3.22		.022[b]		
OCD patients > siblings		–		–		NS		
OCD patients > HC participants		10		3.82		.003[a]		
Post Hoc Pairwise Comparisons in Left Temporo-occipital Cortex								
Siblings > HC participants		18		3.67		.006[a]		
Siblings > OCD patients		2		3.22		.020[a]		
OCD patients > HC participants		–		–		NS		

ANOVA, analysis of variance; BA, Brodmann area; dmPFC, dorsomedial prefrontal cortex; FWE, familywise error; HC, healthy control; K_e, voxel extent of cluster; L, left; MNI, Montreal Neurological Institute; NS, not significant; OCD, obsessive-compulsive disorder; SVC, small volume correction.
[a]Significant between-group findings.
[b]Trend significant.

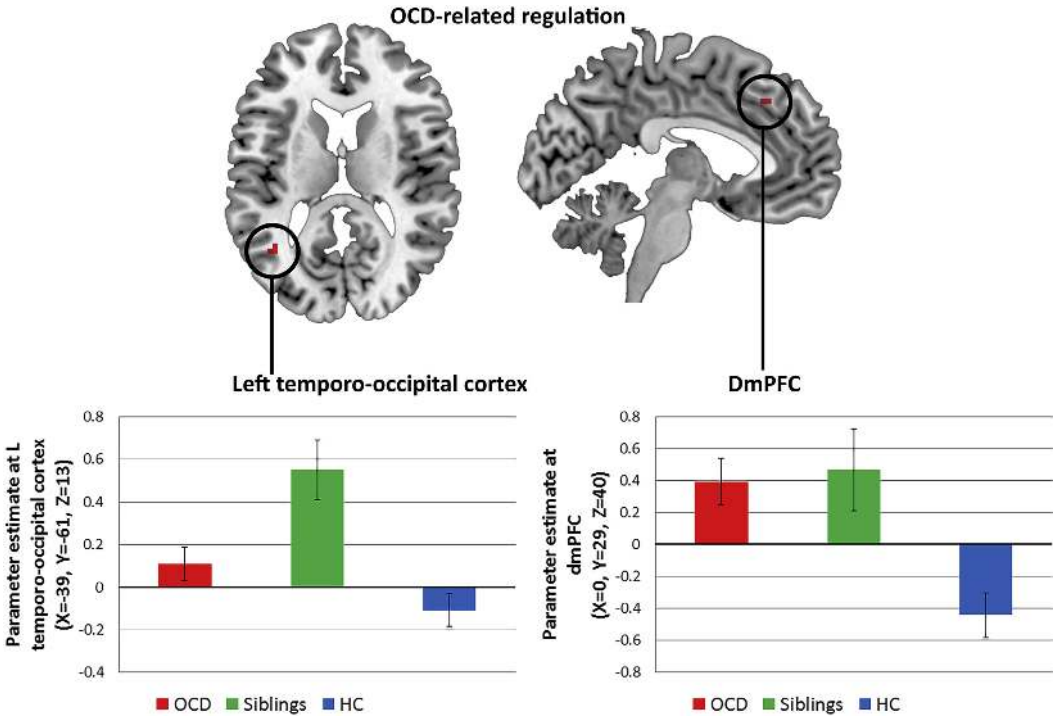

Figure 1. Group comparisons of activation during obsessive-compulsive disorder (OCD)–related emotion regulation. Top left: higher activation of the left temporo-occipital cortex in unaffected siblings compared with healthy control (HC) participants during OCD-related emotion regulation. Top right: higher activation of the dorsomedial prefrontal cortex (dmPFC) in OCD patients and siblings (trend) over HC participants during OCD-related emotion regulation. Bottom left and bottom right: parameter estimates of the blood oxygen level–dependent signal for each group during OCD-related regulation in the left temporo-occipital cortex and dmPFC, respectively. Parameter estimates are in arbitrary units, with standard errors. L, left.

siblings may represent a compensatory mechanism. Larger samples are needed, however, to better investigate this speculation.

It could also be that blood oxygen level–dependent responses in emotional paradigms in siblings are more variable than during executive functioning. This potential variability together with the relatively small sibling group size could have reduced the power to detect differences, resulting in the intermediate activation patterns in the siblings group. This is in contrast with findings in the same sibling group during inhibition and working memory where frontoparietal responses were more robust and/or extensive in the siblings compared with patients (10,12). Alternatively, a more robust provocation of distress in siblings and control participants might be needed to avoid floor effects during symptom provocation paradigms. Future research could consider how to evoke distress in healthy participants that resembles the response typically found in OCD patients.

One criterion for a candidate endophenotype is that the trait is more commonly found in unaffected family members of patients than in unrelated healthy control participants (6). Because we did not find that patients and their siblings showed the same degree of amygdala hyper-responsiveness during OCD-related emotion provocation, dlPFC hypoactivation during fear regulation, dmPFC hyperactivation during OCD regulation, or decreased frontolimbic connectivity during emotion regulation, we conclude that the neural correlates of emotion regulation are likely not a strong endophenotype of OCD.

The siblings showed increased temporo-parieto-occipital activation during regulation of disorder-specific stimuli compared with patients and control participants. The temporo-parieto-occipital brain regions are part of the larger cross-modal association cortex involved in attentional control and visuospatial representation during emotion processing (37). Taken together with the siblings' higher frontal-parietal network (36), our results suggest that siblings draw on additional resources compared with OCD patients and healthy control participants. This region has previously been reported as being especially recruited when distancing oneself from a stimulus to regulate one's emotions, while prefrontal dorsomedial and anterior cingulate activation is recruited more during reappraisal (20,38). We therefore speculate that siblings redirect their attention and distance themselves from aversive

stimuli before they elicit an emotional response, while the patients rely more on reinterpreting stimuli that are already aversively laden. This distinct recruitment of the temporo-occipital cortex in unaffected siblings could be interpreted as a compensatory response to an underlying vulnerability as seen in their afflicted siblings, possibly protecting them from developing the stronger emotional responses seen in their afflicted siblings. Structural abnormalities of nearby brain regions have been reported in siblings, including reduced fractional anisotropy in the right parietal lobule (39), and increased cortical thickness in the right precuneus (40).

Our findings of trend-significant increased dmPFC activation in siblings suggest that the OCD-related stimuli were somewhat more relevant for them than for the healthy control participants at a neural level, although this did not result in higher self-reported distress scores than in healthy control participants. Altered dmPFC activation may be related to the shared genetic vulnerability factors (increased threat sensitivity), or it might be part of a compensatory mechanism: OCD patients with lower Yale-Brown Obsessive Compulsive Scale scores reported more use of reappraisal in daily life, and also showed greater dmPFC activation during OCD-related regulation (26). In combination with the greater dmPFC activation in siblings, this suggests that dmPFC activation is compensatory, and not necessarily a vulnerability factor for OCD. Studying neural correlates of emotion processing using a longitudinal design (e.g., pre- and posttreatment) may help disentangle the neural correlates of genetic vulnerability and environmental risk (6) and the correlates of plasticity that result from disorder chronicity and successful treatment (41).

Limitations of the present study include the small number of siblings, which probably contributed to lower statistical power for this group, which could be especially relevant in the case of heterogeneity. The lower distress ratings and regulation effects in siblings and control participants suggest that the task was not as relevant for them, limiting the generalization of the findings to emotion regulation processes for more distressful situations. Finally, psychophysiological measures could have provided another view of data. Strengths include the large sample of unmedicated patients, the ability to differentiate between general fear and disorder-specific provocation and regulation-related brain activation and connectivity, and the use of rigorous meta-analyses to define a priori ROIs and adequate corrections for multiple comparisons.

Conclusions

Altered frontal and amygdala recruitment during emotion processing and regulation, although present in patients, is not a strong endophenotype of OCD. Siblings show distinct activation of the temporo-occipital cortex and frontolimbic connectivity during OCD-related emotion regulation, which may be a compensatory mechanism.

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Emotion Regulation in Obsessive-Compulsive Disorder, Unaffected Siblings and Unrelated Healthy Controls

Supplemental Information

Participant Recruitment

Patients were recruited through the network of OCD expert clinics within the Netherlands OCD Association, Altrecht Academic Anxiety Center, and online bulletins, while controls were recruited through online bulletins and the community.

Design of the Emotion Regulation Task

The emotion regulation task design is part of the backbone of modern research into how humans can use cognitive reappraisal to increase or decrease their emotional response (1). In the present study the task involved presenting emotionally relevant or neutral pictures during several conditions. The "attend" condition involves participants viewing the pictures naturally and experiencing the emotions they elicit. The "regulate" condition involves having participants use cognitive reappraisal strategies to decrease any negative emotions elicited by the stimuli (for example by thinking to oneself "This picture is not that bad, I have handled worse" or "this is not a real thing"). Neutral stimuli were only presented in the attend condition, which rendered nine conditions in total: four stimulus types (fear-related images and contamination/washing, checking/harm, and symmetry/ordering OCD-related images) presented under two instructions (attend or regulate), as well as the neutral images presented under the "attend" condition.

Prior to performing the task in the scanner the participants underwent a 20 minute training session in which reappraisal strategies were practiced. The practice sessions used stimuli which were not presented in the scanner in order to avoid training effects. After the

scanning session participants were debriefed to ensure that they performed the task as designed, and that they did not experience any adverse effects. Please see (2) for more details.

Acquisition and Preprocessing of MRI Data

Whole-brain structural images were acquired in a 256x256 matrix; voxel size; 1x0.977x0.977mm; 172 slices. Functional images were acquired in a 64x64 matrix; repetition time=2100ms; echo time=30ms; field of view=24cm; flip angle=80^{o}; 40 ascending slices per volume; 3.75x3.75mm in-plane resolution; slice thickness=2.8mm; inter-slice gap=0.2mm. Functional images were preprocessed using slice-time correction, realignment with unwarping, co-registration with the structural T1-image, transformation to Montreal Neurological Institute (MNI) standard space as 3x3x3mm voxels, and smoothed using a 8mm full-width half-maximum Gaussian kernel.

Functional Connectivity

We used psychophysiological interaction (PPI) to model functional connectivity, which involves examining how task-related changes in the BOLD signal of a seed region correspond to the time series of other regions, thereby revealing regional co-activations with the seed region. We applied the Generalized Psychophysiological Interaction toolbox (gPPI), as this allows for the simultaneous fitting of multiple task conditions, which provides better model fit than traditional PPI (3).

Selection of Regions of Interest and SISA Correction

The regions of interest (ROIs) were based on the largest and rigorous meta-analyses of emotion provocation in OCD patients, and emotion regulation in healthy controls. Thorsen et al. (4) found in their meta-analysis of 25 studies of tasks contrasting aversive and neutral

stimuli that OCD patients showed increased activation in five regions, which were used as ROIs for the emotion provocation contrast: the midline orbitofrontal cortex (OFC), bilateral amygdala, left inferior occipital cortex, and the right middle temporal cortex. The two meta-analyses of emotion regulation shared eight reported regions that were activated during cognitive reappraisal (versus attending) of negatively valence stimuli, which were used as ROIs for the emotion regulation contrast: the bilateral inferior frontal gyri, bilateral lateral frontal cortices, midline pre-SMA, left dorsomedial frontal cortex, left parietal-temporo-occipital cortex, and the left middle temporal cortex. The ROIs were functionally placed within the local clusters for the main effect of provocation and regulation, using the cluster maxima best corresponding to the those reported by the meta-analyses of emotion provocation in OCD (4) and emotion regulation in controls (5, 6) (See Supplemental Table S2 for ROI coordinates).

The main effect of emotion provocation was determined using a 2x3 ANOVA with picture type (fear, OCD-related) and HRF (canonical, temporal dispersion) as within-subject factors, with an F-contrast examining the effect of task over both picture types and HRFs. The main effect of emotion regulation was determined using a one-way ANOVA with picture type (fear regulate > attend; OCD regulate > attend) as the within-subject factor, using an F-contrast to determine activation over all participants. Since the right inferior frontal gyrus was not found in our own main effect of regulation, it therefore had to be excluded as ROI. The mean correlations for input into SISA were subsequently computed based on beta values per subject per ROI per analysis, that were obtained in the following way: fear and OCD-related provocation betas were derived from separate one-way ANOVAs with the three HRFs as the within-subject factor, using the mean of each participants activation over the three HRFs per ROI. The betas for the provocation picture type interaction were extracted from a 2x3 ANOVA, with picture type and HRFs as within-subjects factors. For emotion regulation,

separate one-sample t-tests for fear and OCD-related regulation were used to derive the beta per ROI per subject. The beta values were extracted with MarsBaR (http://marsbar.sourceforge.net/), using 3mm spheres around the peak voxel of the ROI.

Results were corrected for the number of ROIs for each contrast using a SISA-Bonferroni correction: the p-values were adjusted for the relatedness of the data by correlating the ROIs, converting r to Fisher's z before calculating the mean z, and then converting the mean z back to Pearson's r. SISA-Bonferroni corrected p-values were calculated at 0.016 for fear provocation, 0.017 for the OCD-related provocation and picture type interaction, 0.023 for fear regulation, and 0.021 for OCD-related regulation. The corrected p-value for functional connectivity between the dmPFC and amygdala was set at 0.025. Whole-brain group comparisons at uncorrected $p<0.001$ with a minimum cluster extent of 3 voxels are also presented below, to allow for their use in future meta-analyses.

Supplemental Results

Separate correlation analyses within each group showed that dmPFC and left temporo-occipital cortex activation did not correlate with OC symptom severity (Y-BOCS or OCI-R scores), age, gender, or years of education. MADRS score showed a negative correlation with temporo-occipital cortex activation in the OCD patient group only ($r(41) = -0.41$, $p < 0.01$). Regression analyses showed that MADRS scores did not moderate the difference between OCD patients and siblings ($B = -.003$, $t = -.09$. $p = .93$), or healthy controls and siblings ($B = -.009$, $t = -.14$, $p = .89$). Finally, an ANCOVA including both the effect of group and MADRS scores showed that the main effect of group on temporo-occipital activation during OCD-related regulation remained significant when MADRS scores were controlled for ($F(2, 96) = 9.83$, $p < .001$).

Supplemental Table S1. Comparisons of demographics and clinical measures in the sample

	Patients (N=43)			**Siblings (N=19)**			**HC (N=38)**			**Analysis**	
	N	**%**		**N**	**%**		**N**	**%**		**χ^2**	**p**
Gender										2.55	0.27
Male	21	49		13	68		18	47			
Female	22	51		6	32		20	53			
Handedness										1.20	0.55
Right	36	84		15	79		34	89			
Left	7	16		4	21		4	11			
Any comorbidity	21	49		1	5		-	-			
Depressive	10	23		-	-		-	-			
Specific phobia	10	23		1	5		-	-			
Social anxiety	5	12		-	-		-	-			
Panic	2	5		-	-		-	-			
Eating	2	5		-	-		-	-			
Somatoform	2	5		-	-		-	-			
Tourette's	2	5		-	-		-	-			
Agoraphobia	1	2		-	-		-	-			
	M	**SD**	**Range**	**M**	**SD**	**Range**	**M**	**SD**	**Range**	**F**	**p**
Age (years)	37.58	10.00	19-55	37.32	13.10	21-62	39.05	11.27	21-64	0.34	0.97
Education level (years)	12.72	3.22	5-18	12.88	2.60	9-18	13.00	3.19	9-18	0.08	0.92
Y-BOCS	21.63	6.15	12-35	0.06	0.24	0-1	0.00	0.00	0-1	336.88	**< 0.01**
OCI-R	24.67	11.79	5-59	3.47	3.16	0-10	3.37	4.71	0-10	66.87	**< 0.01**
MADRS	11.21	8.10	0-32	2.06	3.60	0-12	0.82	1.41	0-12	37.66	**< 0.01**
ERQ-reappraisal	4.12	1.31	1-6.67	4.46	1.31	1.67-7	4.86	1.06	1-7	3.67	**0.03**
ERQ-suppression	3.16	1.36	1-6.5	3.34	1.02	1.75-5	2.95	1.09	1-5	0.71	0.50

Significant between-group findings in bold. ERQ = Emotion Regulation Questionnaire; ERQ-reprais = ERQ reappraisal score (mean); ERQ-suppress = ERQ suppression score (mean); MADRS = Montgomery-Åsberg Depression Rating Scale (mean of sum score); OCI-R = Obsessive Compulsive Inventory-Revised (mean of sum score); Y-BOCS = Yale-Brown Obsessive Compulsive Scale (mean of sum score).

Supplemental Table S2. MNI coordinates for the regions-of interests, based on previous meta-analyses (4-6)

Region	Side	MNI coordinates		
		X	Y	Z
Emotion provocation				
OFC	Midline	0	44	-2
Amygdala	R	24	-1	-17
Amygdala	L	-24	-4	-20
Inferior occipital cortex	L	-33	-91	-11
Middle temporal cortex	R	57	-49	7
Emotion regulation				
Pre-SMA	Midline	-6	8	61
Lateral frontal	L	-39	2	52
Lateral frontal	R	54	2	43
Inferior frontal gyrus	L	-51	26	4
DmPFC	L	-6	23	40
Temporo-occipital cortex	L	-39	-61	22
Middle temporal cortex	L	-54	-40	-2

DmPFC = dorsomedial prefrontal cortex; MNI = Montreal Neurological Institute; L = left; OFC = orbitofrontal cortex; Pre-SMA = Pre-supplementary motor area; R = right.

Supplemental Table S3. Three-group comparisons of activation during emotion provocation for regions of interest

Region	BA	Side	MNI coordinates			Z	pFWE-SVC
			X	Y	Z		
Fear provocation							
OFC	32	Midline	3	44	7	2.75	0.126
Amygdala	N/A	R	30	-1	-17	2.86	0.098
Amygdala	N/A	L	-27	-1	-14	2.49	0.210
Inferior occipital gyrus	19	L	-33	-91	-8	2.92	0.083
Middle temporal gyrus	22	R	54	-40	4	1.89	0.496
OCD provocation							
OFC	10	Midline	3	47	4	1.81	0.527
Amygdala	**N/A**	**R**	**27**	**-7**	**-17**	**3.58**	**0.013**
Amygdala	N/A	L	-27	-1	-14	2.75	0.122
Inferior occipital gyrus	19	L	-36	-88	-11	3.46	0.018*
Middle temporal gyrus	21	R	63	-46	4	1.38	0.702
Picture type interaction							
OFC	10	Midline	0	47	7	0.61	0.841
Amygdala	N/A	R	27	-7	17	3.45	0.020*
Amygdala	N/A	L	-24	-1	-11	2.37	0.264
Inferior occipital gyrus	19	L	-36	-88	-11	2.70	0.140
Middle temporal gyrus	21	R	63	-46	4	1.86	0.514

Significant between-group findings in bold. BA = Brodmann's area; FWE = Family-wise error; L = Left; MNI = Montreal Neurological Institute; OCD = Obsessive-compulsive disorder; OFC = Orbitofrontal gyrus; R = Right; SVC = Small volume correction. * = trend significant.

Supplemental Table S4. Three-group comparisons of activation during emotion regulation for regions of interest

Region	BA	Side	MNI coordinates			Z	pFWE-SVC
			X	Y	Z		
Fear regulation							
Pre-SMA	6	Midline	-3	-1	58	1.81	0.398
Lateral frontal PFC	6	L	-36	-1	43	1.86	0.377
Lateral frontal PFC	6	R	48	-1	43	2.18	0.240
Inferior frontal gyrus	45	L	-48	32	7	0.60	0.786
DmPFC	32	L	-15	20	37	2.37	0.174
Temporo-occipital cortex	19	L	-30	-64	25	0.97	0.710
Middle temporal gyrus	21	L	-51	-49	-5	0.59	0.787
OCD regulation							
Pre-SMA	6	Midline	-3	5	61	2.60	0.115
Lateral frontal PFC	6	L	-39	-4	58	1.87	0.381
Lateral frontal PFC	44	R	51	11	40	1.30	0.625
Inferior frontal gyrus	45	L	-42	23	7	0.85	0.743
DmPFC	**32**	**L**	**0**	**29**	**40**	**3.75**	**0.005**
Temporo-occipital cortex	19	**L**	**-39**	**-61**	**13**	**3.43**	**0.013**
Middle temporal gyrus	21	L	-57	-46	-5	2.26	0.218

Significant between-group findings in bold. BA = Brodmann's area; dmPFC = Dorsomedial prefrontal cortex; FWE = Family-wise error; L = Left; MNI = Montreal Neurological Institute; OCD = Obsessive-compulsive disorder; Pre-SMA = Pre-supplementary motor area; R = Right; SVC = Small volume correction.

Supplemental Table S5. Main effect of group for functional connectivity in the bilateral amygdala during emotion regulation

Region	Side	MNI coordinates			Z	pFWE-SVC
		X	Y	Z		
Fear regulation dmPFC-amygdala connectivity: main effect of group (ANOVA)						
Amygdala	R	27	-4	-20	2.68	0.124
Amygdala	L	-30	-4	-20	2.34	0.235
Fear-related regulation: post-hoc pairwise comparisons in right amygdala						
	K_e		Z		pFWE-SVC	
Siblings > OCD					NS	
HC > Siblings					NS	
HC > OCD	3		3.30		**0.019**	
Fear-related regulation: post-hoc pairwise comparisons in left amygdala						
	K_e		Z		pFWE-SVC	
Siblings > OCD					NS	
HC > Siblings					NS	
HC > OCD	14		3.36		**0.016**	
OCD-related regulation dmPFC-amygdala connectivity: main effect of group (ANOVA)						
Amygdala	L	-24	-4	-17	2.21	0.283
Amygdala	R	30	-7	-11	1.62	0.561
Fear-related regulation: post-hoc pairwise comparisons in left amygdala						
	K_e		Z		pFWE-SVC	
Siblings > OCD	3		3.22		**0.023**	
Siblings > HC					NS	
HC > OCD					NS	
Fear-related regulation: post-hoc pairwise comparisons in right amygdala						
	K_e		Z		pFWE-SVC	
Siblings > OCD	2		3.30		**0.019**	
Siblings > HC					NS	
HC > OCD					NS	

FWE = Family-wise error; L = Left; MNI = Montreal Neurological Institute; R = Right; SVC = Small volume correction.

Supplemental Table S6. Whole-brain main effect of group on BOLD signal during emotion provocation at uncorrected p < 0.001

Region	Side	K_e	MNI coordinates X	Y	Z	Z	Post-hoc tests of the group differences
Fear-related provocation							
Posterior cingulate gyrus	R	16	15	-46	31	3.83	Sibs vs HC[b]
Supramarginal gyrus	R	19	63	-28	25	3.70	Sibs vs OCD & HC
Inferior parietal lobule	L	6	-45	-37	37	3.57	OCD vs HC[a]
Middle occipital gyrus	L	5	-39	-88	10	3.41	OCD vs HC[a]
Middle temporal gyrus	L	5	-42	-58	-5	3.38	Sibs vs HC[b]
Inferior occipital gyrus	R	6	42	-79	-8	3.35	OCD vs HC[a]
DlPFC	L	5	-36	32	19	3.30	Sibs vs HC[b]
Fusiform gyrus	R	3	36	-64	-17	3.23	NS in post-hoc
OCD-related provocation							
Putamen	L	27	-24	11	-2	3.84	Sibs vs OCD & HC
Cerebellum/lingual gyrus	L	14	-6	-70	-8	3.80	OCD vs Sibs vs HC[a]
Middle temporal gyrus	L	23	-39	-58	-2	3.75	Sibs vs HC[b]
Hippocampus/amygdala	R	15	27	-7	-17	3.58	OCD vs HC[a]
Inferior occipital gyrus	L	8	-36	-88	-11	3.46	OCD vs HC[a]
Thalamus	R	6	6	-16	-2	3.40	Sibs vs HC[b]
DmPFC	L	6	-21	-4	52	3.38	NS in post-hoc
Temporal pole	L	4	-42	17	-17	3.30	Sibs vs OCD[b]
Thalamus	L	3	-21	-28	4	3.29	Sibs vs HC[b]
Cerebellum	R	4	9	-73	-20	3.28	OCD vs HC[a]
Posterior cingulate gyrus	R	3	12	-49	31	3.25	Sibs vs HC[b]
Supramarginal gyrus	R	5	60	-28	28	3.16	NS in post-hoc
Picture type interaction							
Hippocampus	L	10	-36	-22	-11	4.04	OCD vs HC[a]
Cerebellum	L	81	-15	-55	-8	3.88	Sibs & OCD vs HC
Caudate nucleus	R	11	6	11	-2	3.88	OCD vs HC[a]
Putamen	L	23	-24	11	-5	3.63	NS in post-hoc
Posterior insula	L	8	-39	-13	4	3.49	Sibs vs OCD & HC
Amygdala	R	6	27	-7	-17	3.45	OCD vs HC[a]
Thalamus	R	8	6	-13	-2	3.41	Sibs vs HC & OCD
Thalamus	L	5	-21	-28	4	3.22	Sibs vs HC[b]

[a] Siblings vs. OCD and siblings vs. controls: not significant. [b] Patients vs. siblings and patients vs. controls: not significant. DmPFC = dorsomedial prefrontal cortex; DlPFC = dorsolateral prefrontal cortex; HC = healthy controls; L = left; *K*e = voxel extent of cluster; MNI = Montreal Neurological Institute; NS = not significant. OCD = Obsessive-compulsive disorder; R = right; Sibs = unaffected siblings.

Supplemental Table S7. Whole-brain three-group comparisons of BOLD activity during fear and OCD-related emotion regulation at uncorrected p < 0.001

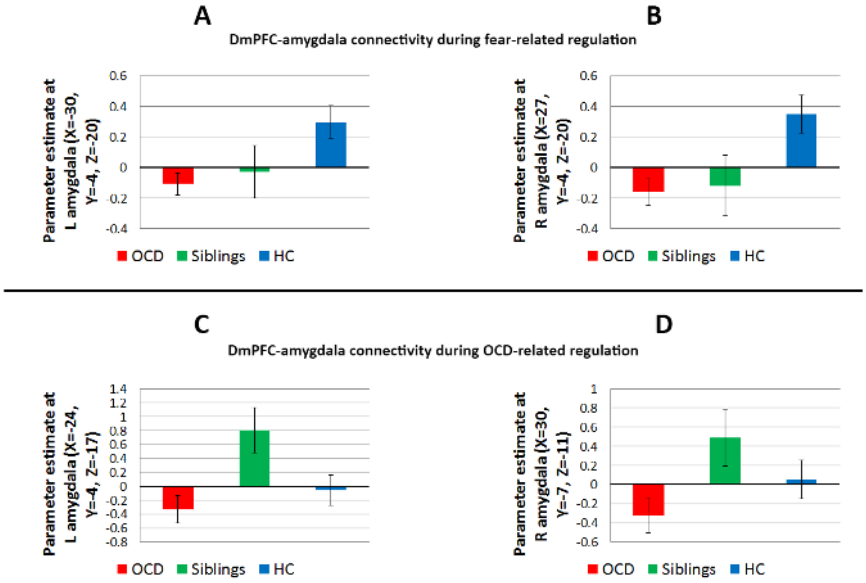
Region	BA	Side	K_e	MNI coordinates			Z	Direction post-hoc tests
				X	Y	Z		
Fear regulation								
Middle frontal gyrus	9	L	14	-18	38	25	3.37	HC > OCD[a]
Occipital pole	18	R	8	21	-91	4	3.31	Sibs > OCD[b]
Superior temporal gyrus	22	R	3	54	-16	-5	3.13	Sibs & HC > OCD
OCD regulation								
Superior frontal gyrus	32	R	30	3	32	40	4.01	OCD & Sibs > HC[a]
Lingual gyrus	17	R	20	3	-82	1	3.58	OCD & Sibs > HC
Angular gyrus	21	R	3	57	-58	22	3.44	Sibs > HC[c]
Middle temporal gyrus	37	L	4	-39	-61	13	3.43	Sibs > HC[c]

[a] Siblings vs. OCD and siblings vs. controls: not significant. [b] Patients vs. siblings and patients vs. controls: not significant. HC = healthy controls; L = left; *K*e = voxel extent of cluster; MNI = Montreal Neurological Institute; OCD = Obsessive-compulsive disorder; R = right; Sibs = unaffected siblings. Post-hoc tests: data not shown.

Supplemental Table S8. Whole-brain group comparisons of functional connectivity during fear and OCD-related regulation at uncorrected p < 0.001

Region	BA	Side	K_e	MNI coordinates X	Y	Z	Z	Direction of post-hoc tests
HC > OCD during fear regulation*								
Posterior insula	48	L	8	-42	-16	-2	3.50	HC > OCD[a]
Right amygdala	N/A	R	4	24	-7	-20	3.46	HC > OCD[a]
OCD regulation								
Middle temporal gyrus	21	L	29	-42	-52	13	3.76	Sibs > OCD & HC
Middle cingulate gyrus	23	L	17	-6	-16	43	3.57	Sibs > OCD & HC
Supramarginal gyrus	48	R	3	63	-34	22	3.42	Sibs > OCD[b]
Precuneus	23	L	22	-3	-52	34	3.37	Sibs > OCD & HC
Precuneus	23	L	9	-3	-58	22	3.31	Sibs > OCD & HC
Superior frontal gyrus	10	L	3	-9	56	31	3.20	Sibs > OCD & HC

* Three-group comparison showed no significant voxels at uncorrected p < 0.001. [a] Siblings vs. OCD and siblings vs. controls: not significant. [b] Patients vs. siblings and patients vs. controls: not significant. HC = healthy controls; L = left; *K*e = voxel extent of cluster; MNI = Montreal Neurological Institute; OCD = Obsessive-compulsive disorder; R = right; Sibs = unaffected siblings. Post-hoc tests: data not shown.



Supplemental Figure S1. Group comparisons of dmPFC-amygdala functional connectivity during fear and OCD-related emotion regulation.

Panels show BOLD signal parameter estimates of functional connectivity between the left dmPFC and amygdala for each group during emotion regulation. Panel A and B shows lower fronto-limbic connectivity in OCD patients compared to healthy controls in the left and right amygdala during fear-related regulation, while siblings were not significantly different from either group. Panel C and D shows trend-level higher fronto-limbic connectivity in siblings compared to patients during OCD-related regulation, while healthy controls were not significantly different from either group. Parameter estimates are in arbitrary units, with standard errors.

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	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.

	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.
	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.

	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.
1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.

H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.
	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.
2001 V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.

	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.
	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 V	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.

	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.

	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints

	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledereres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
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