THE OBSESSED BRAIN

Functional and structural neural correlates in obsessive-compulsive disorder

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Dissertation der
Graduate School of Systemic Neurosciences der
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submitted by
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Summary

A number of neuropsychological studies have evaluated the conspicuous features of obsessive-compulsive disorder (OCD), a heavily impairing psychiatric illness. While the neuropsychological model seems to be well understood and therefore the diagnose well established, the therapy effects are rather short term and go along with high relapse rates. This is probably the consequence of the still undetected disorder causes and therefore therapy is mainly symptom alleviation treatment, with only rarely lasting long term effects.

Advances in research tools such as brain imaging have enabled the exploration of the core-driving organ in which OCD related processes take place, namely the brain. Against the background of findings from various OCD neuroimaging studies, a neurobiological model of the disorder has evolved including disturbances in cortico-striato-thalamo-cortical (CSTC) areas and their functional circuits. Nevertheless, as there is a high inconsistency between study results and the analysis tools for brain imaging data are advancing fast, more recent studies reinforced the need for a revision of the OCD model by including additional areas.

Thus, the integration of multiple variables from neuro-psychology, -biology as well as genetics and basic research, shifted the research approach from a region-focused thinking to concepts of network disruption in OCD.

To disentangle the recent inconsistent neuroimaging findings, the aim of the current thesis was to investigate the neural patterns of brain function (e.g. activation, connectivity) and structure (e.g. measures of gray and white matter GM/WM), their associations with each other and their link to clinical characteristics such as symptom severity and duration of illness.

The aim was accomplished in form of three recently published studies, in which we compared a large sample of OCD patients with age-, and gender- matched healthy controls. We examined brain function and structure using a 3T MRI, the functional images were acquired during OCD-sensitive tasks.

Overall, in the three studies, we provided evidence for an overactive circuit during symptom provocation associated with structural impairments of underlying WM tracts. Moreover, we observed a globally decreased GM in patients in various properties of the cortical mantle, one of which has been associated with early brain development.

Our results are partly in agreement with previous studies, but bring also additional evidence on interconnections between several neuronal measures. They as well suggest that in order to elucidate the neurobiological substrates of OCD, research questions need to be addressed on the network level rather than on regional dysfunctions. Furthermore, these findings should

encourage future studies to replicate and validate existing results, ideally in the form of meta-analyses or multi-center studies. Valid and reliable information about the interrelations of all measurable properties of the brain, but also their links to OCD onset and progression, will help in furthering our understanding about the neural mechanism of the disorder, but also in the clinical conceptualisation and categorisation. Moreover, this would enable future studies to investigate whether there is a trait-like neurobiological pattern common to all patients, or if the various symptom spectra are characterized by unique and partly distinct neural patterns. Answers to these questions might improve treatment and clinical handling of OCD, potentially leading to more individualized therapeutic interventions. These could also be of relevance for OCD drug-treatment research in detecting more specialized medication, with less side effects and fewer relapse rates, to be used as an additional supportive factor in therapy.

Zusammenfassung

Zwangsstörung ist eine stark einschränkende psychiatrische Erkrankung und dessen Auffälligkeiten wurden bereits in einer Reihe von neuropsychologischen Studien untersucht. Obwohl das neuropsychologische Modell der Erkrankung gut verstanden zu sein scheint und durch genaue Diagnosekriterien definiert ist, beinhaltet die Therapie nur eine Symptombehandlung mit eher kurzweiligen Effekten und hohen Rückfallraten. Möglicherweise ist das auch die Folge von den noch nicht erkannten Erkrankungs - ursachen bzw. - auslösern.

Die technologischen Fortschritte im Bereich der Bildgebungsverfahren, haben es ermöglicht, das steuernde Organ zu untersuchen in dem die meisten zwangsbezogenen Prozesse ablaufen, nämlich das Gehirn. Somit ist aus den Erkenntnissen von verschiedenen Hirnbildgebungsstudien, ein neurobiologisches Modell der Zwangserkrankung entstanden. Dessen Mittelpunkt beinhaltet die kortiko-striato-thalamo-kortikalen Regionen und assoziierte Regelkreise. Dennoch besteht eine große Inkonsistenz zwischen den existierenden Studien, bezüglich der angewandten Methodik und den daraus entstehenden Ergebnissen. Aufgrund neuerer Analyseverfahren von Gehirndaten, haben weitere Studien die Notwendigkeit der Überarbeitung und Aktualisierung des aktuellen neurobiologischen Modells der Zwangsstörung angedeutet, in dem sie die Einschließung zusätzlicher Gehirnregionen in das bestehende Modell fordern. Durch die immer häufigere Einbindung von verschiedensten Faktoren (z.B. Neuro - psychologie und - biologie, Genetik und Erkenntnissen aus der Tier- und Zellforschung) hat sich die aktuelle Gehirnforschungsansicht von einer Regionen-basierten zu einer eher Netzwerk-basierten geändert.

In Anbetracht der bestehenden, teilweise widersprüchlichen Erkenntnisse aus der Bildgebungsforschung der Zwangsstörung, ist das Ziel der vorliegenden Arbeit die Gehirnfunktion (z.B. Gehirn Aktivität und Konnektivität d.h. funktionelle und strukturelle Vernetzung von Gehirnregionen), der Gehirnstruktur (z.B. Maße von grauer und weißer Substanz), als auch deren Wechselbeziehungen und deren Zusammenhänge zu klinischen Aspekten, wie z.B. Zwangssymptomatik und Erkrankungsdauer zu untersuchen. Dieses Ziel wurde erfüllt und umgesetzt in drei kürzlich publizierten wissenschaftlichen Studien, in denen wir eine große Stichprobe von Zwangspatienten mit einer alters- und geschlechts - entsprechenden Stichprobe von gesunden Probanden, hinsichtlich Gehirndaten verglichen haben. Die Gehirndaten wurden mittels eines 3T Magnetresonanztomographen erhoben. Dabei wurde die Gehirnfunktion und - Struktur während Ruhe und Zwangsstörungs - spezifischen Aufgaben erfasst und ausgewertet.

Zusammenfassend bringen diese drei Studien Nachweise für einen überaktiven Regelkreis während der Symptomprovokation bei Zwangspatienten. Dieser überaktive Regelkreis steht im Zusammenhang mit strukturellen Beeinträchtigungen der Fasern der weißen Substanz. Darüber hinaus, haben wir eine allgemein verringerte graue Substanz in verschiedenen Maßen des Kortex festgestellt. In der dritten Studie haben wir eine verringerte Gyrifizierung in Patienten ge-

funden. Dieses Maß wurde auch häufig im Zusammenhang mit den früh in der Entwicklung stattfindenen Gehirnentwicklungsprozessen gebracht.

Unsere Ergebnisse entsprechen nicht nur insgesamt den Erkenntnissen aus früheren Studien, sondern bringen auch neue Hinweise auf zusätzliche, bisher fehlende Zusammenhänge zwischen den verschiedenen neuronalen Maßen zu Tage. Weiterhin deuten die daraus gezogenen Erkenntnisse darauf hin, dass es nötig ist eher Netzwerk-bezogene Fragen, als fokussierte Regionen-bezogen Fragen zu beantworten, um die neurobiologischen Pfade der Zwangserkrankung zu entziffern.

Unter Betrachtung der diskutierten methodologischen und klinischen Beschränkungen, könnten zukünftige Studien die Gültigkeit und Zuverlässigkeit der dargestellten Ergebnisse überprüfen, z.B. in Form von Megaanalysen und multizentrische Studien. Valide und reliable Informationen über die Wechselbeziehungen der unterschiedlichen Gehirnmaße, aber auch deren Zusammenhänge zu Krankheitsbeginn und Verlauf, könnten nicht nur bei der Feststellung der neuronalen Erkrankungsmechanismen helfen, sondern auch in deren klinischen Konzeptualisierung und Kategorisierung. Darüber hinaus, könnten die hier dargestellten Ergebnisse zukünftigen Studien ermöglichen, besser unterscheiden zu können ob es ein allgemeines Zwangsstörungsmuster im Gehirn gibt was durch ein beeinträchtigtes Impuls- bsw. Angst - gesteuertes System begünstigt wird, oder ob es eher unterschiedliche Symptomkategorien gibt die sich in teilweise überlappende, teilweise unterschiedlichen Gehirnmustern wiederspiegeln. Zudem könnten die Beantwortungen all dieser Fragen zur Verbesserung der Behandlung und des klinischen Umgangs mit der Zwangsstörung beitragen. Das könnte auch von Bedeutung für die medikamentöse Behandlung der Zwangsstörung sein, vor allem bei der Entwicklung und Identifizierung von individualisierter Medikation, mit weniger Nebeneffekten und niedrigeren Rückfallquoten.

Rezumat

Un număr relativ mare de studii neuropsihologice au evaluat caracteristicile marcante ale tulburării obsesiv-compulsive (TOC), o boală psihică cu un impact restrictiv asupra calității de viață a pacienților. În timp ce modelul neuropsihologic al acestei boli, este bine înțeles și prin urmare criteriile diagnostice bine definite, efectele terapeutice sunt mai degrabă de scurtă durată si deseori însoțite de rate de recidivă crescute. In plus, cauzele încă neclare ale acestei boli psihice, constituie si motivul pentru care terapia curentă a acestei boli implică printre altele, un tratament al simptomelor și nu al cauzelor.

Progresul tehnologic făcut în dezvoltarea diverselor tehnici de neuroimagistică, a permis o analizare mai precisă a funcțiilor și structurii organului cheie, în care au loc majoritatea proceselor asociate cu TOC, și anume a creierului. Prin urmare, rezultatele studiilor TOC din domeniul neuroimagisticii au ajutat la elaborarea unui model neurobiologic al bolii, care include regiunile cortico-striato-talamo-corticale și circuitele funcționale ale acestora. Cu toate acestea, există numeroase inconsistențe între studii. Însă prin dezvoltărea unor metode mai noi de analiză a datelor din neuroimagistica, s-a subliniat importanța revizuirii acestui model neurobiologic, prin adăugarea unor regiuni adiționale. De asemenea, prin integrarea altor factori de influență din domeniul neuropsihologic, neurobiologic, genetic și ale rezultatelor din cercetarea de bază (d.e. al celulelor, animalelor), atenția cercetării neuroimagiste s-a schimbat de la o gândire fixată pe variații neuronale ale anumitor regiuni anatomice spre o gândire associată variațiilor neuronale intr-un întreg sistem interconectat, de tipul unei rețele.

Pentru a clarifica într-o oarecare măsură aceste inconsistențe cu privire la actualele rezultate neuroimagiste ale bolii TOC, scopul acestei lucrări este de a evalua și analiza probele neuronale rezultate din funcțiunea creierului (d.e. activitatea și conectivitatea) dar și structura creierului (d.e. măsuri ale substanței cenușii și a celei albe, SC/SA), a asociațiilor dintre acestea și a legăturii cu caracteristicile clinice ale pacienților, d.e., severitatea simptomelor și durata boli.

Acest obiectiv a fost atins cu ajutorul a trei studii științifice publicate recent, în care am comparat un număr mare de pacienți cu TOC cu subiecți sănătoși asemănători în privința vârstei și sexului. In acest fel au fost analizate funcția și structura creierului cu ajutorul unui RMN functional, cu o putere magnetica de 3T. Achiziționarea datelor a avut loc în timpul unor stări de relaxare și de asemenea în timpul expunerii la stimuli senzitivi TOC.

În ansamblu, prin cele trei studii aducem evidențe pentru un circuit hiper-activ, indicat prin hiper-conectivitatea unor regiuni anatomice ale pacienților cu TOC în timpul expunerii la stimuli specifici, care pot provoca simptomele tipice. Aceasta hiper-connectivitate funcțională a fost de asemenea associată cu alterări ale SA mai specific ale fibrelor axonale implicate în acest circuit. Totodată, datele au arătat o alterație semnificativa a SC la nivel global în diferite măsuri ale cortexului cerebral, dintre care una a fost asociată frecvent în alte studii cu alterări

în perioade timpurii ale dezvoltării creierului.

Aceste rezultate sunt în concordanță cu studii anterioare, însă într-un mod remarcabil ele aduc dovezi adiționale pentru interconexiunea dintre diferitele măsuri neuronale. În plus, rezultatele prezentate în această lucrare indică faptul, că pentru a putea elucida posibilele amprente neurobiologice ale TOC, întrebările care necesită a fi adresate pe viitor, ar trebui sa fie legate de circuite neuronale, și nu ca și până acum, legate de alterațiile unor regiuni specifice ale creierului. Luând în calcul limitările discutate în studiile publicate, referitoare la metodologie și caracteristicile subiecților partcipanți, studiile viitoare sunt încurajate sa reproducă și să valideze rezultatele prezentate, în forma unor mega-analize, în studii multi-centrice care au mai multa putere statistică și cu caracter mai reprezentativ. Prin urmare, informația câștigată din aceste tipuri de studii, legate de interdependențele dintre aceste diferite măsuri ale activității și structurii neuronale, cât și ale legăturilor cu declanșarea și progresia bolii, ar putea ajuta în detectarea mecanismelor neuronale ale bolii, dar și în conceptualizarea și categorizarea clinică a acesteia. Totodată, aceste informații ar putea facilita studiile viitoare în investigațiile încă fără concluzii generalizabile cu referire la urmatoarea problematică: 1) dacă TOC este o boală caracterizată printr-o configurație neuronala generalizabilă pentru toate categoriile de pacienți de acest tip și declanșată de tulburări ale sistemului impulsiv și anxios sau dacă 2) diferitele categorii simptomatice întâlnite în TOC sunt mai degraba caracterizate prin configurări neuronale unice și caracteristice pentru fiecare categorie în parte (cele mai frecvente fiind d.e., frica de contaminare, obsesii de verificare).

Răspunsurile la aceste întrebări ar putea îmbunătății și consolida tratamentul și tratarea clinică a pacienților care suferă de această boală, adițional ele ar putea contribui la dezvoltarea unor intervenții terapeutice individualizate pe nevoile și caracteristicile fiecărui pacient. Mai mult, rezultatele din aceste studii ar putea fi relevante și pentru cercetarea tratamentului farmaceutic pentru tratarea TOC, în special în detectarea unei medicații specializate, cu efecte secundare reduse și rate de recidivă scăzute, putând astfel sa fie utilizate mai eficient ca factori de sprijin in terapie.

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Thesis Outline

This thesis contains three major parts which aim to give a detailed overview across the research topic of OCD and functional and structural neural correlates of this disorder, thus providing valuable insights into exciting recently published research findings.

The first part is divided into six chapters and aims at introducing the reader to the clinical characteristics of the disorder, as well to its neuropsychological and neurobiological research findings. Additionally, this part provides brief descriptions of the various analysis methods and further describes the recent neurobiological disorder model. It concludes with the main objectives of the thesis.

The second part contains three research studies that bring insight into structural as well as functional neural correlates of OCD and their associations. In the *first study*, we evaluate the link between functional and structural neural connectivity in the context of symptom provocation. In the *second study*, we analyze the structural changes of various cortical gray matter measures in OCD. In the *third study*, we investigate cortical folding alterations in OCD patients, as a strong indicator for early brain development. All three studies are already published in peer-reviewed journals and are included in the thesis in the format they were published in the specific journals.

The third and last part of this thesis aims to integrate the separate results of the three studies into an overall picture of OCD. In this part, the three main highlights that stand out from the common viewpoint of all three studies, are presented and their contribution to the neurobiological disorder model is discussed. Furthermore, the results and their interrelations are discussed in light of the existing literature. This final part of the thesis ends with describing the achievements, limitations and potential future work that is needed and finishes with some concluding remarks.

Part I.

Introduction

Motivation

Obsessive-compulsive disorder (OCD) is a psychiatric illness with a relatively high prevalence rate (2-3%) compared to other related disorders (Ruscio, Stein, Chiu, & Kessler, 2010). OCD can cause strong negative affects and significant impairment in the quality of daily life. This, in turn, is often followed by a lack of social interactions leading to comorbid disorders such as depression and anxiety (Torres et al., 2006).

Treatment options for OCD exist and have been proven to result in improvement of symptom severity. However, complete remission (i.e., 100% symptom reduction) is rare, and if it occurs, relapse or reoccurrence is very frequent. This rather negative prognosis after therapy speaks in favor of the fact that little is known about the causes of OCD. Hence, current therapies have been working on symptom reduction, but did unfortunately not contribute in detecting the causes or the mechanistic processes of the disorder.

Up to now the disorder is well understood in terms of symptom manifestation. Hence, a well-described cognitive-behavioral model exists, which is based on the visible symptoms and their presumed triggering factors. However, little is known about the exact pathophysiology, in terms of biological mechanistic processes underlying these symptoms. Biological models of neuronal processes in OCD have been proposed, but, so far, research has brought heterogeneous results, which have slowed down the research progress in OCD. A potential reason for the existing result inconsistencies might be that surprisingly little work has been done in terms of integrative studies. More specifically, there is a lack of multimodal studies that bring together findings from various perspectives, such as brain function, structure and circuitry. Having this type of studies could facilitate the achievement of a better picture about the various assays contributing to the mechanistic processes of OCD.

By integrating findings from the three recently published multimodal studies, this thesis aims to broaden the understanding of the potential neurobiological alterations in this disorder. To do so, we applied recent analysis techniques of brain structure and function (study 1, 2 and 3 - Chapter 7 to Chapter 9) and combined some of them in an innovative fashion (study 1 - Chapter 7). The results from these studies support the revision of the recent OCD neurobiological model.

1. Clinical Characteristics of OCD

1.1. Symptoms

OCD is characterized by the experience of obsessions, which could be unwanted, intrusive thoughts about certain themes (e.g. contamination, fear of causing harm to oneself or others), but also taboo topics (e.g. blasphemy, sex, violence) and which are normally incongruent with the person's general self-concept and principles. The intrusiveness of obsessions can be very persistent, and the intention to resist them causes strong anxiety, followed by the fear of disastrous consequences. To reduce this anxiety, patients usually perform compulsions (i.e. repetitive, impulsive and ritualistic behaviours). The active behavioural performance of these compulsive acts (e.g. washing, cleaning, checking, reassuring) can lead to a temporary reduction of anxiety and is therefore normally experienced as relieving. The motivation of performing these compulsions can also be triggered by the need to resist the intrusive obsessions.

Compulsions, are not obligatory only behavioural actions, they can be also performed mentally, such as avoiding or distracting oneself which still have the scope to prevent or resist to the obsessional thought or react to it (Foa et al., 1995). It is worth noting that these compulsions are not necessarily visible in a physical way (i.e. hand washing can still be present in the form of avoiding thoughts). Compulsions are excessive in relation to the trigger that caused them. They can be excessively time-consuming, as patients feel the urge to perform them repeatedly according to strict rules. Unfortunately, due to positive reinforcement of these compulsions through short term relief, this vicious cycle is always self-sustained (Figure 1.1, left upper box). This vicious cycle together with the further introduced research on OCD is descriptively depicted in Figure 1.1.

The result is in most cases an endless loop of escalating obsessions and subsequent compulsions to neutralize the reoccurring anxiety (Abramowitz & Jacoby, 2014). Interestingly, clinical observations and studies have shown that most patients acknowledge that their obsessions are irrational and overweighed and that the compulsions are unnecessary, yet this insight can vary (Abramowitz, 2006a; Foa et al., 1995). Moreover, since the last update of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013) the disorder insight is no longer an obligatory diagnostic criterion for OCD and the insight range can be evaluated. In previous

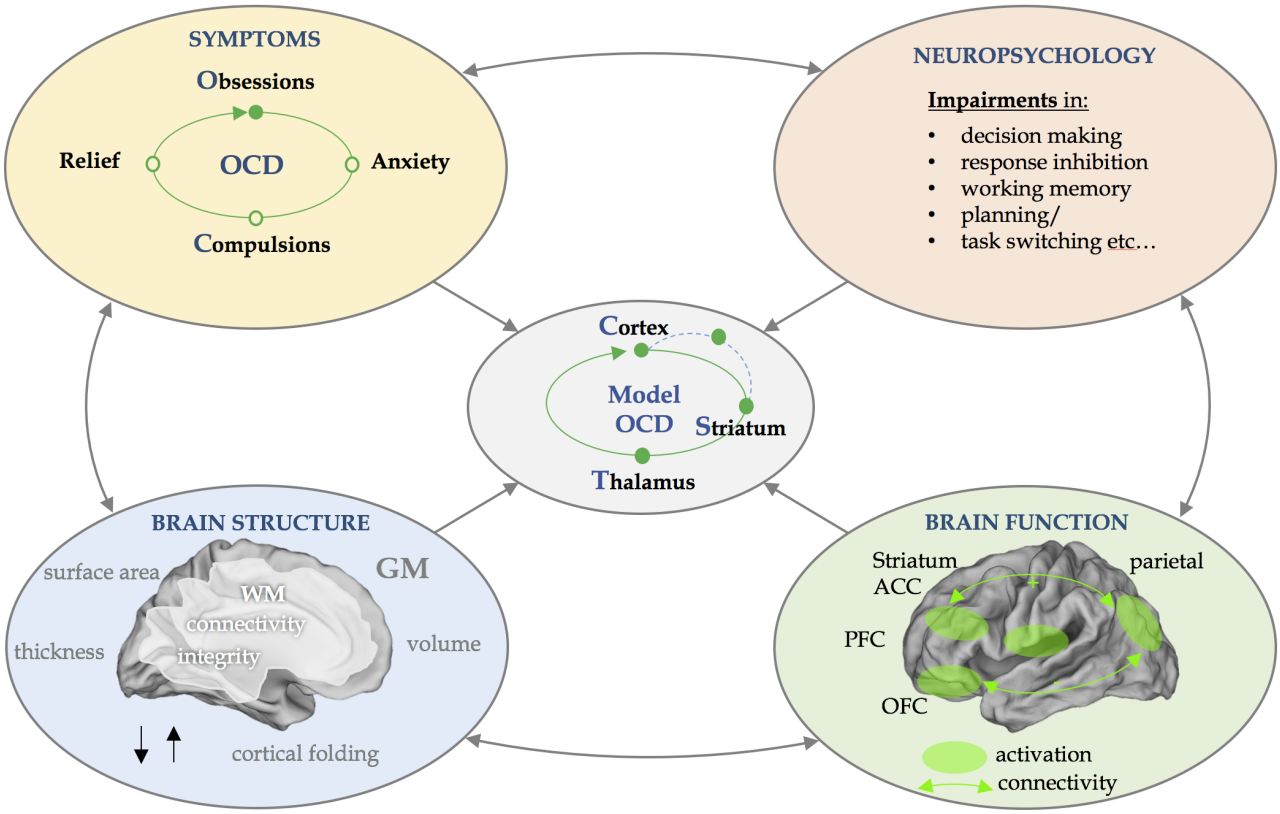

Figure 1.1.: An overview about the factors (clinical, neuropsychological, brain function and brain structure) discussed in part 1 which influenced the development of the OCD model.
Upper left-yellow oval presents the cognitive-behavioural model of OCD evolved from the clinical perspective.
Upper right-orange oval some of the impairments that OCD patients have, that evolve from neuropsychological findings discussed in Introduction, Chapter 2.
Lower right-green oval some of the brain regions which were shown to have altered functional activation or connectivity in OCD, resulted mostly from functional neuroimaging studies discussed in Introduction, Section 3.1 and Section 3.2.
Lower left-blue oval indicators for brain structural alterations evolved from the structural neuroimaging studies discussed in Introduction, Section 3.3.
Arrow up/down - represents increased/decreased structural alterations, as these results are inconsistent in the recent literature.

DSM versions, OCD was classified as an anxiety disorder. Since 2013, however, it belongs to a new category of mental disorders, namely, obsessive-compulsive and related disorders (OCDR). Obsessions or compulsions can occur combined or isolated, and there is a vast range of possible combinations regarding the exact theme of these symptoms. There have been several attempts to cluster or categorize these symptoms (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008; Mataix-Cols, Rosario-Campos, & Leckman, 2005; McKay et al., 2004). Overall the symptom dimensions can be summarized into four main categories: 1) obsessions about responsibility of causing harm; 2) symmetry obsessions; 3) contamination obsessions; 4) taboo subject obsessions (e.g. sex, violence, religion). These obsession categories are encountered in most of the patients and some of them can be accompanied by checking compulsions, though this is not compulsory.

1.2. Aetiology

The causes of OCD are still unknown, but several indicators for high family load or shared environment seem to represent some of the high-risk factors. Accordingly, Nestadt et al. (2001) reported that about 16.3 % of first-degree relatives also suffer from OCD. This family overload indicates that certain genetic factors might play a role. The risk is even higher when there is a relative with an early-onset OCD (Pauls, 2010). Family, twin and gene association studies can give more insight into the extent to which the disorder expression can be explained by environmental or genetic factors. From these studies we know that in OCD 27-47 % of the variance can be explained by heritability factors, whereas the remaining variance is explained by environmental factors such as psychosocial stressors, trauma or - in rare cases - perinatal events and inflammatory processes (van Grootheest, Cath, Beekman, & Boomsma, 2007). However, in children with OCD the variance explained by heritable factors is higher (i.e. 45-65%) than that encountered in adults (van Grootheest, Cath, Beekman, & Boomsma, 2005). A recent meta-analysis takes the view that, in general, genetic factors are important for the manifestation of OCD behaviours. Their findings, however, support the assumption that non-genetic and non-shared environmental factors have a considerable influence on the manifestation of the disorder pointing towards epigenetically mediated mechanisms (Taylor, 2011).

Overall, genes seem to play a mild to moderate role in OCD. They most probably increase the vulnerability/risk for the disorder rather than being responsible for its manifestation. Hence, environmental factors seem to contribute to a higher degree to disorder manifestation than genes.

1.3. Treatment

The recommended and most effective treatments for OCD are cognitive behavioural therapy (CBT), pharmacotherapy or a combination of both (Bandelow et al., 2008; Koran et al., 2007). The most adequate type of psychotherapy is CBT, with particular emphasis on exposure (to feared situations, objects or thoughts) and response prevention (ERP) (Franklin, Abramowitz, Kozak, Levitt, & Foa, 2000). This specific type of CBT is based on the following milestones: *first*, detection of feared objects, situations or thoughts that trigger anxiety; *second*, exposure to these triggering factors and inhibition of compulsions and *third*, habituation to experienced anxiety, which after several repeating sessions is expected to significantly drop in intensity. Studies show an immediate and long-term effect of about 60-70% symptom reduction after CBT with ERP. However, during therapy about one quarter of patients can drop out due to strongly experienced anxiety (Abramowitz, 2006b).

There are several studies showing anomalies in different neurotransmitter systems to be as-

sociated with OCD (Abramowitz, Taylor, & McKay, 2009). For example, a postsynaptic hypersensitivity of serotonin receptors has been associated with OCD (Barr, Goodman, & Price, 1993; Baumgarten & Grozdanovic, 1998). However, more recent studies emphasized that not only the serotonergic neurotransmitter system is associated with OCD. Hence, disruptions in the dopamine (Perani et al., 2008; Zohar, Chopra, Sasson, Amiaz, & Amital, 2000), but also in the glutamatergic system have been proposed (Kariuki-Nyuthe, Gomez-Mancilla, & Stein, 2014). In accordance with these previous findings, a recent meta-analysis pointed towards abnormalities in genes involved in serotonin, dopamine or glutamate pathways. They concluded that all three neurotransmitter systems interact and affect to a certain degree the functioning of the CSTC circuit in OCD (Taylor, 2013). Nevertheless, the most recommended pharmacological treatments in OCD which targets some of the mentioned neurotransmitter systems involve Selective Serotonin Reuptake Inhibitors (SSRI e.g. clomipramine paroxetine, fluoxetine, fluvoxamine, sertraline) (Dougherty, Rauch, & Jenike, 2004; Pittenger & Bloch, 2014). For non-responders, adding antipsychotics to the regular treatment (e.g. risperidone and haloperidol) seem to have an additive effect (Bloch et al., 2006).

Another effective drug originally used to treat tuberculosis and known to facilitate fear extinction without significant side effects, is D-cycloserine. It has been used for several other anxiety disorders (Otto et al., 2016) as well. In OCD, the few existing studies evaluating its effect (Mataix-Cols et al., 2017; Storch et al., 2016) have shown that it can accelerate the effects of exposure and response prevention and reduces the symptoms rapidly. These preliminary studies suggest that this drug should be used at the beginning of therapy because it can interact with other medication, such as antidepressants, and weaken their effect (Andersson et al., 2015). Overall, treatment studies in OCD have shown that medication is relatively effective, i.e. in 50-60% of the patients it goes along with 20-40% symptom reduction (Abramowitz & Jacoby, 2014). However, the sole use of medication has a rather temporary effect with high relapse rates (24-89%) and residual symptoms (Greenberg et al., 1998). Thus, several therapy studies in OCD (Eddy, Dutra, Bradley, & Westen, 2004; Foa et al., 2005) attribute the combined pharmaco-cognitive-behavioural-therapy, which has the best therapy effect with the lowest relapse rate (only about 12%). This combined therapy is as well the recent recommended treatment for OCD with best therapy outcomes (Koran et al., 2007).

For treatment resistant OCD, the following methods have shown promising results: neurosurgery (i.e. interrupting certain circuits), ablative surgical procedures (i.e. cingulotomy) (Dougherty et al., 2002), deep brain stimulation (i.e. implanting electrodes that continuously apply current to a specific brain region)(Alonso et al., 2015), or noninvasive transcranial magnetic stimulation (TMS) (Sachdev, Loo, Mitchell, McFarquhar, & Malhi, 2007; Trevizol et al., 2016). The ventral striatum, sub-thalamic nucleus, nucleus accumbens and anterior limb of the internal capsule have been often targets for these types of interventions. All these partly-

invasive techniques have the same goal, which is to interrupt certain imbalances in the neural circuit. However, the decision to use this type of therapy should be weighted properly, given the well-known risk of a surgical intervention.

2. Neuropsychological Markers in OCD

Neurocognitive studies in OCD have reported that patients as well as their first-degree relatives show lower performance in tasks that evaluate executive functions which are necessary for the control of behaviour (Abramovitch, Abramowitz, & Mittelman, 2013). Executive functions can be tested by established and specialized psychological tests such as go-/no-go tasks, stop signal tasks, reaction time or Stroop tasks (for cognitive or motor inhibition), the Tower of London (for executive planning), probabilistic learning and reversal tasks (for set shifting) or the Iowa gambling task (for decision making). Studies assessing executive functions have found that OCD patients seem to have difficulties in tasks that especially require decision making (Sachdev & Malhi, 2005) or decision making based on reward (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010; Okasha et al., 2000), motor or cognitive response inhibition (Bannon, Gonsalvez, Croft, & Boyce, 2002; Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Penades et al., 2007) and planning or task switching (Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Watkins et al., 2005). Impairments in general cognitive flexibility and response inhibition have often been reported in patients with OCD (Gruner & Pittenger, 2017), potentially explaining the repetitive feature of their symptoms and their difficulties in inhibiting these repetitive actions.

Some studies have provided evidence that an improvement of these cognitive impairments goes along with symptom reduction (Buhlmann et al., 2006; Cavedini et al., 2002). Interestingly, other studies have documented similar cognitive impairments in first-degree relatives of OCD patients (Chamberlain et al., 2007; Delorme et al., 2007). These findings speak in favour of the hypothesis that these impairments in executive functions might constitute an endophenotypic marker of the disorder (Chamberlain et al., 2005). Reviews such as the one by Menzies et al. (2008) but also more recent ones such as a review by Nakao, Okada, and Kanba (2014), present an overview of these neuropsychological findings in OCD and discuss their integration into the OCD model.

3. Neurobiological Markers in OCD

From a clinical point of view, OCD is a psychiatric disorder. However, pioneer studies using neuroimaging techniques have provided evidence for an aberrant brain function compared to healthy individuals. Hence, the term "neuropsychiatric disorder" may be most adequate (Baxter et al., 1987; Fitzgerald, Moore, Paulson, Stewart, & Rosenberg, 2000; Lucey et al., 1995). These pioneering studies in OCD used methods such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS). Such methods allow the indirect assessment of brain activity in different brain areas at rest or during neutral states. More specifically, PET is a sensitive indicator of cerebral metabolic rate, by measuring glucose consumption in a particular time frame; SPECT measures the regional cerebral blood flow with an increased blood flow being an indicator of neuronal activity; and MRS measures the concentration of brain metabolites in brain tissue. A narrative review of these studies (Saxena & Rauch, 2000) suggested that in OCD the orbitofrontal cortex, the caudate nucleus and the thalamus show aberrant neural activity in form of either increase in glucose metabolism or increased or decreased blood flow compared to healthy individuals. A quantitative review of PET and SPECT studies - i.e. a meta-analysis, which has the advantage of providing more standardized and objectively aggregated results - has suggested that only orbital areas and the head of the caudate nucleus have been consistently reported to show alterations compared to healthy controls (Whiteside, Port, & Abramowitz, 2004). Although MRS studies in OCD patients have brought additional evidence of aberrant activity in the striatum, methodological shortcomings at that time, such as restricted measurements to small brain regions rather than the entire brain, have limited result interpretation.

3.1. Functional Activation Studies

With the advancement of imaging techniques, a newer method emerged - the method of functional magnetic resonance imaging (fMRI). This method is less invasive (i.e. no radiotracers have to be injected) and has an improved spatial and temporal resolution. fMRI is blood oxygenation level dependant (BOLD) and blood oxygenation is a strong indicator of regional brain activation during certain states or tasks (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Using fMRI, the functional activation of specific brain areas during specific tasks can be

analyzed. In combination with (structural) magnetic resonance imaging - (s)MRI - information about structural properties of the brain such as white or gray matter (e.g. volume, surface area or thickness) can be gained.

OCD studies using neuropsychological tests during fMRI scanning have shown impaired activation in certain brain regions of patients compared to healthy controls. Hence, this newer technology has enabled the identification of regions responsible for certain processes and their altered function in OCD. The so-called activation studies have revealed a general impairment in form of decreased functional activation of the orbitofrontal cortex (OFC), mostly detected when patients performed tasks that required decision making and cognitive flexibility. Activation in ventrolateral (vlPFC) and dorsolateral (dlPFC) prefrontal cortex was altered while patients were performing tasks that required set shifting or working memory. Anterior cingulate cortex (ACC) activation alterations were detected in association with inhibitory control tasks, and alterations in parietal cortex and striatum activation in association with executive planning (Menzies et al., 2008).

Collectively, these imaging studies have shown aberrant functional activation in OCD patients compared to healthy controls in various regions and networks. However, findings seem to be inconsistent with respect to the direction of activation (i.e. increased activation vs. decreased activation vs. no significant differences). Nevertheless, these neuroimaging findings complement the impairments found on a behavioural level, and suggest the presence of neurobiological markers in the OCD brain.

One efficient approach to increase our understanding of the neurobiological mechanisms underlying OCD symptoms is the application of fMRI symptom provocation tasks. In symptom provocation tasks patients are exposed to feared objects or negative affective OCD-related stimuli which have a high potential to trigger OCD symptoms. Symptom provocation during fMRI scanning thus allows studying the neuronal processes underlying symptom expectation, initiation or manifestation. OCD symptom provocation studies have used several types of stimulus material, namely: general OCD related pictures (Breiter et al., 1996; Murayama et al., 2013; Nakao et al., 2005), individually tailored picture material (Adler et al., 2000; Simon, Kaufmann, Musch, Kischkel, & Kathmann, 2010; Simon, Kischkel, Spielberg, & Kathmann, 2012), symptom specific picture material (Olatunji et al., 2014), stimuli with negative emotional valence, i.e., emotional faces (Cannistraro et al., 2004; Via et al., 2014), or disgusting stimuli (Husted, Shapira, & Goodman, 2006; Shapira et al., 2003). Most of these symptom provocation studies have provided evidence for aberrant functional activation in areas such as OFC, ACC and dlPFC, which overlap with previous functional but also structural neuroimaging studies in OCD. This overlap suggests a general, task-independent psychopathological relevance of these areas for OCD. Additionally, the inferior frontal gyrus (IFG), insula, and parahippocampal regions were also found to be associated with symptom provocation (Nakao et al., 2014). A

meta-analysis by (Rotge et al., 2008) provided a quantitative estimation of the cerebral activation patterns found in symptom provocation studies. The authors concluded that OFC and ACC might be involved in the mediation of OCD symptoms, whereas regions located in the dorsal fronto-parietal regions might be associated with the patients' attempts to resist the symptoms triggered by these types of tasks.

Interestingly, some of the symptom provocation studies underscore the relevance of additional hyperactive limbic regions as hubs in the networks relevant for the manifestation of OCD symptoms. In particular, increased amygdala activation during symptom provocation tasks has been reported in several studies (Breiter & Rauch, 1996; Cannistraro et al., 2004; Olatunji et al., 2014; Simon, Adler, Kaufmann, & Kathmann, 2014; Via et al., 2014). The amygdala is known to be involved in emotional processing and anxiety. As anxiety is a core symptom in OCD, an involvement of this structure in the pathogenesis of OCD appears plausible. However, other studies have shown either a decrease in amygdala activation (Britton et al., 2010; Cannistraro et al., 2004) or no alteration in amygdala activation (Rotge et al., 2008) during this type of tasks, compared to healthy subjects. Although the exact role of limbic regions needs to be further elucidated, their involvement in OCD during this kind of tasks should, nevertheless, not be neglected.

In sum, functional activation studies bring evidence of aberrant neural activation in OCD, which is also related to cognitive impairments. More specifically, on the one hand, impairments in executive functions seem to be associated mainly with decreases in cortical activation. On the other hand, experimentally triggered OCD symptoms seem to be rather related to increases neural activation in partly overlapping cortical areas. Particularly, symptom provocation seems to go along with a disturbed activation within the limbic system, but the exact magnitude of direction and the characteristics of the triggers (i.e. OCD related stimuli or generally aversive stimuli) need to be further evaluated.

3.2. Functional Connectivity Studies

The interest of neuroimaging studies has shifted from a "core region" approach to a rather "network based" one. Recently, more OCD studies have focused on exploring the interaction between specific brain regions. Consequently, functional connectivity studies are gaining increasing importance. These studies evaluate the functional interaction between certain areas by assessing the correlation of the BOLD time courses of these regions under specific states, i.e., task or rest. These analyses can be performed on the whole brain level or between specific regions of interest (ROI).

3.2.1. Resting State Studies

Resting state fMRI (rs-fMRI) studies analyze the intrinsic interactions between certain regions when the subject is not performing any specific task. These studies mostly focus on between-region functional connectivity alterations, and measure the spontaneous low-frequency fluctuations (<0.1 Hz) of the BOLD signal over time.

Rs-fMRI studies in OCD have found altered functional connectivity in a cortico-striatal network in patients (Harrison et al., 2009). More specifically, increased resting state functional connectivity between ventro-limbic and cortico-striatal regions including OFC, as well as decreased connectivity between caudate/putamen and prefrontal areas has repeatedly been reported (Anticevic et al., 2014; Harrison et al., 2009). Further studies have shown that the altered resting state connectivity in ventro-striatal and OFC regions seem to predict the overall symptom severity in OCD (Harrison et al., 2013).

This intrinsically abnormal functional connectivity and the impairments in cognitive processing have also been found to be associated in OCD patients (Vaghi et al., 2016). Moreover, the OFC also seems to show increased connectivity with other OCD non-specific areas, such as the basal ganglia, and there are indications that a use of medication may alleviate this hyper-connectivity (Beucke et al., 2013). Some studies also support the hypothesis that the abnormality of resting state functional connectivity is not limited to the cortico-striatal circuit, but that it also involves disconnections from limbic areas (Hou et al., 2014).

In line with this assumption, Gottlich, Kramer, Kordon, Hohagen, and Zurowski (2014) and Posner et al. (2014) found a decreased connectivity within the limbic areas as well as a limbic disconnection to fronto-parietal regions, together with a hyper-connectivity within the attention/executive network. In a later work, the same group (Gottlich, Kramer, Kordon, Hohagen, & Zurowski, 2015) could show that one of the two different sub-regions of the amygdala (i.e. superficial and basolateral) and their respective networks are altered in OCD. These networks are associated with risk anticipation and fear processing, respectively. The authors conclude that these impairments might reflect a deficient fear circuit in OCD which could hinder fear extinction as a main component of CBT.

Resting state studies evaluating larger scale networks in OCD have found alterations in the so-called “default mode” network (Beucke et al., 2014). This network comprises regions whose activity is highly correlated when the brain is in a wakeful rest state, i.e. not focused but day-dreaming or mind-wandering (Greicius, Krasnow, Reiss, & Menon, 2003). These studies lead to the assumption that a disruption in a network involved in internal processing could potentially be mirrored in the behaviour of OCD patients who tend to show excessive rumination, to focus strongly on their symptoms, and to question the potential causes or reasonableness.

Moreover, a meta-analysis of our group on resting-state connectivity studies revealed functional

connectivity disturbances in mainly the salience network (associated with attention), fronto-parietal network (associated with goal directed behaviour) and default-mode network in OCD (Gürsel, Avram, Sorg, Brandl, & Koch, 2017), also named the "triple network model". Knowing that the salience network switches between default mode network and fronto-parietal network, and that exactly this connectivity has been shown to be altered in patients in the previous mentioned study suggests that OCD patients have problems of switching to relevant tasks and are stuck in the rumination mode of obsessions and compulsions.

Collectively, these findings bring evidence that the baseline activity of the brain at rest is altered and this is reflected in disturbances at a network level, specially between networks responsible for attention, goal directed behaviour and interior reflection, rumination.

3.2.2. Task Related Studies

Although specific brain regions exhibit aberrant activation during tasks in OCD, an increasing number of studies are now beginning to focus on the functional interactions of particular regions in the form of network connectivity during specific tasks.

For example, Cardoner et al. (2011) showed that during an emotional face matching task, not only the activation of some regions such as amygdala and dlPFC was enhanced but also their connectivity during task, i.e., there was an enhanced connectivity between amygdala and prefrontal, intraparietal as well as visual extra-striatal regions. The enhanced amygdala activation was moreover associated with symptom severity.

Similarly, de Vries et al. (2014) have brought evidence for increased activation in fronto-parietal regions and hyper-connectivity between amygdala and frontal regions in OCD patients during the performance of a working memory task. Interestingly, a recent study by van Velzen et al. (2015) investigated the connectivity and its directionality between different regions of interest during a task that required inhibitory control. The results revealed altered connectivity between the inferior frontal gyrus and the amygdala during response inhibition in OCD patients. A similar result was encountered in their unaffected siblings compared to healthy controls, although to a lesser extent. Moreover, the information between these two regions during task was found to flow top-down in OCD, whereas the opposite directionality was detected in controls, with the amygdala having a bottom-up effect on the inferior frontal gyrus. On a first glance, this result seemed contra intuitive, as previous studies assumed increased influence of limbic regions over areas, such as prefrontal cortex in OCD. However, authors speculated that this task potentially is more salient for patients so that the IFG needs to supress the increased amygdala activation and not the other way around, working like a down regulator which keeps the balance.

Jung et al. (2013) provided evidence for an altered functional connectivity in the cortico-

striatal-limbic network during rest but also during a task (i.e. incentive processing) in OCD. Especially, striatal-amygdala and striatal-OFC circuitries were affected. Similarly, Jhung et al. (2014) also found altered connectivity of the cortico-striatal network involving OFC and temporal areas in OCD during rest and task. However, they detected differential connectivity in OCD patients with contamination fears, who showed aberrant connectivity between striatum and limbic regions during rest or task. This aberrant connectivity was also associated with the severity of contamination symptoms. Beucke et al. (2012) found an altered connectivity between two major nodes that are typical neurosurgical OCD targets, i.e., ventral striatum and anterior middle cingulate cortex. This altered cingulo-striatal coupling was associated with performance in a task in which patients were anticipating potential punishment.

Taken together, the task functional connectivity studies in OCD indicate a dysfunction in a network involving mainly cortico-striatal regions. Nevertheless, regions outside of this circuit (e.g. limbic areas) were also reported to be altered in functional connectivity by some studies. Interestingly, limbic circuit dysfunctions in OCD were mostly present in the context of emotional or negative processing - a finding which fits well to the functional activation findings reported earlier. Despite the evidence regarding limbic region activation during symptom provocation, there is only one study evaluating the functional connectivity of limbic regions during emotional processing (Jhung et al., 2014). Having more information regarding the interactions on a network level during symptom provocation would help to elucidate the mechanistic processes underlying the pathogenesis of OCD symptoms.

3.3. Structural Neuroimaging Studies

With the advent of high-resolution three-dimensional high contrast MRI, structural properties of brain morphology can be measured. These properties involve thickness, volume, surface area or cortical folding of gray matter (GM), or even white matter (WM) properties, such as integrity or connectivity of main WM paths. Although there is a high variance of the methods used to analyze these properties, there has been evidence for structural alterations in brain morphology in both GM and WM in OCD. The affected regions mostly overlap with the previous reports of functional neuroimaging studies (Eng, Sim, & Chen, 2015).

3.3.1. Gray Matter Alterations in OCD

When interpreting previous GM findings, it is important to be aware of the methodological differences. Most studies have used voxel based morphometry (VBM) (Ashburner & Friston, 2000) to measure cortical GM differences in density, volume or thickness. However, more recent studies have adopted surface based approaches (SBA), such as the one developed by Fischl,

Sereno, and Dale (1999). This latter method was implemented in the FreeSurfer software to obtain a more detailed profile of the cortical GM by assessing characteristics such as surface area and gyrification (i.e. a measure of cortical folding).

VBM bases its computations on a voxel grid and performs a voxelwise comparison of the local GM. From these computations the following three properties of GM can be extracted: regional GM concentration/density, which is estimated by the ratio of GM in relation to other tissue types in a voxel (Ashburner & Friston, 2000), absolute amount of GM (i.e. volume) (Good et al., 2001) and thickness, given as the distance in mm in each voxel in the cortical mantle (Hutton, De Vita, Ashburner, Deichmann, & Turner, 2008). However, the VBM GM concentration or volume can be confounded by the extent of convolution/gyrification (i.e. folding) of the brain in certain regions (Hutton et al., 2008; Narr et al., 2005). Therefore, the VBM measure represents a parameter of cortical GM which can be confounded by surface area, cortical folding and thickness (Hutton, Draganski, Ashburner, & Weiskopf, 2009; Palaniyappan & Liddle, 2012; Raznahan et al., 2011).

SBA methods such as the one used in FreeSurfer (Dale, Fischl, & Sereno, 1999; Fischl et al., 1999), in contrast, use 3D surface models and then apply triangulated meshes over the WM and GM. SBA methods have the advantage to be able to compute the GM features independently of each other. Hence, the GM volume evolves out of the subtraction of the two spheres and their inflated surfaces, i.e. the subtraction of WM volume from pial volume. The GM surface area, which represents the total surface area of the pial surface/GM surface, is calculated as the sum of the surfaces of all the vertices (triangles). The GM thickness is calculated as the distance from each vertex on the WM surface to the corresponding vertex on the pial surface.

These methods furthermore overcome the flaws encountered with VBM (e.g. shortcomings in association with the estimation at deep sulcis or problems with image registration, etc.) (Clarkson et al., 2011; Helms, 2016). Additionally, they allow to measure cortical folding or local gyrification index (*l*GI), which provides a valuable insight into the neurodevelopmental aspects of the disorder. As these two methods (VBM vs. SBA) seem to yield slightly different results, there have been suggestions that the two methods should not be employed in a mutually exclusive but in a complementary way, and that the combined use would increase our understanding of the processes underlying changes in GM (Hutton et al., 2009).

Voxel Based Morphometry Studies

A recent review of existing OCD studies analysing brain morphology (Piras et al., 2015) suggests that structural alterations are present and distributed in a widespread network rather than in isolated regions. This review provides consistent evidence for GM reductions in the cortical mantle, and tissue expansion in deeper GM structures, such as the limbic regions, in patients

compared to healthy subjects.

Overall this review allows three main conclusions.

First, structural studies confirm previous activation studies by finding similar regions to be altered in GM or WM (i.e. OFC, ACC, striatum, thalamus and temporo-limbic regions), the so-called "affective circuitry". *Second*, structural alterations are consistently reported in additional regions belonging to the so-called "executive circuitry"(involving the lateral frontal and associated posterior cortices). *Finally*, the structural alterations are significantly related to the OCD symptom severity, which speaks in favour of a potential neural vulnerability for the disease based on these structural changes.

A more recent mega-analysis of structural brain scans from a very large sample gives additional insight (de Wit et al., 2014). The results show changes in GM and WM, i.e. volume decreases in prefrontal and cerebellar regions. Additionally, the alterations in volume seem to be partly affected by aging. In particular, striatal regions (putamen, nucleus accumbens) show a preserved volume, whereas para-limbic regions show a volume loss with age in patients compared to controls. The authors suggest that these structural alterations could be induced by the severity of compulsive symptoms reflected in overactive striatal areas and a preserved volume whereas the greater volume loss in limbic areas would be the result of an exaggerated response to stress and increased anxiety in patients.

Surface Based Studies

Few OCD studies have used the SBA approach to study GM morphology. Most of these studies have focused on one single GM measure or on specific brain regions (i.e. analyses were ROI based) (Kuhn et al., 2013; Nakamae et al., 2012; Shaw et al., 2015). These studies found reduced cortical thickness in ACC (Kuhn et al., 2013), superior temporal and posterior insular regions in un-medicated OCD patients (Nakamae et al., 2012). However, subcortical and cortical morphological anomalies (i.e. surface expansion) in orbito-fronto-striatal and posterior brain regions in OCD patients have also been found (Shaw et al., 2015). This result confirms previous OCD findings and additionally suggests that these morphological alterations might represent an endophenotype for the disorder as a similar pattern was observed in unaffected siblings.

A more representative result, given the big sample size used, was provided by a recent mega- and meta- analysis that provided evidence for distinct subcortical volume alterations in adult and paediatric OCD patients (Boedhoe et al., 2016). The results showed decreased hippocampus volume, probably driven by comorbidity and late disorder onset, as well as larger pallidum volumes, probably linked to early disorder onset, in adult OCD patients. In contrast, paediatric OCD patients showed increased thalamus volumes, mostly encountered in unmedicated and

comorbidity-free patients. The authors suggested that an increased thalamus volume could be seen as an early marker of the disorder, which, although unrelated to symptom severity, could possibly be associated with alterations in early neurodevelopmental processes.

Developmental studies in healthy participants have indicated that a broader variety of GM properties, such as volume, thickness, surface area or cortical folding, could be of importance and should be evaluated. One argument speaking in favour of such a multi-parameter analysis is the fact that these measures can be partly independent in their development (Panizzon et al., 2009; Winkler et al., 2010), but can as well influence each other (Raznahan et al., 2011). Therefore, considering and evaluating all of these measures when analysing brain morphology should provide more reliable and objective results.

Surprisingly, only two studies assessed all of these GM measures concurrently and at a whole brain level in OCD (Q. Fan et al., 2013; Venkatasubramanian et al., 2012). Their results fit to some degree with previous findings, but a detailed comparison reveals a number of discrepancies. These discrepancies refer to the direction of alteration, the specific cortical measure and the precise location of alteration. For example, Q. Fan et al. (2013) reported an increased thickness in a parietal area, whereas Venkatasubramanian et al. (2012) showed mostly deficiencies in ACC with respect to volume, thickness and surface area and, in addition, a reduced surface area of the lingual gyrus. Nonetheless, both studies bring evidence for an association with disorder characteristics such as symptom severity, type or disorder insight. Finally, although these two studies are not sufficient to derive generalizable conclusions for OCD, their findings pave the way for a better and more general understanding of GM alterations in OCD.

Cortical Folding Studies

Another measure of cortical surface is cortical folding, also known as gyrification. The exact mechanism of how the brain folds and arrives at the final stage with its characteristic gyri and sulci has been in the focus of research for many years. Furthermore, the developmental trajectory of folding has been shown to be of relevance for many neurodevelopmental disorders such as autism (Nordahl et al., 2007), attention deficit hyperactive disorder (ADHD) (Shaw et al., 2012), but also for some psychiatric conditions such as schizophrenia (Hirjak et al., 2015) or OCD (Q. Fan et al., 2013; Venkatasubramanian et al., 2012; Wobrock et al., 2010).

A recent review (Zilles, Palomero-Gallagher, & Amunts, 2013) describes gyrification as a reliable morphological hallmark of brain development. As a consequence, several studies interpreted alterations in gyrification as indicators of neurodevelopmental alterations.

As gyrification has been found to be altered in OCD, several studies have suggested that the disorder could be based on disrupted mechanisms early in brain development. These disruptions, in turn, could constitute the basis for an increased vulnerability for the disorder (Rosenberg

& Keshavan, 1998). Therefore, an evaluation of gyrification appears plausible and clinically relevant.

Gyrification has been shown to be characterized by a regional and inter-subject variability in plasticity and could be influenced by pathological conditions. The research on its ontogeny (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995) shows that it starts developing in the early weeks of gestation (i.e. 16th week), together with the growing brain. It then reaches a peak after birth (approximately 40th week) before the age of 2 (66-80th week post conception). Afterwards, it keeps its gross shape, decreasing only slightly between adolescence and adulthood (until age of 23) (Mills & Tamnes, 2014).

Overall, the development of cortical folding has been shown to finish very early and it has also been associated with the hetero-chronous development of different parts of the brain (i.e. first occipital areas, then parietal and superior temporal areas and later increase in size and development of prefrontal cortex and inferior temporal areas).

Interestingly, there are several hypotheses about the driving forces of cortical folding. However, only two of them have been supported by evidence, namely: the gray matter hypothesis and the mechanical tension hypothesis (Zilles et al., 2013).

The *gray matter hypothesis* relies on the growth processes during cortical development and assumes that gray matter grows more strongly than white matter leading to the mechanical formation of buckling that form the gyri. This hypothesis is also supported by simulation studies (Tallinen, Chung, Biggins, & Mahadevan, 2014) which have shown that gyrification is the consequence of a mechanical instability driven by expansion of gray matter, which itself is constrained by white matter.

The second hypothesis, *mechanical force hypothesis*, assumes that because gray matter consists mostly of neurons and white matter of axons, the axons pull mechanically to keep together highly interconnected regions of gray matter, thereby creating a tension that eventually leads to the formation of gyris. Zilles et al. (2013), thus, concluded, that as the exact causal mechanisms of cortical folding are still unknown, both hypotheses should be considered as complementary - in particular because they are based on two developmental windows of different maturational processes that eventually overlap. Cortical folding can be calculated by using the gyrification index (GI), which is obtained by relating the total cortical surface (i.e. the surface of the sulci and gyri) to the exposed cortical surface (i.e. only the visible surface of the gyri). Several ways of measuring the GI involve manual tracing, automated segmentation (Moorhead et al., 2006) or surface based methods (Schaer et al., 2012, 2008). A brief overview can be found also in the review by Zilles et al. (2013).

In OCD, there are too few gyrification studies so as to be able to draw reliable conclusions. One of the few examples is the study by Wobrock et al. (2010), who found a prefrontal hypogyrifi-

cation. Opposite to that result, Venkatasubramanian et al. (2012) found hypergyrification in insular and lateral occipital regions in OCD patients. Q. Fan et al. (2013), however, failed to find any differences in OCD patients compared to healthy controls. This preliminary evidence encourages further investigation of this cortical property in order to be able to answer the question of whether early neurodevelopmental events could be relevant for the pathogenesis of OCD. Gyrification differences in OCD could then be interpreted as early neurodevelopmental markers which might trigger subsequent changes in other GM measures later in the developmental process, thus rendering altered gyrification an important vulnerability factor for the disorder.

In summary, there is increasing evidence for abnormalities in GM volume in OCD. These alterations might be driven by changes in GM surface area, thickness or cortical folding. As only few studies have evaluated these other GM measures and their association with OCD clinical characteristics, it is not yet possible to determine their clinical relevance for the disorder.

3.3.2. White Matter Alterations in OCD

The above reported alterations in GM could be associated with alterations in other structural properties of brain morphology such as WM structure. Using Diffusion Tensor Imaging (DTI), a specific scanning sequence in the MRI, it is possible to measure the organisation of myelinated axons in nervous system tissue (Mori & Zhang, 2006). The analysis of DTI data is based on the diffusion properties of water molecules in tissue and the assumption that these molecules diffuse more freely along myelinated white matter tracts than within cerebral gray matter. The results of this analysis allow drawing conclusions about the integrity of WM tracts. The most common measures are fractional anisotropy (FA), which is the degree of anisotropic diffusion or directionality, and which has a value between 0 (isotropic diffusion) and 1 (anisotropic diffusion) as well as mean diffusivity (MD) indicating - as a parameter of membrane density - the average magnitude of diffusion and. A decreased FA value or increased MD value is assumed to indicate a decreased white matter fiber integrity.

With the development of other analysis methods of DTI data such as tractography approaches it is now also possible to obtain three-dimensional representations of WM pathways or fiber bundles. Tractography has the advantage that isolated fiber bundles connecting specific regions can be tracked and their connectivity as well as integrity can be analyzed. Tractography approaches employ either *deterministic* or *probabilistic* tracking algorithms. The *deterministic* approach reconstructs one fiber from each seed point while *probabilistic* tracking provides information about the multiple possible fiber directions emanating from each seed. The *probabilistic* approach takes into account the estimation of uncertainty and its outcome provides information about the likelihood estimation of a certain point (voxel) being part of a fiber tract (Soares,

Marques, Alves, & Sousa, 2013).

An important note is that in this thesis, the term "WM integrity" is used for studies bringing evidence of FA and MD, whereas "WM connectivity" is used for results of studies using tractography approaches.

White Matter Integrity

A narrative review by Fontenelle et al. (2009) emphasized that in OCD the reported GM alterations are complemented by disruptions in connecting WM pathways and this could reflect disruptions in the brain system on several levels.

A more recent meta-analysis by Radua et al. (2014) also showed widespread abnormalities in WM mostly through decreased FA in anterior midline tracts (crossing between anterior parts of the cingulum bundle and the body of corpus callosum). Their findings confirm a narrative review of our group, where we concluded that most of the studies reported decreased FA in OCD patients in the cingulum bundle, the corpus callosum and the anterior limb of the internal capsule (which connects thalamus with frontal areas, or striatum with cortical areas) (Koch, Reess, Rus, Zimmer, & Zaudig, 2014).

These results emphasize that the WM bundles found to be impaired in OCD connect regions that were also found to be altered in GM, and allow to assume a certain association between these two structural properties (GM and WM). However, few studies have investigated these associations in OCD up to now. A more recent study (S. Fan et al., 2015) reporting a decreased FA in the cingulum bundle in unmedicated OCD patients replicated partly the results from the meta-analysis. Additionally, they found that unaffected siblings showed a similar pattern and - based on the extent of alteration - seemed to represent an intermediate group between patients and controls. The authors concluded from these findings that this alteration in WM might be considered as an endophenotype for OCD.

Overall, the findings of WM integrity changes provide a partly consistent picture of affected WM pathways in OCD. However, inconsistencies between studies with respect to the direction of alteration still persist.

White Matter Connectivity

A later and more systematic review (Piras, Piras, Caltagirone, & Spalletta, 2013) accompanied by a meta-analysis of existing WM studies in OCD found that the WM pathways targeting the regions previously reported to be altered in GM such as OFC and ACC (i.e. corresponding to the internal capsule and the cingulate bundle) show alterations in white matter structural integrity in OCD. Interestingly, this review assumes a broader perspective and concludes that

in OCD disruptions in brain systems or networks seem to be present on a larger scale. It brings additional evidence for areas putatively involved in OCD pathophysiology, such as the intrahemispheric bundles connecting the OFC regions with posterior parieto-occipital regions.

Indeed, the inferior frontal occipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF) seem to exhibit hypo-connectivity, whereas the interhemispheric frontal bundles such as corpus callosum or anterior and posterior limb of internal capsule, seem to show hyper-connectivity.

Another ROI based study using probabilistic tractography found that WM fibers spread dorsally between the striatum and the OFC in patients with OCD and that these connections also exhibit an increased fiber integrity (in terms of FA) (Nakamae et al., 2014). The authors concluded from these findings that part of the pathophysiology of OCD might be characterized by altered topography and connectivity of WM pathways connecting the striatum with the OFC.

A recent paper of our group (Reess et al., 2016), which applied a deterministic fiber-tracking approach and the method of graph theory, provides additional evidence for altered connectivity in OCD. This work found that outside the altered cortico-striatal network, a reduced connectivity of OFC, striatal, insula and temporo-limbic regions might play a role in OCD pathophysiology. Additionally, local temporo-limbic alterations (i.e. an increased clustering coefficient of the amygdala potentially indicating a stronger information flow through the amygdala) once more indicate that these emotional processing areas might be psychopathologically relevant for OCD and should be integrated in the neurobiological model of the disorder.

In sum, structural connectivity studies with respect to WM focused mainly on WM integrity (i.e. FA) in OCD. Consequently, the knowledge about potential alterations in other properties such as directionality or orientation of WM bundles is still limited. Hence, future studies should contribute to increasing our insight into specific white matter connectivity characteristics and their potential alterations in OCD.

3.3.3. Multimodal Studies

Several studies have striven to unravel the functional and structural neurobiological correlates in OCD. The overall conclusion is that in OCD the brain is more affected on a network-system level than in specific regions. Although it seems logical to evaluate structure and function concurrently, surprisingly few studies have indeed explored the potential relationship between these measures in OCD.

Most of the studies that used multimodal approaches found associations between: functional activation and cognitive performance (Nakao et al., 2009), structural connectivity and cognitive performance (Garibotto et al., 2010; Magioncalda, Martino, Ely, Inglese, & Stern, 2016;

Spalletta, Piras, Fagioli, Caltagirone, & Piras, 2014) or structural WM and GM alterations (Peng et al., 2014). The locations of the alterations found on different levels (i.e. structural, functional) are, however, not necessarily overlapping but at least anatomically connected with each other. Thus, it is possible that certain structurally or functionally disrupted regions, or their interactions, can influence more remote areas outside of their direct circuit and thereby inhibit or disturb their normal functioning. This, in turn, could go along with cognitive or emotional deficits which are frequently noticeable in OCD on the behavioural level. Hence, more integrative studies combining the assessment of structure, function, cognitive performance and clinical characteristics are needed to better understand the neurobiological underpinnings of OCD.

Many studies have suggested that structural alterations may underlie disturbances in functional properties of the cortex (Menzies et al., 2008; Milad & Rauch, 2012; Pauls, Abramovitch, Rauch, & Geller, 2014; Piras et al., 2015). However, only few studies have attempted to combine functional and structural imaging in OCD. One of the few studies integrating both modalities was the work by Admon et al. (2012), which evaluated functional and structural neural indices during a risk aversion task in patients with OCD. They found that risk aversion was mediated by abnormal limbic responses during threatening and rewarding stimuli. This abnormality was, moreover, characterized by deficient limbic-frontal functional and structural connectivity. In addition, these neuronal properties were associated with symptom severity as well as with each other, thus supporting the assumption of a general and multi-facetted malfunctioning at a network level. A recent integrative review (Eng et al., 2015) of GM and WM structural as well as functional activation studies during executive processing in OCD used a meta-analytic approach to quantify the associations between these studies. This meta-analysis suggested that both the cerebellum and the parietal cortex should be added to the neurobiological model of OCD, besides the frequently reported striato-thalamo-cortical areas. The review also pointed out that altered GM, task-domain specific neural differences and altered executive processing might be linked to partly overlapping areas in OCD.

Overall, there are only few multimodal studies in OCD up to now. Our work (i.e. the first publication, (Rus et al., 2017a), presented in Chapter 7) tried to follow this integrative approach in order to further a more wholistic understanding of the pathophysiology of OCD.

3.3.4. Basic Animal Studies

Animal studies in OCD partly confirm the neuroimaging findings in humans. The pioneering animal studies (Albelda & Joel, 2012; Szechtman et al., 2016), which managed to evoke OCD like compulsions in mice (Ahmari et al., 2013), also showed that behaviours could be supressed by disturbing circuits involving the cortico-striato-thalamo-cortical network (Burguiere, Mon-

teiro, Feng, & Graybiel, 2013). On the contrary, when hyperstimulating the glutamatergic neurons between OFC and ventromedial striatum, Ahmari and colleagues observed repetitive behaviours in mice (e.g. excessive grooming). As these compulsive-like behaviours could not be triggered by acute stimulation, but only by multiple exposures to stimulation, the authors concluded that these types of behaviours are acquired on the basis of changes in neuroplasticity.

One could argue that, for ethical and methodological reasons, these studies cannot be transferred to human research (Fineberg, Chamberlain, Hollander, Boulougouris, & Robbins, 2011). However, they allow a deeper and probably more precise insight into the neural circuits by linking neuroanatomy, physiology, genetics and behaviour thus enhancing our understanding of the exact mechanisms underlying neural network disturbances in psychiatric disorders (Pauls et al., 2014).

4. The neurobiological Model of OCD

The idea that behaviour is regulated by fronto-subcortical connections, which particularly subserve different behavioural functions was already described by Alexander, DeLong, and Strick (1986). There have been studies showing associations between the function of these frontal-subcortical circuits and the expression of various psychiatric symptoms. The fact that some of the psychiatric disorders associated with this circuit share commonalities in their psychopathology or co-occur in many cases (i.e. Schizophrenia, Depression, Addiction) makes an involvement of this circuitry in OCD also plausible. Thus, Saxena and Rauch (2000) were the first to propose a neurobiological model for OCD that was based on this classical frontal-striatal circuit.

Initially, these fronto-subcortical circuits were described as pathways connecting cortical areas such as frontal cortex with basal ganglia regions, and then passing through the thalamus and back to the cortex. This model assumes that, in healthy subjects, the pathways counterbalance each other, i.e., work together on inhibiting or disinhibiting actions depending on external requirements. The originally named "cortico-basalganglia-thalamo-cortical circuitry" was based on a very simple conceptualisation, namely that of a direct and an indirect pathway.

The *direct pathway*, also known as the excitatory reinforcement path, starts at frontal areas, passes through the striatum, the globus pallidus internus and the substantia nigra complex (GPi/SN), and then runs over the thalamus back to cortical areas.

The *indirect pathway*, known as the inhibitory path, starts at frontal areas, passes - similar to the direct pathway - through the striatum, but then takes a "detour" through the globus pallidus externus (GPe) and the subthalamic nucleus (STN) and then runs "back on track" through GPi/SN over the thalamus back to the cortex.

Most importantly, the two pathways have opposite functions. The inhibitory and excitatory functions of these pathways are based on their neurochemical properties, i.e., the excitatory neurotransmitter system embedded in the glutamate connections vs. the inhibitory neurotransmitter systems embedded in the gamma-aminobutyric acid (GABA) connections. As a consequence, the *direct pathway* has only two inhibitory connections, disinhibiting the thalamus and activating the circuit in a positive feedback loop. In contrast, the *indirect pathway* inhibits the thalamus in a negative feedback loop, and has in total three inhibitory connections (Figure 4.1).

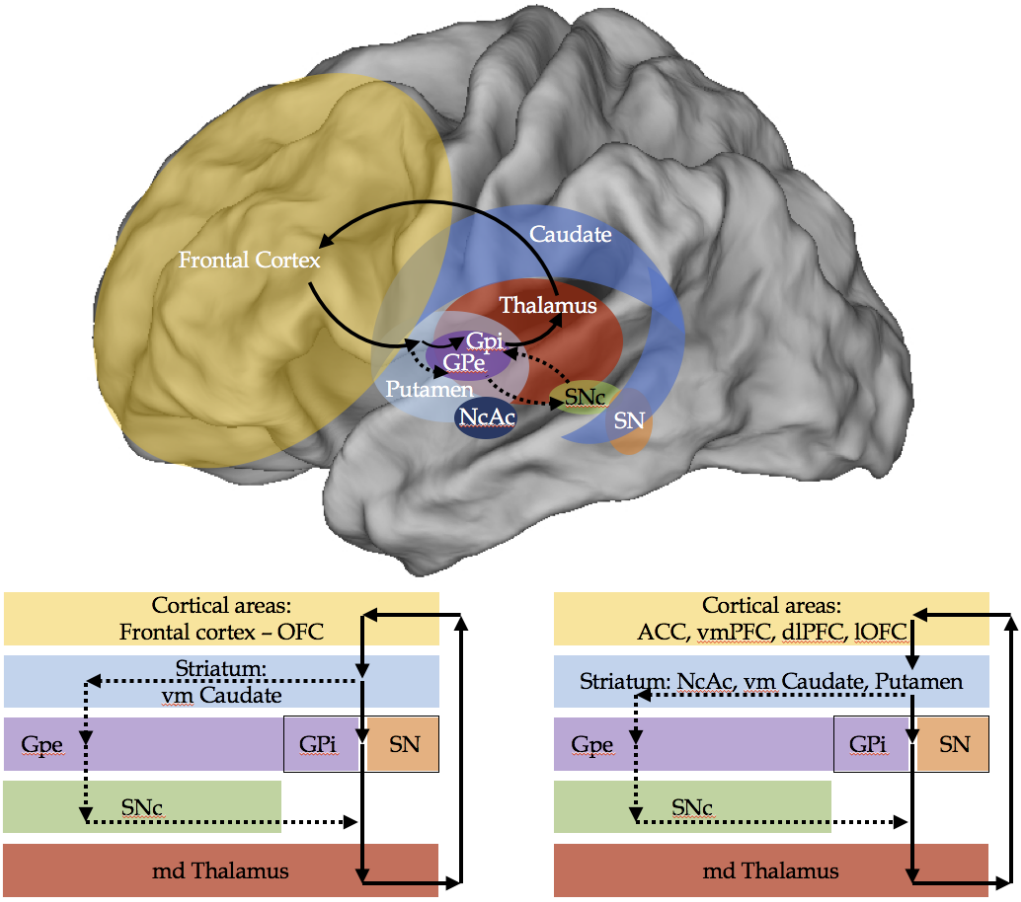

Figure 4.1.: Descriptive visualisation of the cortico-striato-thalamo-cortical circuit with direct excitatory (continuous line) and indirect inhibitory (dashed line) paths. The *left box* illustrates the OCD model proposed by Saxena and Rauch (2000); the *right box* illustrates the revised and more detailed model proposed by Milad and Rauch (2012).

The OCD model proposed by Saxena and Rauch (2000), also known as the cortico-striato-thalamo-cortical circuit (CSTC), generally assumed an imbalance between direct and indirect pathways in OCD. This imbalance was assumed to be due to a preference of information flow via the direct excitatory path with the indirect path losing its inhibitory function resulting in impaired behavioural inhibition (i.e. a hyperactive circuit that mediates fixed repetitive behaviours). Based on imaging findings, Saxena and Rauch (2000) suggested that especially the OFC (belonging to the fronto-cortical areas), ventro medial caudate nucleus (vmCd-belonging to the striatum) and the medial dorsal part of the thalamus might constitute important nodes in the CSTC model of OCD (Figure 4.1, left box).

However, since then, several revisions of this model have been proposed (Menzies et al., 2008; Milad & Rauch, 2012; Nakao et al., 2014; van den Heuvel et al., 2016). The main reason for these amendments was an increasing amount of evidence indicating that the model in its original form was not sufficient to completely explain the disorder mechanism.

With the advancement of neuroimaging techniques and analysis methods, newer findings from functional and structural studies on the neurobiology of OCD came to light. As a consequence,

Milad and Rauch (2012) proposed a revision of the classical CSTC model with a much finer subdivision of the nodes and circuits implicated in OCD (Figure 4.1, right box). The authors emphasized that, besides the dysfunction in behavioural inhibition and self-regulation, several other circuits implicated in various cognitive and executive functions had been shown to be impaired in the context of the disorder and, thus, needed to be integrated into the revised OCD model.

These circuits are also called loops (see Figure 4.2) and pass through three main zones: the cortical, the striatal and the thalamus zone with recurrent projections to the cortical areas. Therefore, the direct and indirect pathways mentioned above are involved in each of these circuits: the affective and reward processing circuit (involving connections from ACC/vm or PFC to nucleus accumbens, thalamus and back to cortical areas); the *ventral cognitive circuit* responsible for motor preparation and response inhibition (starting from alOFC, to putamen, to thalamus and back to cortex) and the *dorsal cognitive circuit* responsible for working memory and executive functioning (involving dlPFC to dorsal caudate, over thalamus and back to cortex).

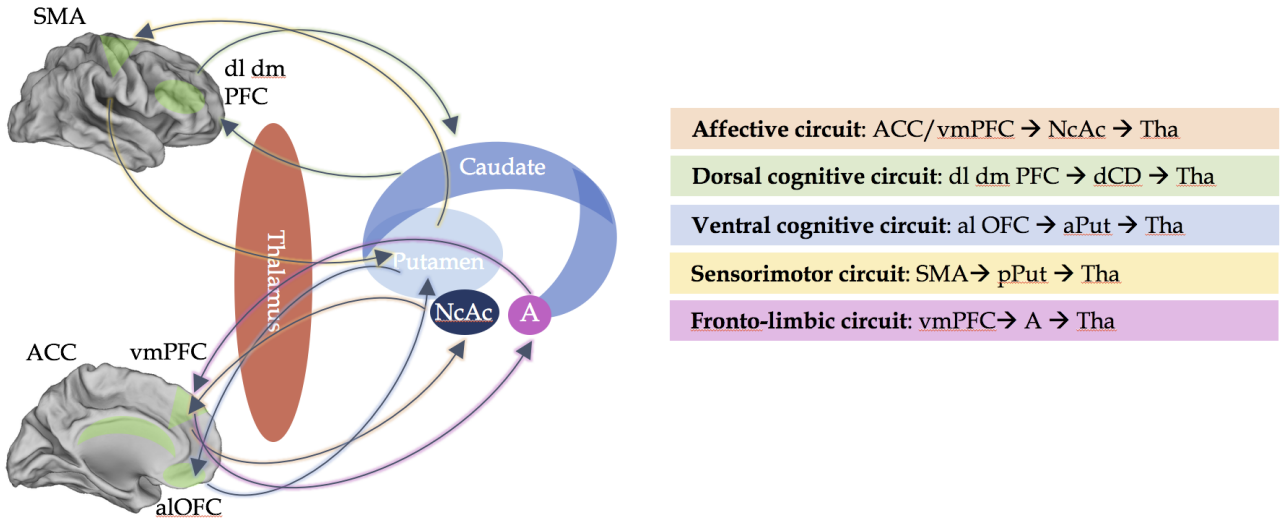

Figure 4.2.: Overview of the circuits involved in the CSTC-model as described by Milad and Rauch (2012), including the additional circuits proposed recently by van den Heuvel et al. (2016).
Abbreviations: **SMA** – sensorimotor area; **dl dm vm PFC** – dorsolateral, dorsomedial, ventromedial prefrontal cortex; **Tha** – Thalamus; **dCD** – dorsal caudate; **aPUT** – anterior putamen; **NcAc** – nucleus accumbens, **A** – amygdala; **ACC** – anterior cingulate cortex; **alOFC** – anterolateral orbitofrontal cortex

Overall, brain imaging studies have provided evidence that not only an imbalance between direct and indirect pathways within the CSTC is present in OCD, but also between the various parallel circuits/loops involved in these different cognitive behavioural domains.

A recent review also suggested that all these pathways, mostly placed in the CSTC circuit, are not as segregated as initially thought. Rather, they are integrated into a system with

information cascading from one loop to the other (van den Heuvel et al., 2016). This review also proposed two more circuits in the CSTC model of OCD, the *sensorimotor* and a *fronto-limbic circuit*.

The *sensorimotor circuit* was receiving more attention when OCD was re-categorized from an anxiety disorder to an OCD and related disorders category (discussed in the first part of introduction) and, thus, the compulsive aspects of the disorder re-gained again more attention. This pathway includes the premotor area, putamen and thalamus and is thought to mediate the transition from goal-directed to habitual behaviours.

The *fronto-limbic circuit* involving vmPFC, amygdala and thalamus is associated with anxiety and distress processing, emphasising the relevance of anxiety for the disorder. Consequently, new brain regions, such as sensorimotor areas and amygdala seem to gain relevance in the revised model of OCD.

Interestingly, a previous review by Menzies et al. (2008) that integrated evidence from cognitive, functional and structural studies, also suggested not only a finer division of the CSTC model, but also an extension, especially towards areas outside of the CSTC circuit. These authors also suggested the involvement of limbic regions such as the amygdala, but additionally indicated the relevance of posterior parietal areas (supramarginal/angular gyri) in the revised CSTC model of OCD. The involvement of parietal regions is especially supported by WM tract studies which bring evidence for WM bundles (ILF, IFOF) passing exactly through these areas and showing alterations in OCD.

Strikingly, through on-going research and the development of novel and more integrative approaches and multimodal studies, the neurobiological model of OCD continuously changes from a simplistic two-way circuit to a more complex circuit integrated in a whole brain network. However, certain paths or nodes (i.e. limbic areas such as the amygdala), that are already included in the model of OCD, still need to be substantiated by further studies, ideally employing multimodal approaches.

5. Knowledge Gaps

With respect to the state of the art reported earlier, several major knowledge gaps emerge. In particular, very few studies up to now employed a multimodal approach evaluating the association between brain function, structure and clinical characteristics of the disorder. These associations have been investigated merely selectively and by only a very limited amount of studies, thus making it difficult to draw valuable conclusions. Although the revised OCD model suggests specific associations, the exact relationship remains unclear due to missing or inconsistent data.

A second important point that demands clarification is the brain morphology in OCD. Although several researchers have delivered evidence for altered cortical GM, the various properties or measures of GM that can be independently influenced by treatment, symptom progression or other external stimuli remain unexplored. Surprisingly, despite the fact that methods have been developed to simultaneously analyze various GM characteristics besides volume, only two studies have done this so far in OCD, making a generalization unfeasible.

A third aspect is the need for clarification of potential neurodevelopmental indicators that could represent vulnerability factors for OCD. The most recent state of research in this direction comprises a few selective studies in pediatric or adult OCD patients with age gaps in between, from which is hard to derive valid conclusions about neurodevelopmental aspects of the disorder. Moreover, there are no real longitudinal studies which would be significantly more informative in this context. However, recent advances in data analysis allowing for the analysis of cortical folding as a potential indicator of early brain developmental processes should significantly contribute to providing an answer to these opened questions. Up to now, although there are indications of altered brain development in OCD, this question still remains unanswered due to missing research studies.

6. Thesis Objectives

Taking into consideration the presented knowledge gaps in OCD research, the following studies have three main aims.

First in Chapter 7, we want to look at task specific connectivity of limbic areas and their direct association to structural connectivity and clinical symptoms using a symptom provocation task. Up to now, the neural mechanism in association with these specific tasks has not been explored with a multimodal approach. As triggering symptoms is an important feature of CBT therapy, we are convinced that investigating the neuronal mechanism underlying symptom provocation in a multimodal fashion will enable us to better understand the mechanistic processes behind OCD symptoms. Our target area will be the amygdala as this is one of the main regions involved in the processing of negative emotions and especially anxiety which usually precedes compulsive behaviour. Although the amygdala has frequently been found to be altered in OCD, its exact role for the disorder remains unclear. The analysis of an association between potential structural and functional alterations should contribute to providing more knowledge about the psychopathological mechanisms at different levels of the neural network.

The second work in Chapter 8 has the purpose of providing a more comprehensive characterization of cortical GM and its association with clinical characteristics by using an analysis approach that enables the independent measurement of various GM properties. This approach accounts for several methodological flaws of previous methods and has - in this comprehensive form - in OCD research rarely been used up to now. The main benefit is that, besides the frequently explored parameter of GM volume, thickness, surface area and cortical folding patterns are also measured. This multi-parameter analysis allows for a more detailed view on GM alterations in OCD. By obtaining a more specific knowledge about the surface anatomical profile of brain morphology in OCD we should be better able to explain the result inconsistencies of previous studies.

The third work in Chapter 9 aims to provide new evidence for potential indicators of neurodevelopmental alterations in OCD by analysing gyrification which - based on its ontogeny and development - has been shown to constitute a useful marker of changes early in brain development. Several studies have already pointed out that certain neurodevelopmental indicators might be of relevance for OCD. Elucidating the the psychopathological relevance of this marker for OCD could change the view about vulnerability or risk factors for the disorder and open

up new opportunities for early treatment and prevention.

The overarching goal of this work is to integrate these separate findings and provide an integrative model of OCD, which considers findings gained from GM analyses, WM analyses and functional activation studies their association with each other and their clinical relevance for the disorder. By unifying these findings, an overall picture of OCD will be created with the primary goal of helping to elucidate the major hallmarks of OCD pathophysiology.

Part II.

Research Articles

7. Functional and Structural Connectivity in OCD

The amygdala has an increased task dependent functional connectivity linked to a decreased structural connectivity of underlying white matter tracts in OCD patients.

This chapter presents a recently published research paper entitled "Functional and structural connectivity of the amygdala in obsessive-compulsive disorder", which was published in the journal Neuroimage: Clinical in 2016, and was written by Oana Georgiana Rus, Tim Jonas Reeß, Gerd Wagner, Claus Zimmer, Michael Zaudig and Kathrin Koch. This article presents an innovative analysis approach and provides first evidence on the link between altered functional and structural brain connectivity during a symptom provocation task in OCD patients.

Contributions:

The author of the present thesis is as well the first author of this research article. O.G.R, T.J.R. and K.K. contributed substantially to conception and design, acquisition of data, analysis and interpretation of data and revised the manuscript critically. O.G.R. additionally drafted the article. G.W. contributed substantially to conception of data and revised the drafted manuscript. C.Z. contributed substantially to data acquisition. M.Z. contributed substantially to patient collection. All authors gave the final approval of the version to be published.

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Functional and structural connectivity of the amygdala in obsessive-compulsive disorder

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ABSTRACT

Background: The amygdala is known to be involved in anxiety processing, but its role in the psychopathology of obsessive-compulsive disorder (OCD) is still unclear.
Aims: In this MRI study we investigated potential alterations in structural and functional connectivity of the amygdala in 42 adult patients with OCD and 37 healthy subjects.
Method: Psychophysiological interaction analysis was used to explore amygdala functional connectivity during a negative affective task. Probabilistic tractography was then employed to study structural connectivity and integrity of underlying white matter fiber tracts.
Results: Compared to controls, OCD patients showed a significantly increased functional connectivity of the left amygdala with mostly parieto-occipital regions during task. No structural connectivity differences could be found between the groups. In addition, only patients showed a significant association between functional and structural connectivity of these regions. Moreover, symptom severity was negatively associated with structural integrity of the underlying white matter tracts.
Conclusions: Present results emphasize the relevance of the amygdala for OCD and may reflect that neuronal alterations in structural connectivity could be associated with functional connectivity alterations in broader networks.

1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric illness characterized by repetitive thoughts (i.e., obsessions) and actions (i.e., compulsions). It is a rather common disorder with a lifetime prevalence of 2.3% (Ruscio et al., 2010). The neurobiological model of the disorder states a disrupted cortico-striato-thalamo-cortical circuit (CSTC) (Saxena et al., 1998). More recent work discussed an extension of this model by limbic structures including the amygdala, anterior cingulate, and hippocampus (Lawrence et al., 1998; Menzies et al., 2008; Phillips et al., 2003). Since the manifestation of obsessions and compulsions is usually accompanied by strong negative affect, such as anxiety, and the amygdala is a region known to mediate anxiety (Milad and Rauch, 2012), a pathogenetic involvement of limbic regions (i.e., predominantly the amygdala) in the disorder is very plausible. However, their exact role in the pathophysiology of OCD remains to be clarified.

Accordingly, fMRI studies using the method of symptom provocation by confronting patients with symptom related picture material provided support for the assumption that the amygdala is a key structure in anxiety disorders in general as well as across OCD symptom dimensions (Breiter et al., 1996; Olatunji et al., 2013; Simon et al., 2014; Simon et al., 2010; Via et al., 2014). Most of these studies reported hyperactivity of the amygdala during symptom provocation. This hyperactivity was found in medicated (Olatunji et al., 2013), as well as unmedicated patients (Simon et al., 2014; Simon et al., 2010), but also in symptom specific populations with predominant contamination fears (Mataix-Cols et al., 2004; Olatunji et al., 2014; van den Heuvel et al., 2004), as well as in multi-symptomatic patients (Simon et al., 2014).

Apart from evidence for alterations in activation in patients with OCD an increasing amount of studies provided evidence for alterations

Abbreviations: restFC, resting state functional connectivity; taskFC, task dependent functional connectivity; SC, structural connectivity; WM tract, white matter tract; probFT, probabilistic fiber tracking.

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in task dependent functional connectivity (taskFC). Several studies evaluated taskFC in OCD in various contexts (such as, e.g., reinforcement learning (Beucke et al., 2012), working memory (de Vries et al., 2014) or reward processing (Jung et al., 2013)) and brought evidence for disturbances in a network involving the CSTC, orbitofrontal regions (OFC) but also limbic structures. Surprisingly, only few OCD studies explored taskFC using symptom-provoking paradigms based on negative affective stimuli. Findings from these studies showed taskFC disruptions in OCD patients, also mainly in striatal and limbic regions (Jhung et al., 2014), with the latter showing connectivity disruptions in OCD also during rest (Anticevic et al., 2014; Beucke et al., 2013; Gottlich et al., 2014; Harrison et al., 2009). Moreover, alterations in limbic (i.e., amygdala) resting state functional connectivity (restFC) were found to be positively associated with response to treatment (i.e., CBT), underlining the potential relevance of limbic/amygdala disturbances for therapy outcome (Gottlich et al., 2015).

When viewing the previous findings from a network point of view, it seems reasonable to assume that disruptions in the functional circuitry of the brain may go along with underlying structural alterations. Most of the relevant OCD studies bring evidence for whole brain structural alterations in areas within the CSTC but also outside of this circuit (i.e., in temporal, parietal and occipital areas) (Piras et al., 2015). A recent meta-analysis on structural connectivity studies in OCD pointed out that findings are rather heterogeneous, although most studies reported decreased fractional anisotropy (FA) in OCD patients in the cingulate bundle, the corpus callosum, and the anterior limb of the internal capsule (Koch et al., 2014). Moreover, fronto-basal pathways targeting the orbitofrontal cortex and the anterior cingulate cortex are reported while intra-hemispheric white matter bundles linking specific areas of the prefrontal cortex to posterior parietal and occipital association cortices have also repeatedly been found to be altered in OCD (Piras et al., 2013).

In sum, existing MRI studies investigating functional activation, functional connectivity or structural connectivity, suggest with some consistency that OCD may be characterized by network alterations which are not restricted to the frequently reported cortico-striatal circuit but which affect, amongst others, also the limbic network. Moreover, previous findings indicate that these alterations might be linked and therefore their altered interplay might be of psychopathological relevance.

Surprisingly, there are only few studies analyzing the link between functional and structural neural correlates in OCD. One of the few studies exploring both structure and function in OCD was a study by Admon et al. (2012). Using a gambling task, they showed a deficit in limbic-frontal connectivity both on a functional and a structural level which was associated with the severity of OCD symptoms. Of note, they also found increased amygdala activation to threat stimuli. Despite increasing support of altered functional or structural alterations in a widespread network including cortico-striatal but also limbic/amygdalar areas in OCD, most studies focused on either functional or structural connectivity, whereas a potential association between both measures has been barely investigated up to know.

Against this background and taking into account the relevance of the amygdala for anxiety in OCD, the aim of the present study was to evaluate potential alterations in functional connectivity of the amygdala using a negative affective paradigm. Moreover, we aimed at investigating a potential association with structural connectivity (SC) properties of underlying white matter fiber tracts and with symptom severity to find out more about the clinical relevance of these potential alterations.

Based on the assumption that structural connectivity alterations may underlie functional connectivity changes, we hypothesized that during exposure to negative affective stimuli, OCD patients would show a significantly increased task dependent functional connectivity of the amygdala and that this altered functional connectivity would be related to alterations in morphological properties of underlying white matter fiber tracts (integrity, connectivity, number of tracts).

2. Methods

2.1. Participants

The study included a right-handed sample of 42 OCD patients and 37 healthy controls matched for age and gender (Table 1 in Appendix A).

Handedness was assessed using Annett's questionnaire (Annett, 1970). Exclusion criteria for both groups were a history of clinically important head injuries, seizures or neurological diseases. Healthy controls with a history of psychiatric illness were excluded.

The patients were recruited from the in-patient hospital ward specialized on OCD of the Windach Institute and Hospital of Neurobehavioural Research and Therapy, Germany. This ward has a standardized admission process where all patients receive a psychopathological screening and a disorder history assessment performed by an experienced psychiatrist. The final diagnosis is based on DSM-IV criteria. Prior to the scanning session, we additionally assessed the severity of symptoms and the characteristics of the disorder using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) and the Obsessive-Compulsive Inventory – Revised (OCI-R) (Foa et al., 2002). Patients also completed the Beck Depression Inventory (BDI) (Beck et al., 1961) which measures characteristic attitudes and symptoms of depression. All participants completed a disgust sensitivity questionnaire (Fragebogen zur Erfassung der Ekelempfindlichkeit, FEE) (Schienle et al., 2002). We also included patients with medication and comorbidities, provided that OCD was the primary diagnosis.

All participants gave written informed consent to the study protocol. The protocol is in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Technische Universität München, Medical School.

2.2. Experimental design

All participants underwent one MRI scanning session including a structural (T1), a diffusion tensor imaging (DTI) and a functional (fMRI) scan. Participants were informed about the order of the scans and instructed that in the fMRI scan they would see alternating blocks of neutral and unpleasant pictures which they had to attend to.

The negative affective blocks consisted of pictures with OCD relevant content carefully selected from the International Affective Picture System (IAPS) and the internet and included scenes or objects related to disgust or contamination. Previous work (Simon et al., 2014) has shown that the presentation of contamination related picture material is a highly effective method for evoking amygdala activation in OCD. Based on this motivation we chose picture material with a clear contamination related content.

The neutral blocks consisted of pictures from nature or landscapes which served as a baseline. Before each block the participants were instructed to watch the pictures carefully. To evaluate the compliance to the instruction, all participants were debriefed after the scanning with regard to the potential impact of these pictures (e.g. arousal, unpleasantness). The fMRI task was created using the Presentation® software (Version 16.3, http://www.neurobs.com/). The task which was modeled as a block design had the following sequence: instruction (4 s), negative affective block (4 pictures shown for 6 s each), fixation cross (4 s) followed again by instruction (4 s), neutral block (3 pictures shown for 6 s each). In total, 16 blocks of pictures (8 negative affective and 8 neutral blocks) were presented resulting in a total task duration of about 7 min.

2.3. Image acquisition

Data were collected on a Philips Ingenia 3.0 T whole body system equipped with a 12-element receive-only head matrix coil. Foam pads were used to position and immobilize the subject's head within the coil.

2.3.1. High resolution imaging

High-resolution anatomical T1-weighted scans were obtained using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following scanning parameters: repetition time (TR) = 9 ms, echo time (TE) = 4 ms, inversion time = 1000 ms, flip angle = 8°, field of view (FOV) = 240 × 240 × 170 mm, matrix size = 240 × 240, number of slices = 170, acceleration factor (SENSE) = 2 with an isotropic resolution of 1 × 1 × 1 mm^3.

2.3.2. Functional imaging

T_2^* weighted images were obtained using echo-planar imaging (EPI) with the following parameters: TR = 2.0 ms, TE = 30 ms, flip angle = 90°, FOV = 192 × 192 × 122 mm, matrix size = 64 × 64. We acquired 37 transverse slices with 3.0 mm thickness, covering the entire brain with a resolution of 3 × 3 × 3 mm. A series of 224 whole-brain volumes were recorded, with the first three images of each series being discarded.

2.3.3. Diffusion Tensor Imaging

Diffusion tensor images were acquired using an EPI sequence with the following parameters: TR = 9000 ms, TE = 57 ms, flip angle = 90°, FOV = 224 × 224 × 120 mm, in-plane resolution = 2 mm^2, slice thickness = 2 mm, number of slices = 60, matrix size = 112 × 112, SENSE = 2. Diffusion-sensitizing gradient encoding was applied in 32 directions with a diffusion-weighted factor of b = 1000 s/mm^2 and two b0 (b = 0) images. Images were acquired parallel to the anterior-posterior commissure.

2.4. Data analysis

The single analysis steps were based on each other, meaning that the functional data analysis was based on the task activation maps, and the structural data analysis was based on the results from the functional data analysis.

2.4.1. Functional data

Preprocessing and statistical analysis of the fMRI data was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) data were corrected for differences in time of acquisition by sinc interpolation, realigned to the mean image of the session and linearly and non-linearly normalized to the Montreal Neurological Institute (MNI, Montreal, Canada) reference brain (MNI 152). Data were spatially smoothed with a Gaussian kernel (8 mm, full-width at half-maximum) and high-pass filtered with a 128 s cut-off. All data were inspected for movement artifacts. Three healthy controls and one patient with movement parameters exceeding 3 mm translation on the x-, y-, or z-axis or 3° rotation were excluded, resulting in a final study sample of 79 participants. In addition, individual movement parameters entered analyses as covariates of no interest.

On the first level, brain activations were then analyzed voxel-wise to calculate statistical parametric maps of t-statistics for the negative affective compared to neutral pictures condition.

Blood oxygenation level dependent (BOLD) signal changes for the different conditions were modeled as a covariate of variable length boxcar functions and convolved with a canonical hemodynamic response function (HRF). These HRFs were then used as individual regressors within the general linear model (GLM).

To investigate taskFC of the amygdala functional imaging data were then analyzed using the generalized form of context-dependent psychophysiological interaction (gPPI) (McLaren et al., 2012) analysis implemented as gPPIv13 toolbox in SPM8.

2.4.1.1. Task dependent functional connectivity. We used the gPPI analysis to investigate potential alterations in taskFC between each of the two seed ROIs – left and right amygdala – and the rest of the brain. Amygdala seed ROIs were identified based on the peak activation from the second-level analysis (i.e., negative affective vs. neutral images, one-sample t-test with a familywise error correction (FWE) $p < 0.0001$ at a voxel level). In patients seed ROIs were left amygdala with activation maximum: x = −22, y = −4, z = −18, ROI size = 275 voxels and right amygdala with activation maximum: x = 26, y = −6, z = −16, ROI size = 146 voxels. In healthy controls seed ROIs were left amygdala with activation maximum: x = −20, y = −4, z = −22, ROI size = 110 voxels and right amygdala with activation maximum: x = 26, y = −2, z = −20, ROI size = 83 voxels. In order to get the common amygdala activation seed (i.e., those amygdala voxels which were activated in both groups) we overlapped the amygdala clusters from both groups using the SPM toolbox MarsBaR 0.21 (Brett et al., 2002) and used the intersection (left amygdala: x = −23.1, y = −5.2, z = −18.8, ROI size = 102 voxels; right amygdala: x = 24.3, y = −3.6, z = −18.4, ROI size = 67 voxels) as seed ROIs for both patients and controls for further gPPI analyses (see Fig. 1, left section in Appendix A).

Next, we extracted the individual time series from the common amygdala ROI clusters (left and right) for each participant. These time series constituted the physiological component of the gPPI, which is based on bilinear interaction terms. The contrast between the two conditions of the fMRI-task "negative affective vs. neutral pictures" constituted the psychological component. The interaction between the two previously defined components was used as a gPPI regressor in the analysis. Thus, a significant activation of a certain area reflects increased taskFC with the seed ROI (i.e., left/right amygdala) during "negative affective vs. neutral pictures".

To illustrate the regions functionally connected with the amygdala ROIs in each group we computed a one-sample t-test. To compare connectivity between the groups we used a two-sample t-test with a false discovery rate correction (FDR) $p < 0.05$ at a voxel level. The expected number of voxels per cluster was used as an extent threshold.

2.4.2. Structural data

Diffusion tensor imaging (DTI) data analysis was performed using FSL (FMRIB Software Library, FMRIB, Oxford, UK) software package, more specifically the FMRIB's Diffusion Toolbox – FDT v2.0 toolbox from FSL (Behrens et al., 2007). First, data were corrected for the effects of head movement and eddy currents. After creating a brain mask the diffusion tensor model fit was performed to create individual fractional anisotropy (FA) and mean diffusivity (MD). We used FA and MD maps in the further analysis of probabilistic fiber tracking (probFT). DTI data were further analyzed using probFT, a method which allows to delineate white matter fiber tracts (WM tracts) in the brain between predefined ROIs, while counting in the expected uncertainty into the tracking algorithm, and to produce a connectivity distribution value for each voxel (Behrens et al., 2007).

2.4.2.1. Structural connectivity. After identifying the regions showing an altered taskFC with the amygdala in OCD we then proceeded with exploring potential alterations in SC between those regions showing an altered FC in patients. To this aim we performed a probFT analysis. This analysis requires a seed region, i.e., the left amygdala, which showed a significantly altered taskFC with a left parieto-occipital region in OCD (see results section). This latter region constituted the target ROI (i.e., largest cluster in the left hemisphere, see results section) for the probFT analysis. Moreover, for the probFT analysis prior knowledge about WM tract anatomy should be taken into account. According to Catani and de Schotten (2012) a potential WM tract connecting the amygdala with these occipital regions could be the inferior longitudinal fasciculus (ILF). As there were no significant group differences in taskFC for the right amygdala (see results section), SC analyses were restricted to the left amygdala.

We analyzed two characteristics for SC, the number of WM tracts connecting the amygdala ROI with the target region, and the average

connectivity distribution values of the WM tracts connecting the seed and the target region.

Next, we ran the preparatory steps for probFT using the FDT integrated function of Bayesian estimation of diffusion parameters obtained using sampling techniques (bedpostX). This step estimates the individual diffusion parameters at each voxel and automatically takes into account the number of crossing fibers per voxel. We used the default parameters implemented in FDT: 2 fibers per voxel, weight 1, burning period 1000. Subsequently, we used the previously computed diffusion parameters to run the tractography analysis using the FDT integrated function probtrackx2. As a seed mask we applied the amygdala ROI from the previous gPPI analysis and as a target region the parieto-occipital cluster, using the option "waypointmask" implemented in probtrackx2. Both masks were previously converted to the individual diffusion space. This analysis step generates connectivity distributions from the specified seed voxels.

For the tracking algorithm we used the default parameters: 5000 samples per voxel, path length of 2000 × 0.5 mm steps, curvature threshold of 80° and loop checking criteria enabled.

The result is a single image per participant (fdt_paths) visualizing the WM tracts connecting seed and target region, where each voxel value represents the connectivity distribution value between that voxel and the seed voxel (i.e., from the amygdala seed region). Another individual output is the total number of generated WM tracts (waytotal) between the amygdala and the target region. To extract the average SC distribution value, i.e., the connectivity distribution values of the obtained WM tracts, we normalized the output image from the probFT step, by dividing the individual WM tracts image by the individual number of generated WM tracts (Arnold et al., 2012; Zhang et al., 2010). The normalization is necessary because of the high intersubject variability in terms of individual number of generated WM tracts, which was also due to the fact that probFT analysis is usually processed in the individual diffusion space of each participant.

2.4.2.2. Structural integrity. In order to additionally assess the structural integrity of the WM tracts connecting the seed region (i.e., left amygdala) with the target region (i.e., parieto-occipital cluster) we extracted FA and MD of these fiber tracts for both patients and controls. To this end, we multiplied the binarized individual WM tract images from the probFT analysis with the individual FA and MD images from the DTI data analysis. From the WM tracts of the resulting image we extracted the individual average FA and MD.

2.4.3. Statistical analysis

Statistical analyses were conducted using SPSS Inc. (2002) (SPSS 11.5.1., Chicago) and MATLAB and the Statistics Toolbox (Release 2013a, The MathWorks, Inc., Natick, Massachusetts, United States).

To explore potential group differences in SC (i.e., number of WM tracts, average connectivity distribution values of WM tracts) and integrity (i.e., FA and MD) two-sided Bonferroni corrected parametric tests were used.

Pearson's correlation analyses were conducted to investigate potential associations between taskFC (i.e., betas of gPPI connectivity map results) and SC measures as well as between taskFC and structural integrity measures in each group. Finally, all functional and structural measures were correlated with symptom severity (i.e., Y-BOCS total scores).

A two-sided parametric test was performed to analyze the difference in disgust sensitivity score between the groups. To investigate whether disgust sensitivity was associated with the taskFC we performed a Pearson correlation.

To control for the possible effect of comorbidity on the present results we also investigated a potential correlation between the above mentioned functional and structural connectivity measures and the depression score (BDI total score).

To explore if medication affected taskFC or SC differences between patients and controls, we furthermore performed an ANCOVA with taskFC or SC parameters as dependent variables, medication status as independent variable, and age and gender as covariates.

3. Results

3.1. Task dependent activation

OCD patients showed an increased activation during the task mainly in middle occipital gyrus, amygdala, precentral and inferior frontal regions. The control group showed a significantly increased activation during the task in similar brain areas, i.e., mainly in inferior occipital, inferior frontal and amygdala (for more details see Tables 4, 5 and Fig. 2 in Supplement). No significant group difference in activation during the task could be found.

3.2. Task dependent functional connectivity

OCD patients had a significantly increased taskFC of the left amygdala to a network comprising bilateral occipital, parietal and temporal areas (Table 2, Fig. 1, middle section in Appendix A), as well as a significantly increased taskFC of the right amygdala and a network comprising mainly occipital areas (Table 2, Fig. 1, middle section in Appendix A). No significant amygdala taskFC could be found in the control group.

The between group gPPI analysis yielded a significantly increased taskFC in OCD patients between the left amygdala and mostly left-lateralized occipital, parietal, temporal and frontal areas, as well as right parietal, occipital, thalamus areas and bilateral cerebellar areas (Table 3, Fig. 1, middle section in Appendix A). The right amygdala showed no significant differences in taskFC between the groups.

3.3. Structural connectivity

There was no significant group difference in number of WM tracts (mean patients: 2386.64, SD = 4810.43, mean controls: 4249.08, SD = 9360.36, $t = 1.13$, $p = 0.26$) connecting the left amygdala with the left parieto-occipital cluster. There was also no significant group difference in connectivity distribution values of the WM tracts (mean patients: 0.02, SD = 0.02, mean controls: 0.03, SD = 0.04, $t = -1.41$, $p = 0.16$).

3.4. Structural integrity

There were no significant between group differences in FA or MD (FA patients: 0.3418, SD = 0.0235, FA controls: 0.3427, SD = 0.0241, $t = 0.15$, $p = 0.88$; MD patients: $9.0260 * 10^{-4}$, SD = $4.4107 * 10^{-5}$, MD controls: $9.0208 * 10^{-4}$, SD = $4.2405 * 10^{-5}$, $t = -0.05$, $p = 0.96$).

3.5. Associations of brain function, structure and symptom severity

3.5.1. Functional and structural connectivity

In OCD patients, a significant positive correlation between taskFC and connectivity distribution values of the WM tracts was found ($r = 0.32$, $p = 0.04$). No significant association between taskFC and SC could be found in controls. There was no significant association between taskFC and the number of white matter fiber tracts in none of the groups.

3.5.2. Functional connectivity and structural integrity

There was no significant correlation between taskFC and structural integrity measures neither in patients nor in controls (patients: gPPI betas and FA $r = 0.15$, $p = 0.35$, gPPI betas and MD $r = -0.23$, $p = 0.15$; controls: gPPI betas and FA $r = -0.24$, $p = 0.15$, gPPI betas and MD $r = 0.09$, $p = 0.60$).

3.5.3. Connectivity and symptoms

There was a significant negative association between symptom severity (Y-BOCS total) and structural integrity (FA) in OCD patients ($r = -0.33$, $p = 0.04$). There was no significant association between the symptom severity score (Y-BOCS total) and taskFC or SC, the same applied to the correlation between depression score (BDI total) and taskFC or SC in OCD patients.

3.6. Effect of medication

We found that medication status of the patients affected the taskFC group difference ($F = 14.07$, $p < 0.01$), i.e., medicated patients showed a significantly higher taskFC in the parieto-occipital cluster than controls (post hoc t-test: medicated patients ($N = 27$): mean = 0.38, SD = 0.35, controls ($N = 37$): mean = −0.08, SD = 0.37, $t = 4.95$, $p < 0.01$), as well as compared to unmedicated patients (unmedicated patients ($N = 15$): mean = 0.11, SD = 0.18, $t = -2.75$, $p = 0.01$).

3.7. Disgust sensitivity

Patients had a significantly increased disgust sensitivity score compared to controls (patients ($N = 42$): mean = 2.43, SD = 0.55, controls ($N = 37$): mean = 2.01, SD = 0.61, $t = 3.22$, $p = 0.002$). No association between disgust sensitivity and taskFC could be found in OCD patients.

4. Discussion

The aim of the present study was to investigate if amygdala shows taskFC disturbances in patients with OCD during attendance to negative affective stimuli and to evaluate if these functional disturbances are linked to alterations in structural properties (connectivity and integrity) of underlying WM tracts. As a main finding, our study demonstrated that OCD patients showed a significantly increased left-lateralized taskFC from the left amygdala to the parieto-occipital cortex and that this increased functional connectivity was positively associated with the structural connectivity (SC distribution values) of the underlying WM tracts. In addition, the structural integrity of these WM tracts was negatively correlated with symptom severity (i.e., an increase in symptom severity was associated with a decrease in structural integrity of WM tracts FA).

4.1. Task dependent functional connectivity

More specifically, the significantly increased left amygdala taskFC to the parieto-occipital cortex during exposure to negative affective stimuli suggests a stronger interplay in patients between a core limbic area (i.e., the amygdala), which is predominantly responsible for emotional processing, and a network known to be responsible mainly for attention and visual processing (Goncalves et al., 2010).

Previous studies in healthy subjects showed that the presentation of emotional content goes along not only with increased activation in "classical" emotion related regions such as the amygdala and inferior-temporal areas but also with an increased activation in extra-striate and ventral stream visual areas (Wendt et al., 2011). Our study results reveal that in OCD the functional coupling between these regions seems to be altered when attending to stimuli with a negative valence. As OCD patients reported also a significantly increased disgust sensitivity a more sensible and affective perception of these mainly contamination related stimuli may be one mechanism underlying this increased functional coupling between emotional and visual processing areas. Thus, we speculate that in OCD both the affective perception as well as the visual processing of these specific stimuli might be altered.

Furthermore, regarding the psychopathological importance of these areas found to be hyperconnected in OCD, a review by Menzies et al. (2008) pointed out the need to consider the relevance of these posterior brain regions in the pathogenesis of the disorder. Study results of Olatunji et al. (2013) support this. by showing that visual areas might play a central role in the mechanisms of emotional processing, especially during symptom provocation, in OCD.

The finding that patients showed a rather normal neural activation similar to healthy subjects during task along with an altered functional coupling could indicate that although the processing of anxiety partly taking place in the amygdala might not be disturbed, the "communication" with visual areas might be more intense in patients, possibly going along with higher stimulus attendance and a more intensive sensation of negative stimulus valence.

Accordingly, previous studies likewise showed alterations in visual attention in OCD, such as problems with disengaging attention from salient stimuli (Cisler and Olatunji, 2010) or processing abnormalities when OCD-relevant material had to be visualized (Moritz et al., 2009). Overall, these findings together with our results speak in favor of the idea that OCD patients may have a certain attentional bias, more specifically in the processing and attribution of emotional valence, towards disorder relevant stimuli.

Moreover, present findings of a subcortical-cortical hyperconnectivity confirm results of a review by Diniz et al. (2012) who concluded that besides neural disruptions comparable to those in other anxiety disorders, OCD patients seem to be affected by additional alterations within the amygdalo-cortical circuitry, which plays a major role in processes of fear conditioning and extinction. Our results complement this by showing that dysfunctions within these networks are visible already during the perception and processing of negative, fear-provoking stimuli. Future studies should investigate this aspect in more detail.

Regarding the role of the amygdala it has been shown that the amygdala is more strongly involved in the processing of immediate fear while other areas such as the insula are more relevant for the processing of potential threats (Fiddick, 2011). Considering that exactly these anxiety-associated regions showed altered functional connectivity while patients were perceiving pictures with negative affective content emphasizes the necessity to more strongly focus on exploring neural activity in OCD during exposition to feared objects or situations.

Several attempts have been made to identify symptom specific neural patterns in OCD (Mataix-Cols and van den Heuvel, 2006; Mataix-Cols et al., 2004; van den Heuvel et al., 2009). It is therefore a valid question if the present results represent a general or symptom specific pattern of OCD psychopathology.

Interestingly, a recent study by Simon et al. (2014) showed that amygdala hyperactivation during symptom provocation was present across different OCD symptom dimensions and suggested that it might constitute a common correlate which links OCD to other anxiety disorders. Our findings complement and support this assumption by giving insights into the functional coupling of this same region and by showing that, although a multi-symptomatic group was exposed to negative affective (mainly contamination related) stimuli, alterations in amygdala function were still present. Thus, present findings indicate that limbic areas might be involved in a more general rather than a symptom specific neural mechanism of the disorder.

4.2. Left lateralized connectivity

It is noteworthy that only left amygdala showed a between group taskFC connectivity difference. This finding is in accordance with other studies reporting an asymmetry in OCD patients, both structurally (Cannistraro et al., 2007) as well as functionally (Simon et al., 2014). Interestingly, this lateralization was also often reported in animal models of OCD (Ahmari et al., 2013) or in transcranial magnetic stimulation (TMS) studies with treatment resistant OCD patients (Mondino et al., 2015), where a left-lateralized stimulation seemed to be more effective than stimulation of the right side.

According to Phelps et al. (2001) there is a left-hemispheric amygdala engagement when the emotional property of a stimulus is cognitively learned, while there tends to be right-sided amygdala response when

the emotional property of the stimulus is obvious and visual (e.g., in the case of generally aversive, threatening stimuli). Moreover, the authors speculate that the difference in laterality of amygdala activation may be dependent on the modality in which the stimulus is represented (visual, verbal, obvious etc.) and its elaboration and interpretation by the subject. In our study, all subjects received the same negative affective visual stimuli with a mostly contamination related content, but with no direct threat component, with the instruction to carefully attend to these stimuli. As a consequence, an increased coupling between left amygdala and visual areas could be observed. Moreover, the OCD symptomatic model shows that OCD symptoms are mostly based on learned negative attribution to specific stimuli, which evoke anxiety and then lead to obsessions and repetitive behaviors (compulsions) to reduce anxiety.

Against this background and in light of Phelps et al. (2001) conclusions there is reason to speculate that this increased left amygdala connectivity in OCD might reflect the fact that patients generally attribute higher emotional valence to these stimuli than controls. In other terms, stimuli might be emotionally overvalued and interpreted in relation to personal obsessions or compulsions.

4.3. Structural connectivity

Interestingly, despite the significantly increased taskFC in patients compared to controls the structural connectivity and integrity measures per se did not show any significant difference between the groups.

In contrast to this finding, previous OCD studies do report structural alterations in main WM tracts (Koch et al., 2014). One potential reason for this inconsistency is that – instead of investigating whole brain SC – we restricted our analysis to a specific WM tract of the functionally coupled areas, following a results driven approach. The WM tracts we found in the present study represent most probably major parts of the inferior longitudinal fasciculus (ILF) (Catani and de Schotten, 2012). Alterations in these specific fiber bundles have been reported in adolescent OCD patients (Jayarajan et al., 2012; Zarei et al., 2011) as well as in OCD adults (Garibotto et al., 2010). Although results regarding the direction of disruption (increased vs. decreased) or characteristics of the WM tracts (FA, axial, radial diffusivity or directionality of tracts) were heterogeneous, they overall point to the potential relevance of the ILF for the disorder. A review of Piras et al. (2013) showed that alterations in intra-hemispheric bundles linked to posterior parietal and occipital association cortices are also consistently reported in the OCD literature. Our findings support these results.

4.4. Association between function, structure and symptoms

According to Jones et al. (2013) the measures obtained from tractography, indicating connectivity distribution or connectivity extent, can be considered as good estimates for the variations in the anatomical connections and as a good direct estimate of connection strength at the macroscopic level of an anatomical structure. Our study results revealed that exactly this structural connectivity characteristic of the WM tracts, i.e., strength or extent of WM tracts, was associated with an increase in functional connectivity of the connected areas only in the OCD group.

This finding suggests that an increased extent of WM tracts may constitute the basis of an increased functional connectivity in patients. Thus, stronger structural connectivity (in terms of higher connectivity distribution values of the ILF) might reflect an increased efficiency in transmitting information which, in turn, is reflected by a stronger functional connectivity between the respective regions connected by the ILF (i.e., amygdala and parieto-occipital areas) in patients. Although it is a matter of debate which neurophysiological characteristics (e.g., varying degree of myelination, axonal branching, fiber complexity, diameter) are mainly mirrored by connectivity distribution, microstructural characteristics have been shown to change with experience (Zatorre et al., 2012). Myelinogenesis, caused by neural activity in fiber tracts during intensive processing or training, is one possible mechanism underlying increased structural connectivity. Mice studies have demonstrated that increasing neuronal electrical activity by the use of specific neurotoxins known to increase the firing of neurons caused increased myelination (Demerens et al., 1996). Transferred to the present findings, it can be speculated that the more intensive visual perception, as discussed above, may be the mechanism underlying increased structural and functional connectivity in patients in respective regions and their connecting white matter fiber tracts.

Finally, our results reveal that a specific characteristic of this group, i.e. symptom severity, goes along with a decrease in WM tract integrity (FA), which is considered a stable indicator of altered myelination.

Although present correlation results need to be interpreted with caution as they were not corrected for multiple comparisons, they still give reason to assume that the functional connectivity disruptions may underlie alterations in structural connectivity, indicating that structural disruptions may be the basis of broader network functional disruptions. The negative association of structural integrity and symptom severity underlines the psychopathological relevance of these structural changes for the disorder and confirms previous studies which also showed that structural impairments can go along with symptom severity increase despite the directionality of this association being inconsistent.

Moreover, one should keep in mind that our analysis was restricted to specific regions and that further research on this association is needed to find out whether the association of functional and structural characteristics is detectable in other OCD relevant networks also.

There are several limitations that need to be taken into account when interpreting the present findings. First, we used only the OCI-R to assess the symptom spectrum of each participant which has the disadvantage that patients can score high on several subscales. Hence, using the Y-BOCS dimensional symptom checklist would have been more appropriate in order to identify the most prevalent symptom dimensions in this patient sample. As another limitation it should be noted that no quantitative data on the level of arousal and unpleasantness experienced during observation of the negative pictures are available as debriefing was done only in the form of an unstructured interview after the scanning. Future similar tasks should assess the level of experienced arousal and unpleasantness as an additional parameter to support and facilitate interpretation of observed neural activity.

Finally, although our sample had the primary diagnosis OCD, it should not go unmentioned that patients were not comorbidity- and medication-free, which may have influenced our results to some extent. As our results showed, medicated patients had higher taskFC values than unmedicated patients and controls. Hence, we cannot exclude the fact that our increased taskFC results could have been influenced by medication to some extent. Further studies with an age and gender matched sample of medicated and unmedicated or medication naive patients are needed to clarify this effect.

5. Conclusion

To the best of our knowledge, this is the first study to explore the relationship between amygdala task dependent functional and structural connectivity in OCD. The main contribution of our study is the comprehensive assessment of functional and structural connectivity of the amygdala, a region previously discussed as OCD relevant, and the direct association between these measures. Our study demonstrated that besides the well-known CSTC circuit, limbic brain regions, responsible for emotional processing, and their parieto-occipital connections, need to be taken into account to increase our understanding of the neuronal mechanisms underlying the OCD psychopathology.

Conflict of interest

We declare that we have no conflict of interest to report.

Acknowledgements

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Appendix A

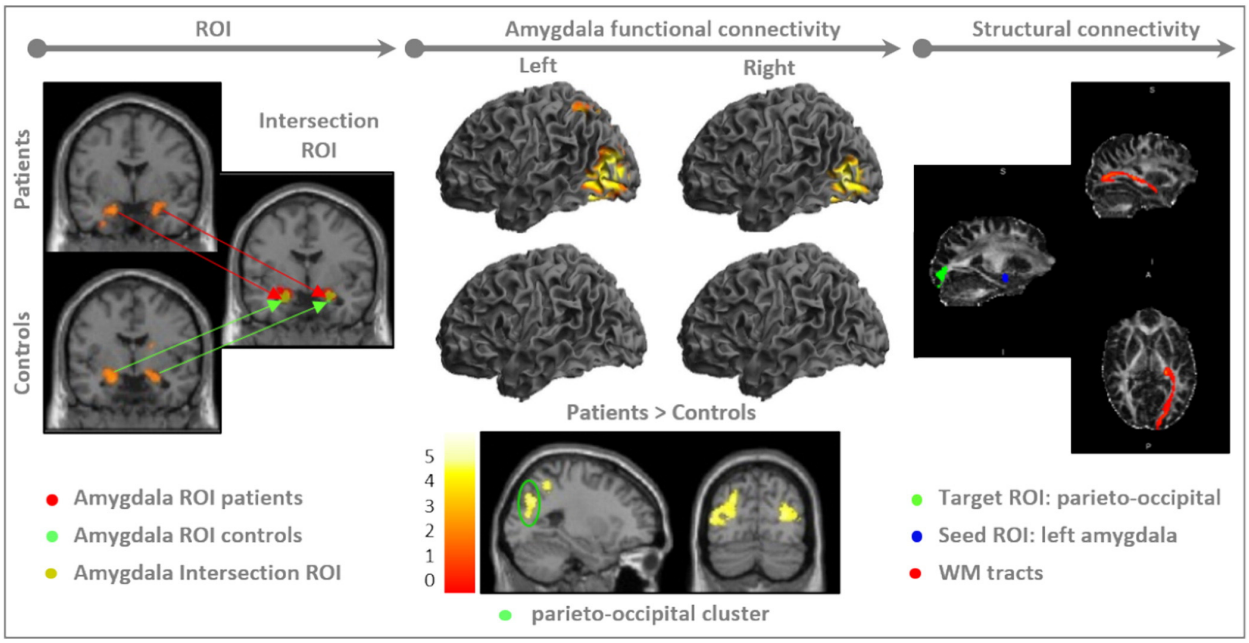

Fig. 1. Left section: Construction of ROI. (left images) Amygdala activation cluster resulting from one-sample t-tests ($p < 0.05$, FWE corrected at voxel level) for the contrast "negative affective vs. neutral pictures" in OCD patients (top) and in controls (bottom). (right image) Amygdala seed ROI for the connectivity analyses (i.e., intersection of group specific activation clusters).Middle section: Functional connectivity analysis results. Brain regions showing increased taskFC (negative affective vs. neutral pictures) with the amygdala separately in both groups (first two rows) and in group contrast last row: (top row) brain regions (bilateral occipital, parietal areas) showing an increased taskFC with the left and right amygdala in the patient group. (middle row) no significant increase in taskFC of left amygdala in the control group (right). (bottom row) brain regions showing an increased taskFC with the left amygdala in OCD patients compared to controls. Color bar represents t-values ($p < 0.05$, FDR corrected at voxel level). Marked in green is the target cluster for the probabilistic fiber tracking. Shown is the left side (slice: $x = -26$). No differences in taskFC of the right amygdala between the groups.Right section: Results from the probabilistic fiber tracking analysis. (left image) intersection ROIs used for the analysis (i.e., probFT analysis) for both groups (seed ROI marked in blue, target ROI marked in green). (right image) output images from the probFT in individual space. Shown are the WM tracts connecting the seed ROI amygdala (marked in blue) with the target ROI (marked in green) in sagittal and axial orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic and clinical data of participants.

	OCD (N = 42)	Controls (N = 37)	Group difference
Characteristic	Mean (SD)	Mean (SD)	p-value
Sex, male:female	15:27	15:22	n.s. ($p = 0.48$)
Age, Years	32.50 (9.95)	30.99 (7.56)	n.s. ($p = 0.45$)
Medication, yes/no	27/15		NA
Medication type	17 SSRI 3 SNRI 4 TrA 1 Benzo 2 no info		
Patients with more than one drug:	3 Antipsy 1 NDRI		
Comorbidities Present/not present	24/18		NA
Comorbidity type	14 depression 3 anxiety disorders 5 depression & anxiety disorder 1 personality disorder 1 impulse control disorder-not otherwise specified		

Table 1 (*continued*)

	OCD (N = 42)	Controls (N = 37)	Group difference
Years since onset	16.23 (10.64)		NA
YBOCS total	20.71 (5.58)		NA
	10.90 (3.24)		
	9.76 (3.77)		
– obsessions			
– compulsions			
OCI-R total	24.07 (10.09)		NA
	2.48 (2.90)		
	5.52 (3.51)		
– Hoarding	3.33 (3.75)		
– Checking	2.17 (4.19)		
– Ordering	4.31 (3.65)		
– Neutralizing	6.62 (3.26)		
– Washing			
– Obsessing			
BDI	17.60 (11.53)		
FEE	2.43 (0.55)	2.01 (0.61)	s. (p = 0.002)

*Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
*OCI-R = Obsessive-Compulsive Inventory – Revised;
*BDI = Beck Depression Inventory.
*FEE = disgust sensitivity questionnaire.
*n.s. = not significant.
*NA = not applicable.
*M (SD) = mean (standard deviation).
*SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TrA = tricyclic antidepressant; Benzo = benzodiazepine; Antipsy = Antipsychotic; NDRI = Norepinephrine-dopamine reuptake inhibitor.

Table 2
MNI coordinates of activation maxima for taskFC (negative affective vs. neutral pictures) in patients with the left amygdala as seed region and the right amygdala as seed region (one sample t-test at p < 0.05, FDR corrected at voxel level). The expected voxels per cluster (k = 12 for left, k = 16 for right) were than taken as a spatial extent threshold.

Brain regions	side	k	p FDR	T	x, y, z
Left amygdala connectivity					
Fusiform gyrus, middle temporal gyrus, middle occipital gyrus, precuneus, cuneus	L	3694	0.001	6.68	−38 −60 18
Middle occipital gyrus, fusiform gyrus, cuneus, precuneus	R	3502	0.001	6.44	40 −80 14
Superior parietal lobule, precuneus	L	415	0.001	4.87	−30 −56 54
Parahippocampal gyrus	L	38	0.004	4.11	−16 −4 −14
Inferior parietal gyrus	L	61	0.008	3.78	−38 −36 40
Right amygdala connectivity					
Temporal lobe, fusiform gyrus, inferior temporal gyrus, lingual gyrus	L	1779	0.005	5.96	−40 −56 −18
Occipital lobe, inferior occipital gyrus, fusiform gyrus, inferior occipital gyrus, middle occipital gyrus	R	1037	0.005	5.61	40 −62 −12

*L/R = left/right side; k = number of voxels in cluster; p = FDR correction at voxel level; T = t value; x, y, z = MNI coordinates in mm.

Table 3
MNI coordinates of activation maxima for increased taskFC (negative affective vs. neutral pictures) in patients compared to controls with the left amygdala as seed region (two sample t-test at p < 0.05, FDR correction at voxel level). Expected voxels per cluster (k = 12) were than taken as a spatial extent threshold.

Brain regions	Side	k	p FDR	T	x, y, z
Inferior parietal lobule, superior parietal lobule, precuneus	L	303	0.026	5.07	−36 −50 56
Middle occipital gyrus, middle temporal gyrus	R	623	0.026	4.79	34 −78 16
Posterior lobe, Cerebellum	R	92	0.026	4.48	16 −76 44
Middle occipital gyrus, superior parietal lobule, precuneus	L	554	0.026	4.44	−46 −76 14
Occipital lobe, fusiform gyrus	L	127	0.026	4.40	−34 −58 12
Anterior lobe, Cerebellum	R	42	0.027	4.18	24 −54 28
Parietal lobe, Inferior parietal lobule	L	128	0.027	4.02	−38 −36 36
Anterior lobe, Cerebellum	L	32	0.028	3.97	−18 −52 26
Posterior lobe, Cerebellum	L	22	0.029	3.93	−14 −62 38
Temporal lobe, superior temporal gyrus	L	14	0.030	3.88	−36 12 30
Frontal lobe, middle frontal gyrus	L	34	0.030	3.87	−30 −2 42
Parietal lobe, Superior parietal lobule	R	110	0.031	3.83	28 −70 48
Parietal lobe, inferior parietal lobule	L	36	0.031	3.81	−58 −18 28
Sub lobar, thalamus	R	14	0.035	3.68	2 -14 12

*L/R = left/right side; k = number of voxels in the cluster; p = FDR correction at voxel level; T = t value; x, y, z = MNI coordinates in mm; bold = target parieto-occipital cluster used for further analysis.

Appendix B. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.12.007.

References

Admon, R., Bleich-Cohen, M., Weizmant, R., Poyurovsky, M., Faragian, S., Hendler, T., 2012. Functional and structural neural indices of risk aversion in obsessive-compulsive disorder (OCD). Psychiatry Res. 203, 207–213.

Ahmari, S.E., Spellman, T., Douglass, N.L., Kheirbek, M.A., Simpson, H.B., Deisseroth, K., Gordon, J.A., Hen, R., 2013. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 340, 1234–1239.

Annett, M., 1970. A classification of hand preference by association analysis. Br. J. Psychol. 61, 303–321.

Anticevic, A., Hu, S., Zhang, S., Savic, A., Billingslea, E., Wasylink, S., Repovs, G., Cole, M.W., Bednarski, S., Krystal, J.H., Bloch, M.H., Li, C.S., Pittenger, C., 2014. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. Biol. Psychiatry 75, 595–605.

Arnold, J.F., Zwiers, M.P., Fitzgerald, D.A., van Eijndhoven, P., Becker, E.S., Rinck, M., Fernandez, G., Speckens, A.E., Tendolkar, I., 2012. Fronto-limbic microstructure and structural connectivity in remission from major depression. Psychiatry Res. 204, 40–48.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Behrens, T.E., Berg, H.J., Jbabdi, S., Rushworth, M.F., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? NeuroImage 34, 144–155.

Beucke, J.C., Kaufmann, C., Linnman, C., Gruetzmann, R., Endrass, T., Deckersbach, T., Dougherty, D.D., Kathmann, N., 2012. Altered cingulostriatal coupling in obsessive-compulsive disorder. Brain Connect 2, 191–202.

Beucke, J.C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., Kaufmann, C., Kathmann, N., 2013. Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 70, 619–629.

Breiter, H.C., Rauch, S.L., Kwong, K.K., Baker, J.R., Weisskoff, R.M., Kennedy, D.N., Kendrick, A.D., Davis, T.L., Jiang, A., Cohen, M.S., Stern, C.E., Belliveau, J.W., Baer, L., O'Sullivan, R.L., Savage, C.R., Jenike, M.A., Rosen, B.R., 1996. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch. Gen. Psychiatry 53, 595–606.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using an SPM toolbox [abstract]. Presented at the 8th International Conference on Functional Mapping of the Human Brain. Vol 16. Available on CD-ROM in NeuroImage (No. 2., abstract 497, Sendai, Japan).

Cannistraro, P.A., Makris, N., Howard, J.D., Wedig, M.M., Hodge, S.M., Wilhelm, S., Kennedy, D.N., Rauch, S.L., 2007. A diffusion tensor imaging study of white matter in obsessive-compulsive disorder. Depress Anxiety 24, 440–446.

Catani, M., de Schotten, M.T., 2012. Atlas of Human Brain Connections. Oxford University Press, New York.

Cisler, J.M., Olatunji, B.O., 2010. Components of attentional biases in contamination fear: evidence for difficulty in disengagement. Behav. Res. Ther. 48, 74–78.

de Vries, F.E., de Wit, S.J., Cath, D.C., van der Werf, Y.D., van der Borden, V., van Rossum, T.B., van Balkom, A.J., van der Wee, N.J., Veltman, D.J., van den Heuvel, O.A., 2014. Compensatory frontoparietal activity during working memory: an endophenotype of obsessive-compulsive disorder. Biol. Psychiatry 76, 878–887.

Demerens, C., Stankoff, B., Logak, M., Anglade, P., Allinquant, B., Couraud, F., Zalc, B., Lubetzki, C., 1996. Induction of myelination in the central nervous system by electrical activity. Proc. Natl. Acad. Sci. U. S. A. 93, 9887–9892.

Diniz, J.B., Miguel, E.C., de Oliveira, A.R., Reimer, A.E., Brandao, M.L., de Mathis, M.A., Batistuzzo, M.C., Costa, D.L., Hoexter, M.Q., 2012. Outlining new frontiers for the comprehension of obsessive-compulsive disorder: a review of its relationship with fear and anxiety. Rev. Bras. Psiquiatr. 34 (Suppl. 1), S81–S91.

Fiddick, L., 2011. There is more than the amygdala: potential threat assessment in the cingulate cortex. Neurosci. Biobehav. Rev. 35, 1007–1018.

Foa, E.B., Huppert, J.D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., Salkovskis, P.M., 2002. The obsessive-compulsive inventory: development and validation of a short version. Psychol. Assess. 14, 485–496.

Garibotto, V., Scifo, P., Gorini, A., Alonso, C.R., Brambati, S., Bellodi, L., Perani, D., 2010. Disorganization of anatomical connectivity in obsessive compulsive disorder: a multi-parameter diffusion tensor imaging study in a subpopulation of patients. Neurobiol. Dis. 37, 468–476.

Goncalves, O.F., Marques, T.R., Lori, N.F., Sampaio, A., Branco, M.C., 2010. Obsessive-compulsive disorder as a visual processing impairment. Med. Hypotheses 74, 107–109.

Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006–1011.

Gottlich, M., Kramer, U.M., Kordon, A., Hohagen, F., Zurowski, B., 2014. Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. Hum. Brain Mapp. 35, 5617–5632.

Gottlich, M., Kramer, U.M., Kordon, A., Hohagen, F., Zurowski, B., 2015. Resting-state connectivity of the amygdala predicts response to cognitive behavioral therapy in obsessive compulsive disorder. Biol. Psychol. 111, 100–109.

Harrison, B.J., Soriano-Mas, C., Pujol, J., Ortiz, H., Lopez-Sola, M., Hernandez-Ribas, R., Deus, J., Alonso, P., Yucel, M., Pantelis, C., Menchon, J.M., Cardoner, N., 2009. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch. Gen. Psychiatry 66, 1189–1200.

Jayarajan, R.N., Venkatasubramanian, G., Viswanath, B., Janardhan Reddy, Y.C., Srinath, S., Vasudev, M.K., Chandrashekar, C.R., 2012. White matter abnormalities in children and adolescents with obsessive-compulsive disorder: a diffusion tensor imaging study. Depress Anxiety 29, 780–788.

Jhung, K., Ku, J., Kim, S.J., Lee, H., Kim, K.R., An, S.K., Kim, S.I., Yoon, K.J., Lee, E., 2014. Distinct functional connectivity of limbic network in the washing type obsessive-compulsive disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 53, 149–155.

Jones, D.K., Knosche, T.R., Turner, R., 2013. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. NeuroImage 73, 239–254.

Jung, W.H., Kang, D.H., Kim, E., Shin, K.S., Jang, J.H., Kwon, J.S., 2013. Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing and resting-state. Neurol. Clin. 3, 27–38.

Koch, K., Reess, T.J., Rus, O.G., Zimmer, C., Zaudig, M., 2014. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): a review. J. Psychiatr. Res. 54, 26–35.

Lawrence, A.D., Sahakian, B.J., Robbins, T.W., 1998. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends Cogn. Sci. 2, 379–388.

Mataix-Cols, D., van den Heuvel, O.A., 2006. Common and distinct neural correlates of obsessive-compulsive and related disorders. Psychiatr Clin North Am 29, 391–410 (viii).

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L., 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch. Gen. Psychiatry 61, 564–576.

McLaren, D.G., Ries, M.L., Xu, G., Johnson, S.C., 2012. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. NeuroImage 61, 1277–1286.

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., Bullmore, E.T., 2008. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci. Biobehav. Rev. 32, 525–549.

Milad, M.R., Rauch, S.L., 2012. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn. Sci. 16, 43–51.

Mondino, M., Haesebaert, F., Poulet, E., Saoud, M., Brunelin, J., 2015. Efficacy of cathodal transcranial direct current stimulation over the left orbitofrontal cortex in a patient with treatment-resistant obsessive-compulsive disorder. J ECT 31 (4):271–272. http://dx.doi.org/10.1097/YCT.0000000000000218.

Moritz, S., Von Muhlenen, A., Randjbar, S., Fricke, S., Jelinek, L., 2009. Evidence for an attentional bias for washing- and checking-relevant stimuli in obsessive-compulsive disorder. J. Int. Neuropsychol. Soc. 15, 365–371.

Olatunji, B.O., Ferreira-Garcia, R., Caseras, X., Fullana, M.A., Wooderson, S., Speckens, A., Lawrence, N., Giampietro, V., Brammer, M.J., Phillips, M.L., Fontenelle, L.F., Mataix-Cols, D., 2013. Predicting response to cognitive behavioral therapy in contamination-based obsessive-compulsive disorder from functional magnetic resonance imaging. Psychol. Med. 1–13.

Olatunji, B.O., Ferreira-Garcia, R., Caseras, X., Fullana, M.A., Wooderson, S., Speckens, A., Lawrence, N., Giampietro, V., Brammer, M.J., Phillips, M.L., Fontenelle, L.F., Mataix-Cols, D., 2014. Predicting response to cognitive behavioral therapy in contamination-based obsessive-compulsive disorder from functional magnetic resonance imaging. Psychol. Med. 44, 2125–2137.

Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nat. Neurosci. 4, 437–441.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R., 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol. Psychiatry 54, 504–514.

Piras, F., Piras, F., Caltagirone, C., Spalletta, G., 2013. Brain circuitries of obsessive compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies. Neurosci. Biobehav. Rev. 37, 2856–2877.

Piras, F., Piras, F., Chiapponi, C., Girardi, P., Caltagirone, C., Spalletta, G., 2015. Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. Cortex 62, 89–108.

Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry 15, 53–63.

Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, L.R., 1998. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl 26–37.

Schienle, A., Walter, B., Stark, R., Vaitl, D., 2002. Ein Fragebogen zur Erfassung der Ekelempfindlichkeit. Z. Klin. Psychol. Psychother. 31, 110–120.

Simon, D., Adler, N., Kaufmann, C., Kathmann, N., 2014. Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction. Neurol. Clin. 4, 549–557.

Simon, D., Kaufmann, C., Musch, K., Kischkel, E., Kathmann, N., 2010. Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. Psychophysiology 47, 728–738.

van den Heuvel, O.A., Remijnse, P.L., Mataix-Cols, D., Vrenken, H., Groenewegen, H.J., Uylings, H.B., van Balkom, A.J., Veltman, D.J., 2009. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain 132, 853–868.

van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Dolan, R.J., Cath, D.C., Boellaard, R., Mesina, C.T., van Balkom, A.J., van Oppen, P., Witter, M.P., Lammertsma, A.A., van Dyck, R., 2004. Amygdala activity in obsessive-compulsive disorder with contamination fear: a study with oxygen-15 water positron emission tomography. Psychiatry Res. 132, 225–237.

Via, E., Cardoner, N., Pujol, J., Alonso, P., Lopez-Sola, M., Real, E., Contreras-Rodriguez, O., Deus, J., Segalas, C., Menchon, J.M., Soriano-Mas, C., Harrison, B.J., 2014. Amygdala activation and symptom dimensions in obsessive-compulsive disorder. Br. J. Psychiatry 204, 61–68.

Wendt, J., Weike, A.I., Lotze, M., Hamm, A.O., 2011. The functional connectivity between amygdala and extrastriate visual cortex activity during emotional picture processing depends on stimulus novelty. Biol. Psychol. 86, 203–209.
Zarei, M., Mataix-Cols, D., Heyman, I., Hough, M., Doherty, J., Burge, L., Winmill, L., Nijhawan, S., Matthews, P.M., James, A., 2011. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. Biol. Psychiatry 70, 1083–1090.
Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15, 528–536.
Zhang, D., Snyder, A.Z., Shimony, J.S., Fox, M.D., Raichle, M.E., 2010. Noninvasive functional and structural connectivity mapping of the human thalamocortical system. Cereb. Cortex 20, 1187–1194.

8. Gray Matter Alterations in OCD

The cortical mantle of OCD patients shows variations in gray matter, mirrored by regionally restricted reductions in volume and more extended surface area alterations.

This chapter presents a research article entitled "Structural alterations in patients with obsessive-compulsive disorder: A surface based analysis of cortical volume, surface area and thickness", which has been accepted for publication by The Journal of Psychiatry and Neuroscience on May 31st 2017 and was written by Oana Georgiana Rus, Tim Jonas Reeß, Gerd Wagner, Michael Zaudig, Claus Zimmer and Kathrin Koch. This study focuses on the surface anatomical profile of the cortical mantle in OCD patients by concurrently analysing several measures of grey matter, namely volume, surface area and thickness in a comparatively large sample.

Contributions:

The author of the present thesis is also the first author of this research article. O.G.R, T.J.R. and K.K. contributed substantially to conception and design, acquisition of data, analysis and interpretation of data and revised the manuscript critically. O.G.R. additionally drafted the article. G.W. contributed substantially to conception of data and revised the drafted manuscript. C.Z. contributed substantially to data acquisition. M.Z. contributed substantially to patient collection. All authors gave the final approval of the version to be published.

Research Paper

Structural alterations in patients with obsessive–compulsive disorder: a surface-based analysis of cortical volume, surface area and thickness

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Background: Mounting evidence indicates the presence of structural brain alterations in individuals with obsessive–compulsive disorder (OCD). Findings are, however, rather heterogeneous, which may be partly because of differences in methodological approaches or clinical sample characteristics. The aim of the present study was to analyze the whole brain cortical volume, surface area and thickness in a large sample of patients with OCD compared with age- and sex-matched healthy controls. **Methods:** We conducted whole brain surface-based analyses of grey matter measures using the automated FreeSurfer software in patients with OCD and matched controls. Group analyses were performed and corrected for multiple testing using Monte Carlo simulations ($p < 0.05$). Altered brain regions and their average morphological values were associated to symptom severity and type (Yale–Brown Obsessive Compulsive Scale scores). **Results:** We included 75 patients and 75 controls in our analyses. Patients with OCD showed decreases in both volume and surface area compared with healthy controls in inferior-superior parieto-occipital regions. In addition, the precuneus, posterior cingulate areas, middle frontal and orbitofrontal areas, and middle inferior temporal areas extending to the fusiform gyrus were characterized by a reduced surface area only. There were no differences in grey matter thickness between the groups. **Limitations:** The presence of comorbidities, medication usage and the multisymptomatic feature of OCD could have influenced our results to a certain degree. **Conclusion:** Our results suggest decreased grey matter volume and surface area in several key regions in patients with OCD. Parietal regions showed reductions in both volume and surface area, which underlines the potential relevance of these regions for the pathophysiology of the disorder.

Introduction

Studying the brain anatomic structure offers a promising approach to improve our understanding of neural functional alterations often encountered in individuals with psychiatric disorders. In those with obsessive–compulsive disorder (OCD), a psychiatric disorder with a 2%–3% lifetime prevalence[1] that causes strong impairment of daily life, findings up to now show disruptions on a functional and a structural neural level, mainly in a network including cortico-striato-thalamo-cortical (CSTC) areas. Overall, these findings are rather inconsistent and limited by confounding factors, such as differences in clinical characteristics of the study sample or varying methodological approaches.

Meta-analytic reviews showed that cortical areas, mainly the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and parietofrontal regions, seem to be predominantly affected by grey matter volume deficits in patients with OCD, whereas the lenticular nuclei and thalamus were found to be characterized by increases in grey matter volume.[2–4] A recent review article[5] confirmed these results and concluded that structural alterations in patients with OCD are widespread and occur most probably at a network level, with cortical tissue reductions and a tendency toward increases in grey matter volume of subcortical limbic areas. These subcortical tissue increases were also corroborated by a recent meta/mega-analysis of the ENIGMA OCD imaging consortium.[6] Additionally, this meta/mega-analysis showed that the neuroplasticity of specific areas depends on the age of the studied sample (i.e., smaller hippocampal but larger pallidum volumes were prominent in adults with OCD, whereas only larger thalamic volumes were specific for pediatric patients). Besides grey matter volume alterations in patients with OCD, significantly decreased grey matter thickness in partly overlapping areas (i.e., limbic, parietal and temporal areas) was also found in another recent mega-analysis.[7] It is

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interesting to note that these findings also partly confirmed a previous mega-analysis on volume by de Wit and colleagues,[8] which described reductions in grey but also white matter in partly overlapping (i.e., frontostriatal limbic) areas.

Regarding these structural alterations in patients with OCD, most previous studies focused either on grey matter volume or thickness using voxel-based morphometry (VBM),[9] with results being partly inconsistent in terms of the direction of alteration (increase v. decrease of cortical parameters), but also with respect to the cortical parameter itself (grey/white matter volume or thickness) or the anatomic region found to be altered.

It has been shown that, on the one hand, grey matter parameters (i.e., volume, surface area, cortical folding or thickness) are genetically and phenotypically independent from each other.[10,11] On the other hand, changes in 1 parameter can contribute to changes in the others to varying degrees, as shown by longitudinal developmental studies.[12] Therefore, focusing on only 1 grey matter parameter can obscure information about the others. Moreover, these parameters are known to differ strongly with regard to their developmental start and general course of development. Thus, cortical surface area develops as a consequence of cortical folding in prenatal brain development,[13] whereas grey matter volume is fully developed only in later stages of postnatal development.[14,15]

Hence, studying these parameters of cortical structure can give more insight into the repeatedly discussed question of whether these morphological properties are independently affected in patients with OCD and whether they might help to explain the rather inconsistent findings.

Surface-based analysis (SBA) methods allow an exact determination of all these cortical parameters. Compared with VBM, SBA has several advantages. It is not prone to smoothing across neighbouring gyri as it uses smoothing on the inflated cortical surface. Moreover, it can assess these parameters of brain morphology and their contribution independently from each other and is not so sensitive to image registration as it computes the morphometric parameters in native space.[16–18]

To the best of our knowledge, only 2 studies have used the SBA approach in OCD samples to study gyrification, volume, surface area and thickness at the same time.[19,20] Venkatasubramanian and colleagues[19] applied SBA by using the automatic FreeSurfer software and provided first evidence of altered volume, surface area and thickness in a number of different regions comprising the ACC, OFC and occipital cortex in medication-naive patients with OCD. These alterations were partly associated with clinical characteristics (i.e., symptom severity, symptom type, disorder insight). Despite using the same method in an OCD sample with similar clinical characteristics (i.e., unmedicated patients), Fan and colleauges[20] found alterations that partly diverged from the findings of Venkatasubramanian and colleagues,[19] both regarding direction and location. Thus, the results by Fan and colleagues[20] revealed a significant increase in thickness in parietal areas and gyrification increases in a network containing the insula and frontal and occipital areas in patients with OCD that were positively associated with symptom severity.

Several other OCD studies used the SBA approach. However, they analyzed only 1 measure of grey matter — thickness — with heterogeneous results.[21–25] A more recent study by Kühn and colleagues[26] explored cortical thickness using the same SBA method in a large sample of 101 patients with OCD and 95 controls and partly confirmed results of both previous studies. They reported cortical thinning in the bilateral subgenual and dorsal ACC as well as in middle frontal, inferior temporal, supramarginal and occipital areas of the left hemisphere and the right insula. They also found an increase in thickness in the left precentral gyrus.

Taken together, existing SBA and VBM studies in OCD samples are scarce and rather inconsistent, whereby the ACC appears to be most frequently reported as altered in thickness, surface and volume, and the middle frontal, insular and parieto-occipital areas are also found to be altered in patients with OCD, albeit with less consistency. Hence, previous findings need to be treated with caution and should be interpreted against the background of existing differences in sample characteristics and partly different methodological approaches.

In order to extend recent findings and to bring more light to the heterogeneous picture of the cortical grey matter alterations in patients with OCD, we performed a whole brain SBA of grey matter volume, surface area and thickness in a large and carefully selected sample of patients with OCD and matched healthy controls. Based on previous findings[19,20] we expected a significantly altered cortical morphology in these various grey matter measures in patients with OCD compared with controls. Additionally, we hypothesized that these structural alterations would be significantly associated with OCD psychopathology, which we investigated by correlating the detected structural abnormalities with clinical scores (i.e., symptom severity).

Methods

Participants

We recruited patients from the Windach Institute and Hospital of Neurobehavioural Research and Therapy (WINTR), Germany, and the University Hospital for Psychiatry and Psychotherapy, Jena, Germany. All were in-house patients in wards specialized in OCD with a standardized admission process, psychopathological screenings and assessment of disorder history performed by an experienced psychiatrist. This sample has been described in detail elsewhere.[27] The healthy controls were recruited in Jena and in Munich through local study announcements (e.g., blackboards, newspapers).

Both patients and healthy controls were screened using a standardized questionnaire, including questions on the presence of any (additional) psychiatric or neurologic illness, psychiatric or neurologic disorders in first-degree relatives, medication and MRI compatibility. Exclusion criteria for both groups were a history of clinically important head injuries,

seizures or neurologic diseases. Healthy controls with a history of psychiatric illness were excluded. Exclusion criteria for patients were schizophrenia, autism, substance and alcohol abuse/dependency, mental retardation, pregnancy and severe medical conditions.

After a complete description of the study aims, we obtained written informed consent from all participants. The study protocol was in compliance with the Declaration of Helsinki and approved by the ethics committees of the Klinikum rechts der Isar and the University of Jena. Prior to the scanning session we assessed demographic characteristics and symptom severity using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS).[28]

Image acquisition

Controls and patients recruited from WINTR were scanned at the Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Germany. Controls and patients from Jena were scanned at the University Hospital Jena.

High-resolution anatomic T_1-weighted scans from Jena were acquired using a 3 T whole body system equipped with a 12-element receive-only head matrix coil (MAGNETOM TIM Trio, Siemens Medical Solutions). High-resolution anatomic T_1-weighted volume scans (magnetization-prepared rapid gradient-echo [MPRAGE]) were obtained in sagittal orientation under the following parameters: repetition time (TR) 2300 ms, echo time (TE) 3.03 ms, inversion time (TI) 900 ms, flip angle 9°, field of view (FOV) 256 × 256 mm^2, matrix 256 × 256 mm^2, 192 sagittal slices, acceleration factor (PAT) of 2, with an isotropic resolution of 1 × 1 × 1 mm^3.

Data from Munich were collected using a 3 T whole body system equipped with a 12-element receive-only head matrix coil (INGENIA, Philips Healthcare). High-resolution anatomic T_1-weighted volume scans (MPRAGE) were obtained in sagittal orientation under the following parameters: TR 9 ms, TE 4 ms, TI 900 ms, flip angle 8°, FOV 240 × 240 mm^2, matrix 240 mm × 240 mm^2, 170 sagittal slices, with an isotropic resolution of 1 × 1 × 1 mm^3.

Image processing and computation of surface measures

Using the framework of the general linear modeling (GLM), implemented as an automated function in FreeSurfer (glm_fit), we assessed the regional grey matter differences with respect to volume, surface area and thickness between patients and controls at the level of each vertex for each hemisphere separately, and included age, sex and scanner type (Siemens v. Philips) as covariates to correct for their potential confounding effects. The reconstructed surfaces for each participant were visually inspected, and minor defects were manually corrected as recommended by the software guidelines.

To account for multiple testing across the whole brain, we performed Monte Carlo simulations[29] with 10 000 iterations in order to identify significant contiguous clusters of vertex-wise group differences ($p < 0.05$).

In addition to analysis of covariance (ANCOVA), we assessed the potentially confounding effect of the 2 scanner types (Siemens v. Phillips) and their different sequences. Hence, we performed another glm_fit analysis with age and sex as covariates in which we evaluated whether the 2 scanner groups differed significantly in volume, surface area or thickness.

Statistical analysis

Further statistical analyses were performed using the SPSS Inc. software version 11.5.1. Differences in age between the groups were assessed using the Student t test, and differences in sex were assessed using χ^2 square tests. Within the patient group we performed multiple linear regression to assess the association between 4 clinical characteristics (Y-BOCS total score, obsessions, compulsions and duration of illness) and alteration in parameters of the cortical structure (mean volume, surface area or thickness of altered brain regions). Each of the 4 clinical scores was hereby taken as a separate criterion, with mean volume or surface area extracted from the clusters that emerged from the group comparison as predictors, and age, sex and scanner type as covariates. We conducted the regression analyses separately for each hemisphere, for each of the 4 symptom scores and for each of the cortical parameters showing a group difference. In case of a significant association, the corresponding partial correlation coefficient was reported.

To control for the potential effect of medication or comorbidity on the brain clusters that were found to be different in patients than controls, we performed multivariate ANCOVAs (MANCOVA). Medication and comorbidity were used as independent variables, and average volume and surface area values (extracted from the clusters found to be different in the group comparison) were used as dependent variables. Age, sex and scanner type were entered as covariates. We performed the analyses separately for each hemisphere. We addressed the question of whether medication status (medicated v. unmedicated) or comorbidity (comorbidity v. no comorbidity) affected the surface structure in the clusters that were found to be different in patients than in controls.

Our statistical analyses were Bonferroni-corrected with an α of $p < 0.0025$ for the total of 20 models (10 for each hemisphere and each measure).

In addition, to evaluate if there was a potential difference between medicated and unmedicated patients, we performed separate whole brain GLM analyses for the cortical parameters (volume, surface area, thickness) with age, sex and scanner type as covariates, and corrected for multiple testing using a false discovery rate (FDR) of $p < 0.05$.

Results

Participants

The study sample comprised 75 right-handed patients who met the DSM-IV criteria for OCD and 75 right-handed healthy controls matched for age ($t_{148} = 0.54$, $p = 0.58$) and sex

($\chi^2_1 = 0.1$, $p = 0.73$). Forty-two of the patients were recruited from WINTR and 33 were recruited from the University Hospital in Jena. Slightly more than half (57%) of all patients were medicated, and one-third (32%) had 1 or more comorbid psychiatric disorder (Table 1).

Differences in surface measures

Volume

The whole brain analysis to investigate differences in cortical volume between the groups revealed a significantly ($p < 0.01$) decreased volume in patients with OCD compared with healthy controls in a cluster of the right hemisphere comprising the superior and inferior parietal areas as well as small parts of the lateral occipital cortex and in a similar cluster in the left hemisphere comprising superior-inferior parietal and lateral occipital regions ($p < 0.05$; Table 2 and Fig. 1B).

Table 1: Demographic and clinical characteristics of the sample

	Group; mean ± SD (range) or no.	
Characteristic	OCD ($n = 75$)	Control ($n = 75$)
Age, yr	30.99 ± 9.55 (19–63)	30.17 ± 8.99 (18–57)
Sex, male:female	27:48	30:45
Age at onset, yr	16.90 ± 6.64	—
Medication, yes:no	43:32	—
Medication type		
SSRI	24	—
SNRI	5	—
TrA	2	—
≥ 1 medication	12	—
Comorbidities, yes:no	24:51	—
Comorbidity type		
Depression	13	—
Anxiety disorder	3	—
Personality disorder	1	—
Impulse control disorder NOS	1	—
≥ 1 comorbid disorder	6	—
Y-BOCS score		
Total score	20.77 ± 6.08 (9–38)	—
Obsessions	10.45 ± 3.47 (1–19)	—
Compulsions	10.29 ± 3.96 (0–19)	—

NOS = not otherwise specified; OCD = obsessive–compulsive disorder; SD = standard deviation; SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TrA = tricyclic antidepressant; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.

Surface area

Patients with OCD had a significantly ($p < 0.05$) decreased surface area in 4 clusters of the right hemisphere (parietal cortex, rostral middle frontal cortex, inferior temporal cortex, precuneus) compared with healthy controls. When applying a stricter threshold ($p < 0.01$), only the parietal and the rostral middle frontal cluster remained significant (Table 3). Likewise, 3 clusters of the left hemisphere showed a significantly decreased surface area ($p < 0.05$) in patients with OCD compared with healthy controls, comprising mainly the left lateral occipital, superior parietal and rostral middle frontal regions. When applying a stricter threshold ($p < 0.01$), only the lateral occipital and superior parietal clusters remained significant (Table 3 and Fig. 1A).

Thickness

The whole brain analyses of cortical thickness revealed no significant differences between the groups.

Correlation between surface area and volume

As the parietal cortex showed both decreased surface area and volume in patients compared with controls (Fig. 1), we investigated whether there was a direct association between both parameters in this area. The correlation of volume and surface area in this specific overlapping cluster showed a positive association between these measures in both hemispheres and both groups (left hemisphere: $r = 0.83$, $p = 0.013$ in patients and $r = 0.86$, $p = 0.012$ in controls; right hemisphere: $r = 0.82$, $p = 0.014$ in patients and $r = 0.86$, $p = 0.012$ in controls).

Association between cortical measures and clinical variables

There was no association between the cortical parameters and symptom severity or duration of illness (i.e., the analyses did not survive correction for multiple comparisons).

Influence of medication, comorbidity and scanner sequence

After Bonferroni correction, neither medication nor comorbidity showed a significant effect on the altered volume or surface area regions. Furthermore, no group differences in the whole brain analysis comparing medicated and unmedicated patients could be found in any of the grey matter measures.

Table 2: Clusters showing significantly reduced grey matter volume in patients with obsessive–compulsive disorder*

Cluster annotation	Max t-value	VtxMax	Cluster size, mm²	VtxMax Talairach coordinates, *x*, *y*, *z*	CWP *p* value (90% CI)	NVtxs
Left hemisphere						
Superior-inferior parietal cortex extending to lateral occipital cortex	–4.549	112 174	1031.24	–26.5, –82.4, 17.9	0.044 (0.041–0.046)	1492
Right hemisphere						
Superior-inferior parietal cortex	–4.289	157 870	1432.89	24.7, –79.7, 25	0.006 (0.005–0.007)	2118

CI = confidence interval; CWP = cluster-wise probability; NVtx = number of vertices in cluster; VtxMax = no. of peak vertices of the significant cluster.
*Annotation of clusters according to FreeSurfer atlas.

There was no difference in surface area, volume or thickness between the 2 scanner groups (Siemens v. Phillips).

Discussion

Our study results showed a reduced grey matter surface area and volume mainly in parieto-occipital areas of both hemispheres in patients with OCD. Additionally, we found only the surface area to be reduced in a network comprising frontal, temporal, precuneus and cingulate areas (Fig. 1C). However, our results did not show any significant difference in grey matter thickness between the groups, and none of the alterations showed a significant association with clinical scores.

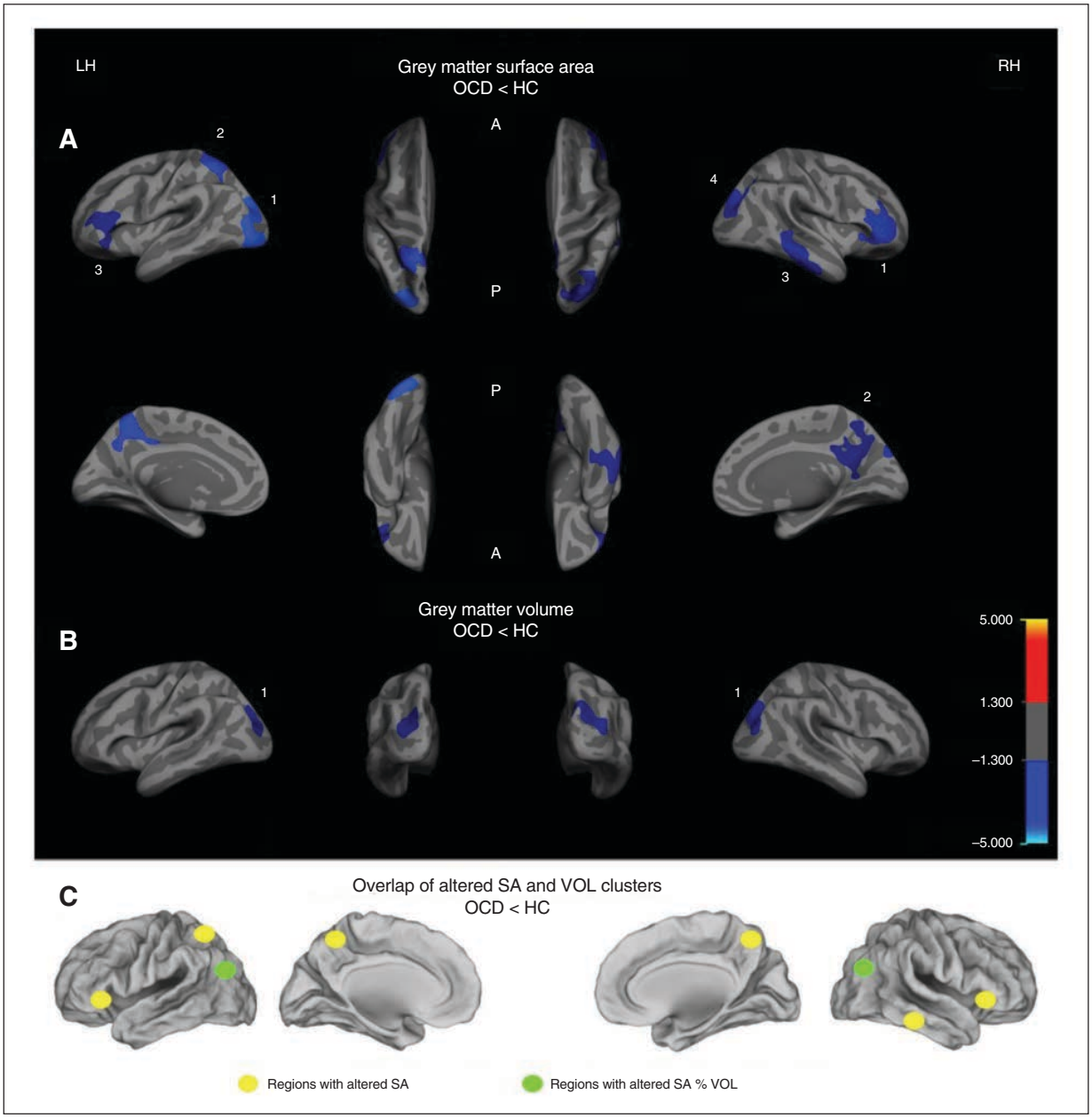

Fig.1: Group differences in (**A**) clusters with significantly reduced grey matter surface area (SA) and (**B**) clusters with significantly reduced grey matter volume (VOL), shown separately for the right (RH) and left hemispheres (LH). Clusters are displayed on the FreeSurfer main surface of the participants' average brain (lateral, medial, dorsal or ventral view). The colour bar indicates the t-value after cluster-wise correction for multiple comparisons using Monte Carlo simulations ($p < 0.05$). (**C**) Overlap between the altered SA and VOL clusters. Cluster numbers correspond to those in Table 3 and in the article text. A = anterior; HC = healthy controls; OCD = obsessive–compulsive disorder; P = posterior.

Comparison with surface-based studies

To the best of our knowledge, the present study is only the third OCD study to analyze several cortical parameters in the same sample using the SBA approach. Our results show a certain overlap with previous SBA studies in OCD samples: alterations in similar areas (i.e., parieto-occipital alterations, including the precuneus) partly overlap with the findings of Fan and colleagues,[20] and the same direction of alteration (i.e., decreases in volume and surface area) has been reported by Venkatasubramanian and colleagues.[19]

However, whereas we found decreased grey matter surface area and volume in similar regions as Fan and colleagues,[20] their results showed mostly increased gyrification and thickness in those areas.

The divergence in the direction of alteration may be partly driven by methodological differences in terms of clinical sample characteristics (i.e., previous studies investigated smaller samples and mainly unmedicated and comorbidity-free[20] or medication-naive patients[19]).

It is compelling that although other SBA studies[21,23,25,26,30,31] found grey matter thickness to be affected in patients with OCD, our results did not show such alterations in this measure, but we did find partly similar alterations in other measures. However, when interpreting these divergent results one needs to be aware that previous studies presented rather heterogeneous results as well. They reported increased but also decreased grey matter thickness in distinct cortical regions, with some of the resulting heterogeneity probably being a consequence of methodological differences among the studies (i.e., SBA approach v. whole brain v. ROI-based analyses) or differences in sample characteristics (e.g., symptom profile, symptom severity, duration of illness, medication, sample size, presence of comorbidities). All this makes a valid comparison of the various findings rather difficult.

This heterogeneity regarding alterations in different structural parameters in partly similar areas may also be explained by the fact that, although these parameters are partly associated, they still can change independently from each other and influence changes in another parameter to a significant degree.[32]

In this context, it is interesting to note that we found similar areas (i.e., inferior-superior parietal regions) to be hypogyrified in the same sample, as reported in a recently published paper by our group.[27]

According to previous studies, gyrification reaches its developmental peak before early toddlerhood.[33–35] Therefore, variations in gyrification are often discussed as useful markers for processes that evolved during a crucial period of early brain development.

Against this background one could speculate that these early changes in brain development could have laid the basis for a certain vulnerability in these areas. Hence, it is possible that these changes, which most probably happened during early brain development, made other grey matter properties (e.g., volume or surface area) more prone to alterations. This would also explain why similar areas were altered with regard to gyrification as well as volume and surface area. It should be noted, however, that this conclusion is speculative, and the precise association between these grey matter properties needs to be disentangled in future studies.

Another notable finding from the present study was the reduced surface area in the bilateral rostral middle frontal areas extending to the pars opercularis, pars triangularis and pars orbitalis. This finding is consistent with the main findings of 2 recent mega-analyses,[7,8] which discussed the possibility that similar pathological processes might underlie reductions in cortical morphology of these frontal areas. Thinking a step further, these frontal areas, which are mainly responsible for cognitive control, have been shown to be linked to OCD-specific repetitive behaviours (compulsions), and fMRI studies show evidence of functional alterations in similar areas in patients with OCD, which lets us speculate that there may be a link between these functional and structural alterations.

Table 3: Clusters showing significant changes in grey matter surface area in patients with obsessive–compulsive disorder

Cluster	Max t-value	VtxMax	Cluster size, mm²	VtxMax Talairach coordinates, *x*, *y*, *z*	CWP *p* value (90% CI)	NVtxs
Left hemisphere						
Lateral occipital cortex, superior-inferior parietal cortex	–3.941	87 140	2971.33	–26.9, –85.3, 18.4	0.0006 (0.0003–0.0009)	4014
Superior parietal cortex, precuneus, posterior cingulate	–3.568	14 332	2422.88	–7.4, –48.9. 59.8	0.002 (0.001–0.003)	5152
Rostral middle frontal cortex, pars triangularis, pars orbitalis, pars opercularis	–2.681	84 578	1701.91	–46.6, 30.5, 9.2	0.025 (0.023–0.027)	2384
Right hemisphere						
Rostral middle frontal cortex, pars triangularis, pars orbitalis, lateral orbitofrontal cortex	–4.278	58 399	2293.91	42.0, 41.8, 0.0	0.006 (0.005–0.007)	3159
Precuneus, isthmus cingulate	–4.237	156 055	1690.44	8.6, –50.4, 24.6	0.030 (0.028–0.032)	3705
Middle-inferior temporal cortex, banks of the superior temporal sulcus, fusiform gyrus	–3.844	59 310	2007.95	66.6, –31.2, –5.9	0.012 (0.010–0.013)	3124
Superior-inferior parietal cortex, lateral occipital cortex, cuneus	–2.720	104 620	2201.18	34.3, –78.3, 19.9	0.007 (0.006–0.008)	3436

CI = confidence interval; CWP = cluster-wise probability; NVtx = number of vertices in cluster; VtxMax = no. of peak vertices of the significant cluster.
*Annotation of clusters according to the FreeSurfer atlas.

Comparison with VBM studies

Compared with previous VBM studies, we likewise found structural alterations in inferior frontal areas, such as reported by de Wit and colleagues;[8] alterations in small parts of the lateral orbitofrontal cortex, such as shown by Radua and Mataix-Cols;[2] and parietofrontal alterations, such as reported by Rotge and colleagues.[4] However, despite the spatial overlaps these alterations affected different cortical parameters, and we could not replicate any increases in cortical grey matter. These differences could have been driven by different methodological approaches; VBM might conceal certain changes that become manifest when analyzing cortical characteristics in a surface-based way,[32] but they may also be triggered by clinical characteristics of the studied sample, such as medication, comorbidities, symptom dimensions or sample size.

More specifically, when comparing our results to earlier findings, it is striking that we tended to detect a reduced surface area in brain regions that were reported in other studies to show a reduced volume.[8,36] Moreover, other areas that showed alterations or even increases in grey matter in these previous studies (e.g., putamen, cerebellum, prefrontal cortex) did not show any significant difference to healthy controls in the present results. A potential reason for these differences may be that the grey matter volume as measured by VBM is a conglomerate of grey matter features that can be influenced by cortical folding properties of the surface area.[16,32,37] Hence, an exclusive VBM analysis of grey matter volume could obscure potential differences in other features, such as surface area or folding, which may have significantly contributed to the volume changes reported in previous studies. Moreover, evidence showing a — to some degree — genetically and phenotypically independent development of some of these grey matter parameters,[10–12] and the fact that SBA methods account for the folded surface when computing volume, supports the conclusion that SBA methods, such as those used in the FreeSurfer software, may contribute to a better understanding of the precise characteristics of grey matter alterations. However, exact interdependencies and potential effects of the grey matter parameters on each other remain unknown[12] and should be evaluated by future studies using combined methodological approaches (VBM and SBA).[32]

Associations of grey matter parameters

Although the way grey matter is measured by the various approaches is relatively clear and varies only slightly, little evidence exists about the precise characteristics and physiologic implications of each grey matter measure that would allow for a meaningful interpretation of the results. There is evidence from basic research that the various neuroanatomical features of the cortex (i.e., thickness, surface area, gyrification), which are all to a greater or lesser degree included in the volume parameter, are highly heritable.[11,38–40] Nevertheless, each of them underlies distinct genetic and evolutionary processes.[11,41,42] Hence, environmental influences, such as diseases, can also have different effects on these subcomponents of grey matter. Therefore, it is important to highlight that the exclusive investigation of grey matter volume might obscure changes in brain morphology.

Interestingly, the parietal cortex showed a reduced surface area and a reduced volume. Moreover, the correlation between both parameters showed a significant association in both patients and healthy controls. Although this result speaks in favour of a direct link between the different characteristics of brain morphology, it is still unknown how exactly these parameters influence each other. Some more recent evidence from longitudinal SBA data suggests that grey matter volume changes may emerge as a result of age- and sex-dependent interaction between grey matter thickness and surface area. These data also suggest that changes in grey matter surface area reflect mainly the more complex interaction between cortical gyrification and the size changes in the exposed convex hull area during brain development, which can vary strongly depending on age or sex.[12]

Associations between structural alterations and clinical scores

The present findings raise the question whether the alterations we detected in brain morphology of patients with OCD constitute a predisposing developmental abnormality or a consequence of disorder progression. Longitudinal studies of brain development in healthy individuals indicate that these cortical parameters (i.e., surface area and volume) can change in the course of life, whereas gyrification seems to constitute a rather stable parameter after early childhood and is therefore often discussed as a potential neurodevelopmental marker.[27,43] Therefore, there is reason to assume that symptom severity, duration of illness or age of onset might be associated with the structural alterations found in the present study. Although several of the discussed studies in adult and pediatric samples of OCD showed associations between morphological changes of grey matter and clinical scores,[6,7,19,20] the present results did not show this on a corrected significance threshold. Hence, in light of the study limitations, such as a potential influence of medication or comorbidities, which may also have confounded these associations, our results need to be treated with caution. Nevertheless, the hypothesis that alterations in cortical morphology could be linked to clinical factors, such as early age of onset, higher symptom severity, poor treatment response or delayed start of treatment, is still a matter of debate and needs further examination in longitudinal studies.

Relating structural alterations to functional alterations

A frequently discussed hypothesis is that structural alterations might constitute the basis for functional impairments in the affected brain. In patients with OCD, this hypothesis is sustained by the fact that partly similar areas are often reported to be altered on a functional as well as on a structural level. In that respect, the present findings as well as previous ones revealed structural alterations in mainly parieto-occipital as well as temporal and frontal regions in patients with OCD.[4,21] Functional OCD studies showed alterations in some of these structurally

altered regions during tasks that required visual, emotional or executive processing; inhibitory control; or working memory processing.[44–50] Moreover, behavioural OCD studies also reported impairments in functions that are known to involve similar brain regions and networks.[51,52] Furthermore, the alteration in surface area in the bilateral posterior cingulate goes in line with resting-state studies of functional connectivity in OCD samples. These studies found alterations in the attention and the default mode network,[53,54] of which the posterior cingulate constitutes an important hub. Based on these findings, one can assume that these functional and structural impairments in patients with OCD are linked and may lead to network disruptions in addition to the reported alterations in specific regions.

Limitations

Psychiatric disorders share certain neural correlates to some degree,[55] and the presence of comorbidities and/or medical treatment can alter or reinforce these morphological commonalities.[7,56,57] However, although our sample was partly medicated and not comorbidity-free, these factors did not show any significant effect on the present results after correcting for multiple comparisons. Considering that on an uncorrected threshold an effect was found in certain clusters, it cannot be excluded that comorbidity or medical treatment had a certain influence on grey matter structure. Of note, the 2 previous SBA studies evaluated either unmedicated[20] or medication-naive patients,[19] with partly similar as well as divergent results compared with our study. Hence, the degree to which these cortical characteristics are really affected by medication or comorbidities needs to be further elucidated.

Another important point is that patients with OCD often experience a broad spectrum of symptoms, and previous imaging studies indicate that OCD may be conceptualized as a spectrum of multiple and potentially overlapping syndromes that might be — both from a functional and a structural perspective — mediated by distinct components of the CSTC.[7,58,59] Against this background, the fact that our sample was multisymptomatic limits our study's explanatory power to some degree. Hence, further studies with even larger samples are needed to allow for a valid differentiation between patients with specific symptom types. Another limitation of our study is the fact that no standardized interview, such as the Structured Clinical Interview for DSM disorders or the M.I.N.I. International Neuropsychiatric Interview, was performed. However, before study inclusion patients had been extensively screened by experienced psychiatrists from the WINTR and Jena hospital, who confirmed the diagnosis of OCD.

Even though we tried to control for the effect of scanner type in the best possible way (i.e., by introducing scanner type as a covariate in the analyses and by comparing data from the 2 scanner groups), we cannot rule out that this variable may have influenced our results to a certain degree.

Another methodological limitation may be the fact that SBA methods limit analyses to cortical regions, whereas structural properties of subcortical brain areas, such as the basal ganglia or amygdala, which are assumed to be psychopathologically relevant for OCD, are not taken into consideration.

Conclusion

Despite these limitations, the present study is one of the few exploring volume, surface area and thickness in patients with OCD. Our results clearly indicate that aside from the frequently reported functional alterations grey matter surface area seems to be altered in patients with OCD and suggest that parieto-occipital and rostral middle frontal regions should be considered in the neurobiological model of the disorder. Mega-analyses should further investigate these whole brain cortical changes by accounting for all possible confounders in order to further isolate the central hubs of structural alterations in patients with OCD. Moreover, more data are needed to elucidate the exact interrelation between these grey matter parameters and their relevance for OCD.

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References

1. Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey replication. *Mol Psychiatry* 2010;15:53-63.
2. Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry* 2009;195: 393-402.
3. Rotge JY, Guehl D, Dilharreguy B, et al. Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry* 2009;65:75-83.
4. Rotge JY, Langbour N, Guehl D, et al. Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology* 2010;35:686-91.
5. Piras F, Piras F, Chiapponi C, et al. Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex* 2015;62:89-108.
6. Boedhoe PS, Schmaal L, Abe Y, et al. Distinct subcortical volume alterations in pediatric and adult OCD: a worldwide meta- and mega-analysis. *Am J Psychiatry* 2017;174:60-9.
7. Fouche JP, du Plessis S, Hattingh C, et al. Cortical thickness in obsessive-compulsive disorder: multisite mega-analysis of 780 brain scans from six centres. *Br J Psychiatry* 2017;210:67-74.
8. de Wit SJ, Alonso P, Schweren L, et al. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. *Am J Psychiatry* 2014;171:340-9.
9. Ashburner J, Friston KJ. Voxel-based morphometry — the methods. *Neuroimage* 2000;11:805-21.

10. Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* 2010;53:1135-46.
11. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex* 2009;19:2728-35.
12. Raznahan A, Shaw P, Lalonde F, et al. How does your cortex grow? *J Neurosci* 2011;31:7174-7.
13. Kapellou O, Counsell SJ, Kennea N, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. *PLoS Med* 2006;3:e265.
14. Frye RE, Liederman J, Malmberg B, et al. Surface area accounts for the relation of gray matter volume to reading-related skills and history of dyslexia. *Cereb Cortex* 2010;20:2625-35.
15. Shaw P, Kabani NJ, Lerch JP, et al. Neurodevelopmental trajectories of the human cerebral cortex. *J Neurosci* 2008;28:3586-94.
16. Hutton C, Draganski B, Ashburner J, et al. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage* 2009;48:371-80.
17. Clarkson MJ, Cardoso MJ, Ridgway GR, et al. A comparison of voxel and surface based cortical thickness estimation methods. *Neuroimage* 2011;57:856-65.
18. Helms G. Segmentation of human brain using structural MRI. *MAGMA* 2016;29:111-24.
19. Venkatasubramanian G, Zutshi A, Jindal S, et al. Comprehensive evaluation of cortical structure abnormalities in drug-naive, adult patients with obsessive-compulsive disorder: a surface-based morphometry study. *J Psychiatr Res* 2012;46:1161-8.
20. Fan Q, Palaniyappan L, Tan L, et al. Surface anatomical profile of the cerebral cortex in obsessive-compulsive disorder: a study of cortical thickness, folding and surface area. *Psychol Med* 2013;43:1081-91.
21. Shin YW, Yoo SY, Lee JK, et al. Cortical thinning in obsessive compulsive disorder. *Hum Brain Mapp* 2007;28:1128-35.
22. Fallucca E, MacMaster FP, Haddad J, et al. Distinguishing between major depressive disorder and obsessive-compulsive disorder in children by measuring regional cortical thickness. *Arch Gen Psychiatry* 2011; 68:527-33.
23. Nakamae T, Narumoto J, Sakai Y, et al. Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;37:90-5.
24. Kim SG, Jung WH, Kim SN, et al. Disparity between dorsal and ventral networks in patients with obsessive-compulsive disorder: evidence revealed by graph theoretical analysis based on cortical thickness from MRI. *Front Hum Neurosci* 2013;7:302.
25. Shaw P, Sharp W, Sudre G, et al. Subcortical and cortical morphological anomalies as an endophenotype in obsessive-compulsive disorder. *Mol Psychiatry* 2015;20:224-31.
26. Kühn S, Kaufmann C, Simon D, et al. Reduced thickness of anterior cingulate cortex in obsessive-compulsive disorder. *Cortex* 2013; 49:2178-85.
27. Rus OG, Reess TJ, Wagner G, et al. Hypogyrification in obsessive-compulsive disorder. *Psychol Med* 2017;47:1053-1061.
28. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;46:1006-11.
29. Hagler DJ Jr, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *Neuroimage* 2006;33:1093-103.
30. Narayan VM, Narr KL, Phillips OR, et al. Greater regional cortical gray matter thickness in obsessive-compulsive disorder. *Neuroreport* 2008;19:1551-5.
31. Fouche JP, du Plessis S, Hattingh C, et al. Cortical thickness in obsessive-compulsive disorder: multisite mega-analysis of 780 brain scans from six centres. *Br J Psychiatry* 2017;210:67-74.
32. Palaniyappan L, Liddle PF. Differential effects of surface area, gyrification and cortical thickness on voxel based morphometric deficits in schizophrenia. *Neuroimage* 2012;60:693-9.
33. Armstrong E, Schleicher A, Omran H, et al. The ontogeny of human gyrification. *Cereb Cortex* 1995;5:56-63.
34. Zilles K, Palomero-Gallagher N, Amunts K. Development of cortical folding during evolution and ontogeny. *Trends Neurosci* 2013;36: 275-84.
35. Magnotta VA, Andreasen NC, Schultz SK, et al. Quantitative in vivo measurement of gyrification in the human brain: changes associated with aging. *Cereb Cortex* 1999;9:151-60.
36. Pujol J, Soriano-Mas C, Alonso P, et al. Mapping structural brain alterations in obsessive-compulsive disorder. *Arch Gen Psychiatry* 2004;61:720-30.
37. Hutton C, De Vita E, Ashburner J, et al. Voxel-based cortical thickness measurements in MRI. *Neuroimage* 2008;40:1701-10.
38. Atkinson EG, Rogers J, Mahaney MC, et al. Cortical folding of the primate brain: an interdisciplinary examination of the genetic architecture, modularity, and evolvability of a significant neurological trait in pedigreed baboons (genus Papio). *Genetics* 2015;200:651-65.
39. Kochunov P, Glahn DC, Fox PT, et al. Genetics of primary cerebral gyrification: heritability of length, depth and area of primary sulci in an extended pedigree of Papio baboons. *Neuroimage* 2010; 53:1126-34.
40. Rogers J, Kochunov P, Zilles K, et al. On the genetic architecture of cortical folding and brain volume in primates. *Neuroimage* 2010; 53:1103-8.
41. Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. *Trends Neurosci* 1995;18:383-8.
42. Chenn A, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* 2002;297:365-9.
43. Mills KL, Tamnes CK. Methods and considerations for longitudinal structural brain imaging analysis across development. *Dev Cogn Neurosci* 2014;9:172-90.
44. van den Heuvel OA, Veltman DJ, Groenewegen HJ, et al. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. *Arch Gen Psychiatry* 2005;62:301-9.
45. Van Velzen LS, Vriend C, de Wit SJ, et al. Response inhibition and interference control in obsessive-compulsive spectrum disorders. *Front Hum Neurosci* 2014;8:419.
46. de Vries FE, de Wit SJ, Cath DC, et al. Compensatory frontoparietal activity during working memory: an endophenotype of obsessive-compulsive disorder. *Biol Psychiatry* 2014;76:878-87.
47. Rus OG, Reess TJ, Wagner G, et al. Functional and structural connectivity of the amygdala in obsessive-compulsive disorder. *Neuroimage Clin* 2017;13:246-55.
48. Olatunji BO, Ferreira-Garcia R, Caseras X, et al. Predicting response to cognitive behavioral therapy in contamination-based obsessive-compulsive disorder from functional magnetic resonance imaging. *Psychol Med* 2014;44:2125-37.
49. Menzies L, Chamberlain SR, Laird AR, et al. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev* 2008;32:525-49.
50. Gonçalves OF, Marques TR, Lori NF, et al. Obsessive-compulsive disorder as a visual processing impairment. *Med Hypotheses* 2010;74:107-9.
51. Bannon S, Gonsalvez CJ, Croft RJ, et al. Executive functions in obsessive-compulsive disorder: State or trait deficits? *Aust N Z J Psychiatry* 2006;40:1031-8.
52. Penadés R, Catalan R, Rubia K, et al. Impaired response inhibition in obsessive compulsive disorder. *Eur Psychiatry* 2007;22:404-10.
53. Zhang T, Wang J, Yang Y, et al. Abnormal small-world architecture of top-down control networks in obsessive-compulsive disorder. *J Psychiatry Neurosci* 2011;36:23-31.
54. Meunier D, Ersche KD, Craig KJ, et al. Brain functional connectivity in stimulant drug dependence and obsessive-compulsive disorder. *Neuroimage* 2012;59:1461-8.
55. Radua J, van den Heuvel OA, Surguladze S, et al. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Arch Gen Psychiatry* 2010;67:701-11.
56. Hoexter MQ, de Souza Duran FL, D'Alcante CC, et al. Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. *Neuropsychopharmacology* 2012;37:734-45.
57. Hoexter MQ, Dougherty DD, Shavitt RG, et al. Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive-compulsive disorder. *Eur Neuropsychopharmacol* 2013;23:569-80.
58. Mataix-Cols D, Wooderson S, Lawrence N, et al. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch Gen Psychiatry* 2004;61:564-76.
59. van den Heuvel OA, Remijnse PL, Mataix-Cols D, et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain* 2009;132:853-68.

9. Cortical Folding in OCD

The cortex of OCD patients is characterised by variations in cortical folding reflected in a significantly reduced gyrification which goes along with an early age of onset.

This chapter presents a research article entitled "Hypogyrification in obsessive-compulsive disorder", which was published in the journal of Psychological Medicine in November 2016 and was written by Oana Georgiana Rus, Tim Jonas Reeß, Gerd Wagner, Michael Zaudig, Claus Zimmer and Kathrin Koch. This study uses the same sample and same methodological approach as the previous study in Chapter 8. However, it focuses specifically on cortical folding, which has been shown to be a reliable indicator for morphological processes during early stages of brain development and which is therefore regarded as a neurodevelopmental marker of brain morphology.

Contributions:

The author of the present thesis is also the first author of this research article. O.G.R, T.J.R. and K.K. contributed substantially to conception and design, acquisition of data, analysis and interpretation of data and revised the manuscript critically. O.G.R. additionally drafted the article. G.W. contributed substantially to conception of data and revised the drafted manuscript. C.Z. contributed substantially to data acquisition. M.Z. contributed substantially to patient collection. All authors gave the final approval of the version to be published.

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ORIGINAL ARTICLE

Hypogyrification in obsessive-compulsive disorder

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Background. Previous studies hypothesized that neurodevelopmental risk factors may play a role in the pathogenesis of obsessive-compulsive disorder (OCD). Cortical folding has been shown to be a reliable indicator for normal and altered neurodevelopment, but in OCD it has barely been investigated up to now. The present study investigates whether alterations in gyrification are detectable in OCD and, if so, how these are associated with clinical characteristics.

Method. We compared the local Gyrification Index (lGI) between 75 OCD patients and 75 matched healthy subjects across the whole brain. In addition, for those regions exhibiting an altered lGI in patients we explored a potential relationship to symptom severity, age of onset, and influence of medication.

Results. OCD patients had a significantly decreased lGI in right parietal, precentral but also insula, temporal, pars triangularis and rostral middle frontal regions compared to healthy subjects. A positive association with age of onset was found but no association with symptom severity. There was no effect of co-morbidity or medication.

Conclusions. The reduced gyrification found in OCD confirms previous findings in other psychiatric disorders and suggests that alterations may already occur during early stages of brain development. Our findings support the idea that altered cortical folding might represent a trait characteristic of the disorder although longitudinal studies are needed to clarify the trajectory of this morphological measure in OCD.

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Key words: Cortical folding, freesurfer, gyrification OCD, local gyrification index, obsessive compulsive disorder.

Introduction

Obsessive-compulsive disorder (OCD) has been discussed as a disorder with potential neurodevelopmental risk factors (Rosenberg & Keshavan, 1998; Huyser *et al.* 2009), but surprisingly few studies investigated the potential neural indicators for this assumption.

One useful marker to assess early defects in neurodevelopment in the brain is cortical folding or gyrification. Cortical folding is known to develop during prenatal life and to be terminated to a very large degree before the age of 2 years (Armstrong *et al.* 1995; Magnotta *et al.* 1999), before it starts to slightly decrease between childhood and young adulthood [according to a review by Mills & Tamnes (2014) by up to 7%]. Therefore, cortical folding seems to be a reliable marker for early neurodevelopmental alterations in the brain.

Answering the question if early developmental alterations already occur in patients would help to better understand the nature and mechanisms behind the existing structural alterations in OCD which – according to a recent review (Piras *et al.* 2015) – provide a rather heterogeneous picture. To the best of our knowledge cortical folding patterns in OCD have been investigated in only four studies up to now (Shim *et al.* 2009; Wobrock *et al.* 2010; Venkatasubramanian *et al.* 2012; Fan *et al.* 2013), which show discrepant results overall.

Two of them found hypogyrification in the OCD sample compared to healthy controls using a classification approach of cortical folding patterns in regions of interest (ROIs). This hypogyrification was detectable in the left anterior cingulate cortex (ACC; Shim *et al.* 2009) and the left prefrontal cortex (PFC; Wobrock *et al.* 2010). The other two studies used a different methodological approach by calculating a local gyrification index (lGI). While Venkatasubramanian *et al.* (2012) did not find any differences in lGI between OCD patients and healthy subjects, Fan *et al.* (2013) found a hypergyrification in OCD patients in the left insula, the left middle frontal and left lateral occipital regions extending to precuneus as well as in the right supramarginal gyrus.

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Little is known about the association between clinical characteristics and altered cortical folding in OCD although there is first evidence indicating that medication, symptom severity and even disorder insight might be related to folding abnormalities in OCD. Comparing severely and mildly affected patients with healthy controls Wobrock *et al.* (2010) reported a stronger hypogyrification in patients with severe symptoms. Venkatasubramanian *et al.* (2012) found a negative association between lGI of right lateral orbitofrontral cortex (OFC) and compulsion score and between lGI left medial OFC and disorder insight. Opposite to these findings Fan *et al.* (2013) reported a positive association between left insula lGI and symptom severity and an effect of medication on lGI values in the left insula in medication naive compared to previously medicated patients that, however, did not reach statistical significance.

Gyrification has also been investigated in several other psychiatric disorders (i.e. schizophrenia, autism, depression, panic disorder). In patients with psychotic disorders and their first-degree relatives, Nanda *et al.* (2014) found a hypogyrification of the cingulate cortex compared to healthy participants suggesting that hypogyrification may mark a certain familial risk for psychotic disorders. In patients with panic disorder Yoon *et al.* (2013) showed a hypogyrification in lateral brain areas extending from fronto-parietal areas (including precuneus) to the temporal pole, as well as an association between hypergyrification in posterior-medial areas and alleviation of symptoms, suggesting that an increased gyrification could constitute a compensational mechanism for hypogyrification affecting other, partly adjacent, areas. Similar findings were reported in major depressive disorder (MDD), where Zhang *et al.* (2009) were the first to show a decreased gyrification in precuneus and posterior cingulate cortex (PCC), insula and OFC. Nixon *et al.* (2014) replicated this finding of decreased precuneus gyrification bilaterally in patients recovered from MDD, and furthermore showed this hypogyrification to be associated with a hyperconnectivity between precuneus and dorsolateral prefrontal cortex (DLPFC).

Overall, these cortical folding studies in psychiatric disorders point towards an altered gyrification in areas responsible for emotional processing but also cognitive control. Considering that these disorders share – to some degree – some of their symptomatology and often co-occur or precede each other, it may be meaningful that they exhibit structural alterations in partly the same anatomical regions. Hence, these findings seem to support the hypothesis that neurodevelopmental deficits, partly mirrored in cortical folding deficits, may represent possible risk factors for the development of psychiatric disorders.

Against this background, the question whether structural alterations in OCD occur with or because of disorder progression or whether they have an early, neurodevelopmental origin needs to be further elucidated. Studying cortical folding in OCD may thus lead to a better understanding of possible neurodevelopmental risk factors that could constitute an early cause for characteristic alterations in OCD, such as disruptions within the cortico-striato-thalamo-cortical circuit (Saxena & Rauch, 2000). The heterogeneity of results from the existing studies (Shim *et al.* 2009; Wobrock *et al.* 2010; Venkatasubramanian *et al.* 2012; Fan *et al.* 2013) as well as methodological differences illustrate the need for further research in this field.

On this account we intended to examine cortical folding differences in a large sample of OCD patients and healthy controls (i.e. 75 OCD patients, 75 healthy subjects) and to investigate how potential structural alterations might relate to age of onset and symptom type (i.e. obsessions *v.* compulsions) or severity. We used the approach described by Schaer *et al.* (2012) to quantify local gyrification by computing the lGI which represents the amount of cortex buried within the sulcal folds as compared with the amount of visible cortex in circular ROIs.

Method

Participants

The study sample comprised 75 right-handed patients meeting the DSM-IV criteria for OCD and 75 right-handed healthy controls matched for age ($t_{148} = 0.54$, $p = 0.58$) and gender ($\chi^2_1 = 0.1$, $p = 0.73$).

Forty-two patients were recruited from the Windach Institute and Hospital of Neurobehavioral Research and Therapy (WINTR), Germany. Thirty-three patients were recruited from the University Hospital for Psychiatry and Psychotherapy Jena, Germany. All 75 were in-house patients in wards specialized on OCD with a standardized admission process, standardized psychopathological screenings and standardized assessment of disorder history performed by an experienced psychiatrist. 57% of all patients were medicated and 32% suffered from one or more co-morbid psychiatric disorder (see Table 1).

Exclusion criteria for both groups were a history of clinically important head injuries, seizures or neurological diseases. Healthy controls with a history of psychiatric illness were excluded. Exclusion criteria for patients were schizophrenia, autism, substance and alcohol abuse/dependency, mental retardation, pregnancy, and severe medical conditions.

After complete description of the study aims, written informed consent was obtained from the subjects. The

Table 1. *Demographic and clinical characteristics of the sample*

	OCD ($N = 75$)			Controls ($N = 75$)		
	n	Mean (range)	S.D.	*n*	Mean (range)	S.D.
Age (years)		30.99 (19–63)	9.55		30.17 (18–57)	8.99
Gender (M/F)	27/48	–	–	30/45	–	–
Age of onset (years)		16.90	6.64	–	–	–
Medication (medicated/unmedicated)	43/32	–	–	–	–	–
Medication type						
SSRI	24					
SNRI	5					
TCA	2					
More than one drug	12					
Co-morbidities (present/not present)	24/51	–	–	–	–	–
Co-morbidity type						
Depression	13					
Anxiety disorder	3					
Personality disorder	1					
Impulse control disorder not otherwise specified	1					
More than one co-morbid disorder	6					
YBOCS total	75	20.77 (9–38)	6.08	–	–	–
Obsessions		10.45 (1–19)	3.47			
Compulsions		10.29 (0–19)	3.96			

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; YBOCS, Yale–Brown Obsessive Compulsive Scale.

study protocol was in compliance with the Declaration of Helsinki and approved by the Ethics Committees of the Klinikum rechts der Isar and the University of Jena. Prior to the scanning session we assessed demographic characteristics and symptom severity using the Yale–Brown Obsessive Compulsive Scale (YBOCS; Goodman *et al.* 1989).

Image acquisition

Controls and patients recruited from WINTR were scanned at the Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Germany. Patients from Jena were scanned at the University Hospital Jena.

High-resolution anatomical T1-weighted scans from Jena were acquired in a 3-T whole body system equipped with a 12-element receive-only head matrix coil (MAGNETOM TIM Trio, Siemens Medical Solutions, Germany). High-resolution anatomical T1-weighted volume scans (MP-RAGE) were obtained in sagittal orientation [TR = 2300, TE = 3.03, TI = 900 ms, flip angle = 9°, FOV = 256 × 256 mm^2, matrix = 256 × 256 mm, number of sagittal slices = 192, acceleration factor (PAT) = 2] with an isotropic resolution of 1 × 1 × 1 mm^3.

Data from Munich were collected on a 3-T whole-body system equipped with a 12-element receive-only head matrix coil (INGENIA, Philips Healthcare, The Netherlands). High-resolution anatomical T1-weighted volume scans (MP-RAGE) were obtained in sagittal orientation (TR = 9, TE = 4, TI = 900 ms, flip angle = 8°, FOV = 240 × 240 mm^2, matrix = 240 × 240 mm, number of sagittal slices = 170) with an isotropic resolution of 1 × 1 × 1 mm^3.

Image processing and computation of lGI

We used the FreeSurfer software package (version 5.3.0, http://surfer.nmr.harvard.edu) to process the T1 images according to the standard and automatic processing stream (Fischl & Dale, 2000). This processing stream includes removal of non-brain tissue, transformation to Talairach-like space, and segmentation of gray/white matter tissue (GM, WM) resulting in two meshes (a white mesh = the WM/GM boundary and a pial mesh = GM/cerebrospinal fluid boundary). The meshes are composed of about 150 000 points (vertices) for each hemisphere. As a next step we computed the lGI at each vertex. This 3D approach of analyzing gyrification takes into account buried sulcis, is not restricted by sulcal walls and takes into consideration the significant variations of lGIs across all sulco-gyral regions of the cortex (Schaer *et al.* 2008). The automatic lGI computation (Schaer *et al.* 2012) involves: the creation of an outer surface (the smoothed pial surface), creation of 800 ROIs on this surface and their corresponding ROIs on

the pial surface. This results in calculation of individual maps, which contain one lGI value for each vertex on the cortical surface. The lGI can have a value ranging between 1 (flat) and 5 (i.e. there is five times more cortical surface buried in sulci than visible cortex in the surrounding area). The individual lGIs were projected on a sample specific template (average subject) and smoothed using a Gaussian kernel of 10 mm.

Statistical analysis

Using the framework of the general linear modeling (GLM) we assessed the regional differences of lGIs between patients and controls at the level of each vertex for each hemisphere separately and included age, gender and scanner type (i.e. Siemens *v*. Philips) as covariates to correct for potential confounding effects. To correct for multiple comparisons across the whole brain, Monte Carlo simulations (Hagler *et al.* 2006) with 10 000 iterations were performed in order to identify significant contiguous clusters of vertex-wise group differences ($p < 0.05$).

Further statistical analyses were performed using the Statistical Package for Social Sciences [SPSS Inc. (2002), version 11.5.1, USA]. Differences in age and gender were assessed using the χ^2 test. The potential association between lGI alterations and clinical parameters (symptom severity: YBOCS total, obsessions and compulsion scores; age of onset) was assessed using multiple linear regression with symptom severity and age of onset as predictors and mean lGI values of the brain regions that were identified as significantly different between the groups as criterion and age, gender and scanner as covariates. The regression analyses were done separately for each hemisphere. In case of a significant relationship the corresponding partial correlation coefficient was reported.

To control for the potential confounding effect of the two scanner types (Siemens *v*. Phillips) and their different sequences, besides taking scanner type as a covariate in the GLM analysis, we also performed a whole-brain lGI comparison between the two scanner groups.

In addition, to control for the effect of medication and co-morbidity we first performed a whole-brain lGI analysis (GLM) comparing medicated *v*. unmedicated patients as well as co-morbidity-free *v*. co-morbid patients with age, gender and scanner type as covariates.

Moreover, to evaluate if medication or co-morbidity affected lGI differences between patients and healthy controls we furthermore performed two MANCOVAs with average lGI values (extracted from the clusters found to be different between patients and controls) as dependent variables, medication or co-morbidity status as independent variables, and age, gender and scanner as covariates.

Results

Differences in gyrification

Whole-brain lGI analysis revealed two clusters in the right hemisphere consistently showing a decreased gyrification (hypogyria) in OCD patients compared to controls. The first cluster (cluster 1 in Table 2) showing a significantly reduced lGI ($p < 0.01$) extended from inferior parietal, superior parietal to supramarginal, post-and precentral and superior frontal areas. The second cluster (cluster 2 in Table 2) showing a significantly reduced lGI ($p < 0.05$) contained insula, superior- and transverse- temporal areas, pars opercularis, pars triangularis, rostral middle frontal and lateral orbitofrontal regions (for details see Fig. 1 and Table 2). The left hemisphere showed no differences in lGI between the groups. No clusters with increased gyrification were noted in patients. Annotation of clusters is according to the Desikan–Killiany Freesurfer atlas (aparc.annot).

Effects of medication, co-morbidity and scanner sequence

The whole-brain lGI GLM analysis revealed no significant differences between medicated and unmedicated patients or between co-morbid and co-morbidity-free patients. Furthermore, the results of the MANCOVA showed that the lGI alterations were not influenced by medication status (medicated *v*. unmedicated patients, cluster 1: $F = 0.238$, $p = 0.788$, cluster 2: $F = 0.878$, $p = 0.418$) or presence of co-morbidity (co-morbid *v*. co-morbidity-free patients, cluster 1: $F = 0.243$, $p = 0.785$, cluster 2: $F = 0.859$, $p = 0.426$). Moreover, no significant differences in lGI between the data from the different scanner types of the two centers could be found.

Gyrification and clinical variables

The regression analysis revealed that in OCD patients altered gyrification (lGI values extracted from the clusters showing a significant alteration in patients *v*. controls) was not associated with any of the symptom severity scores (YBOCS total, obsessions or compulsions). The second regression analysis revealed that age of onset was positively associated ($\beta = 0.27$, $T = 2.35$, $p = 0.02$; partial correlation $r = 0.28$, $p = 0.02$) with the average lGI in the second cluster (see Table 2 and Fig. 1) in the right hemisphere including insula, superior- and transverse- temporal areas, pars opercularis, pars triangularis, rostral middle frontal and lateral orbitofrontal regions. This association remained significant also after Bonferroni correction.

Table 2. *Brain regions with significant group differences in local Gyrification Index (lGI). Clusters with a significantly decreased lGI in OCD patients compared to healthy subjects in the right hemisphere after clusterwise correction for multiple comparisons using Monte Carlo simulation ($p < 0.05$)*

				Talairach MNI						
Cluster	Max *T* value	VtxMax	Cluster size (mm^2)	x	y	z	CWP(*p*)	CWPLow	CWPHi	NVtxs
1	−2.878	76 752	6767.15	29.3	−27.4	56.6	0.00190**	0.00140	0.00250	14 849
2	−2.024	67 892	4297.08	30.6	18.2	9.6	0.02550*	0.02350	0.02750	8510

VtxMax, Number of peak vertex of the significant cluster; CWP, cluster-wise probability and the nominal *p* value; CWPLow, CWPHi – the 90% confidence intervals of the *p* value; NVtx, number of vertices in cluster; *$p < 0.05$, **$p < 0.01$.

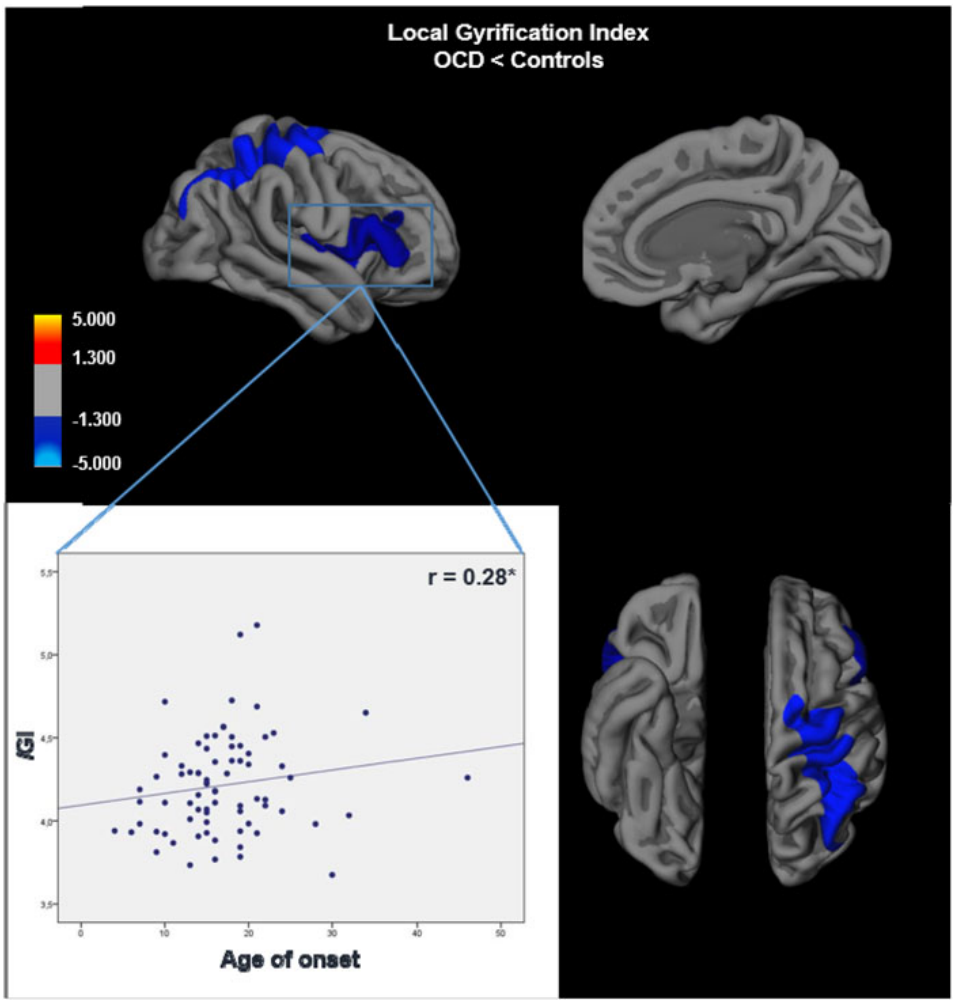

Fig. 1. Group difference in local Gyrification Index (lGI). Shown are clusters with significantly decreased lGI of the right hemisphere in OCD patients. The clusters are displayed on the pial surface of the participants' average brain (lateral, medial, inferior and superior view). The color bar indicates the *t* value after clusterwise correction for multiple comparisons using Monte Carlo simulations ($p < 0.05$). The scatterplot represents the significant positive association between age of onset and mean lGI of cluster 2.

Discussion

The present study which investigated whole-brain lGI in patients with OCD revealed that, compared to healthy controls, OCD patients showed a decreased gyrification in several cortical areas. These morphological alterations were not associated with symptom severity, medication status or co-morbidity although there was a positive association with age of onset.

Hypogyrification in OCD

Our results partly confirm previous findings which reported also hypogyrification in OCD (Shim *et al.* 2009; Wobrock *et al.* 2010), although they used a ROI-based approach and employed slightly different methods in calculating gyrification by either using the automated-gyrification index (Moorhead *et al.* 2006) or employing a manual 2D segmentation (Van Essen & Drury, 1997) instead of an automatic 3D approach.

When relating our findings to the existing OCD studies that are methodologically more comparable to ours [i.e. studies assessing the lGI as proposed by Schaer *et al.* (2008)] such as a study by Venkatasubramanian *et al.* (2012) one notices rather divergent results. Thus, Venkatasubramanian and colleagues found no overall gyrification differences but an association between reduced lGI and increased symptom severity. It should be noted, however, that they employed a ROI based lGI approach and studied medication naive patients whereas we employed a whole-brain lGI analysis and our sample was partly medicated.

Our results moreover contradict the results by Fan *et al.* (2013) who studied, however, unmedicated and co-morbidity-free patients. Fan and colleagues reported altered gyrification in similar regions but in the opposite direction (i.e. they found an increased gyrification in OCD patients compared to controls). As mentioned above, neither medication nor co-morbidity which affected a certain percentage of our patients had a statistically significant influence. Nevertheless, a certain influence of medication and co-morbidity cannot be excluded which might explain the contrary findings.

Overall, comparability between the current study and the existing literature must be regarded as rather limited, mainly due to differences in methodology and clinical characteristics of the sample. From this perspective, a generalization of the results seems premature and, likewise, one can only speculate about the processes and mechanisms underlying altered cortical folding in OCD.

There are several theories regarding the driving force of cortical folding which are discussed in a review paper of Zilles *et al.* (2013), but recent research on the mechanistic processes underlying cortical folding leave a number of open questions (Stahl *et al.* 2013; Tallinen *et al.* 2014, 2016).

One established theory about the driving force of cortical folding assumes that cortical folding is the consequence of too many neurons restricted in a confident space, causing tension along WM axons (Van Essen, 1997). Somewhat in accordance with this theory, previous OCD studies showed widespread alterations in WM fiber bundles (Piras *et al.* 2013; Koch *et al.* 2014), with alterations in pathways targeting the orbitofrontal areas, but also consistent anatomical connectivity alterations between intra-hemispheric lateral frontal and parietal regions. Considering that the present study showed hypogyrification in proximal areas of the right hemisphere, one could speculate that a disrupted fiber integrity going along with a lower tension along these fiber bundles may result in a lower gyrification of connected brain regions.

Structural alterations linked to gyrification

On the one hand, it is known that cortical folding relates to and depends on several other structural measures, such as GM volume, surface area or cortical thickness (Raznahan *et al.* 2011). These measures have been repeatedly shown to be altered in OCD with cortical volume reductions affecting mainly OFC, ACC and temporo-limbic areas (Piras *et al.* 2015). Moreover, a recent mega-analysis also showed a reduction of both GM and WM in various frontal regions, the ACC and the insula (De Wit *et al.* 2014). Results also showed that patients lose more volume in temporal cortex with age compared to healthy subjects. In the present study parts of these areas, which were already known to show structural alterations in OCD were also affected by a decreased lGI. One could speculate that the lGI is altered already during early development and this, in turn, may favor structural alterations found in patients at a later age.

Alterations in the temporal course of development

On the other hand it has been shown that all these structural measures develop and change at their own pace, reaching their morphological maturation at different ages (Raznahan *et al.* 2011). One could assume that a certain delay in the maturational process of one morphological measure will lead to a delay in others, given that the single measures are not completely independent from each other. Furthermore, structural morphology studies in pediatric OCD patients showed structural alterations in subcortical regions in children/adolescents while alterations in more cortical regions could be observed in adult OCD patients (Huyser *et al.* 2009). This review article suggested that structural alterations in adulthood may be related to alterations already present in early childhood and discussed the possibility of a 'migration of pathology' during the course of the disorder. Our results reveal cortical alterations in adult patients with OCD and confirm partly previous results, although more longitudinal studies are needed to confirm this pathology migration hypothesis.

Moreover, studies in healthy individuals show that the lGI is slightly decreasing during adolescence in precentral, temporal and frontal areas (Klein *et al.* 2014). After correcting for age, we could also find similar regions to be significantly reduced in OCD. This can lead to the assumption that, if alterations occurred, they could also be related to an altered developmental pace leading to a decreased overall gyrification in OCD patients compared to healthy subjects. Unfortunately, most results are based on cross-sectional studies up to know, and longitudinal or pediatric studies on brain gyrification in OCD to test this hypothesis are still missing.

General hypogyrification in psychiatric disorders

Interestingly, hypogyrification has been found also in several other psychiatric disorders, some of them known to have a neurodevelopmental predisposition (Zhang *et al.* 2009; Yoon *et al.* 2013; Nanda *et al.* 2014; Nixon *et al.* 2014). Furthermore, it is known that there are similarities between OCD and other psychiatric disorders in terms of circuitries and systems which are presumed to be psychopathologically relevant (e.g. alterations within fronto-striatal circuits in schizophrenia and OCD, altered serotonin/dopamine system in schizophrenia and OCD) as well as a high co-occurrence rate (Tibbo & Warneke, 1999; Bradshaw & Sheppard, 2000). It seems plausible to assume that similar patterns in neurobiology underlie these clinical commonalities between the disorders with altered cortical folding constituting an important common feature characterizing different psychiatric disorders.

Gyrification and clinical characteristics

There was no association between altered *l*GI and clinical scores (i.e. symptom severity) although such associations (i.e. symptom severity, disorder insight) had been previously reported by other OCD gyrification studies (Wobrock *et al.* 2010; Venkatasubramanian *et al.* 2012; Fan *et al.* 2013).

Our results go more in line with neurodevelopmental theories by supporting the assumption that lGI could be considered as a rather stable marker of early neurodevelopment, whereas symptoms are known to dynamically change over time. This lets us speculate that, whereas symptomatology may represent a state marker of the disorder, hypogyrification may indeed constitute a trait characteristic of OCD.

This speculation is also supported by the positive association between age of onset and extent of gyrification alterations in the second cluster containing mainly insular – lateral frontal areas indicating that stronger alteration in gyrification goes along with an earlier age of onset. This finding underlines once more the clinical relevance of these structural alterations and indicates that the degree of folding alterations may represent a neurodevelopmental marker predisposing for an earlier manifestation of the disorder, if we consider cortical folding a measure which remains stable after early childhood.

On the other hand, the above mentioned review by Piras *et al.* (2015) suggests that potential relationships between clinical variables and observed morphological alterations in OCD are rather heterogeneous. Moreover, this review underlines the fact that previous findings which do find significant associations could be triggered by multiple other factors as co-morbid illness or medication use and may even be driven by progressive changes evolving in dynamic trajectories during illness course or merely by the phenotypic heterogeneity of OCD.

Therefore, it is crucial to keep in mind that our knowledge about the influence of disorder onset or progression as well as treatment on brain morphology is still very limited. Thereby, the possibility that cortical alterations occur later in life, potentially as a result of these influencing factors, cannot be ruled out. Hence, further studies, ideally longitudinal designs based on large samples allowing for a stratification of clinical symptoms, are strongly needed to increase our understanding of these mechanisms and relationships regarding the cortical folding and its changes over time.

The current results need also to be viewed in light of certain limitations, i.e. co-morbidities and medication may have influenced our results and their generalizability to some extent. On the other hand, the rather large sample size of 150 participants in total ensures reasonable power and generalizability. Our attempts to control for these confounding effects revealed no significant influence of these variables on our results. It should be noted that these findings need to be interpreted with caution as other OCD studies indicate that medication (e.g. SSRIs) seems to reduce structural brain differences (in terms of GM volume) between healthy controls and patients (Hoexter *et al.* 2012). However, there are no systematic studies on the effects of SSRI treatment on cortical folding and there is little understanding of how medication influences brain morphology in OCD (Atmaca, 2013). But keeping in mind that morphological characteristics (i.e. volume, thickness, surface area, cortical folding) are linked in their development (Raznahan *et al.* 2011; Mills & Tamnes, 2014) and alterations in one characteristic might also affect the other parameters, an indirect effect on cortical folding seems plausible. Moreover, animal research demonstrated that modulations in serotonergic neurotransmission by SSRIs mediate neuroplasticity (neurogenesis and gliogenesis) in various

cortical and subcortical structures involved in OCD (Kodama *et al.* 2004). Hence, more systematic longitudinal studies are needed to clarify potential effects of medication on cortical folding in OCD.

As a final remark it should be mentioned that the hypogyrification found in the present study might not by itself be the core characteristic of the disorder. Altered cortical folding may be at most one aspect of a complex conglomerate with potential alterations at a functional, structural and cellular level.

Conclusion

In summary, our results of hypogyrified areas in OCD point towards disturbances in cortical brain surface and partly confirm previous findings in OCD patients as well as findings in related psychiatric disorders. Longitudinal studies are needed to reveal if such alterations occur due to different developmental pace or variations in time-point of cortical maturation.

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Declaration of Interest

None.

References

Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K (1995). The ontogeny of human gyrification. *Cerebral Cortex* **5**, 56–63.

Atmaca M (2013). The effects of psychopharmacologic and therapeutic approaches on neuro-imaging in obsessive-compulsive disorder. *Current Neuropharmacology* **11**, 109–113.

Bradshaw JL, Sheppard DM (2000). The neurodevelopmental frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization. *Brain and Language* **73**, 297–320.

De Wit SJ, Alonso P, Schweren L, Mataix-Cols D, Lochner C, Menchon JM, Stein DJ, Fouche JP, Soriano-Mas C, Sato JR, Hoexter MQ, Denys D, Nakamae T, Nishida S, Kwon JS, Jang JH, Busatto GF, Cardoner N, Cath DC, Fukui K, Jung WH, Kim SN, Miguel EC, Narumoto J, Phillips ML, Pujol J, Remijnse PL, Sakai Y, Shin NY, Yamada K, Veltman DJ, Van den Heuvel OA (2014). Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. *American Journal of Psychiatry* **171**, 340–349.

Fan Q, Palaniyappan L, Tan L, Wang J, Wang X, Li C, Zhang T, Jiang K, Xiao Z, Liddle PF (2013). Surface anatomical profile of the cerebral cortex in obsessive-compulsive disorder: a study of cortical thickness, folding and surface area. *Psychological Medicine* **43**, 1081–1091.

Fischl B, Dale AM (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences USA* **97**, 11050–11055.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry* **46**, 1006–1011.

Hagler Jr. DJ, Saygin AP, Sereno MI (2006). Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. *NeuroImage* **33**, 1093–1103.

Hoexter MQ, De Souza Duran FL, D'alcante CC, Dougherty DD, Shavitt RG, Lopes AC, Diniz JB, Deckersbach T, Batistuzzo MC, Bressan RA, Miguel EC, Busatto GF (2012). Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. *Neuropsychopharmacology* **37**, 734–745.

Huyser C, Veltman DJ, De Haan E, Boer F (2009). Paediatric obsessive-compulsive disorder, a neurodevelopmental disorder? Evidence from neuroimaging. *Neuroscience and Biobehavioral Reviews* **33**, 818–830.

Klein D, Rotarska-Jagiela A, Genc E, Sritharan S, Mohr H, Roux F, Han CE, Kaiser M, Singer W, Uhlhaas PJ (2014). Adolescent brain maturation and cortical folding: evidence for reductions in gyrification. *PLoS ONE* **9**, e84914.

Koch K, Reess TJ, Rus OG, Zimmer C, Zaudig M (2014). Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): a review. *Journal of Psychiatric Research* **54**, 26–35.

Kodama M, Fujioka T, Duman RS (2004). Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. *Biological Psychiatry* **56**, 570–580.

Magnotta VA, Andreasen NC, Schultz SK, Harris G, Cizadlo T, Heckel D, Nopoulos P, Flaum M (1999). Quantitative *in vivo* measurement of gyrification in the human brain: changes associated with aging. *Cerebral Cortex* **9**, 151–160.

Mills KL, Tamnes CK (2014). Methods and considerations for longitudinal structural brain imaging analysis across development. *Developmental Cognitive Neuroscience* **9**, 172–190.

Moorhead TW, Harris JM, Stanfield AC, Job DE, Best JJ, Johnstone EC, Lawrie SM (2006). Automated computation of the Gyrification Index in prefrontal lobes: methods and comparison with manual implementation. *NeuroImage* **31**, 1560–1566.

Nanda P, Tandon N, Mathew IT, Giakoumatos CI, Abhishekh HA, Clementz BA, Pearlson GD, Sweeney J, Tamminga CA, Keshavan MS (2014). Local gyrification index in probands with psychotic disorders and their first-degree relatives. *Biological Psychiatry* **76**, 447–455.

Nixon NL, Liddle PF, Nixon E, Worwood G, Liotti M, Palaniyappan L (2014). Biological vulnerability to depression: linked structural and functional brain network findings. *British Journal of Psychiatry* **204**, 283–289.

Piras F, Piras F, Caltagirone C, Spalletta G (2013). Brain circuitries of obsessive compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies. *Neuroscence andi Biobehavioural Reviews* **37**, 2856–2877.

Piras F, Piras F, Chiapponi C, Girardi P, Caltagirone C, Spalletta G (2015). Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex* **62**, 89–108.

Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, Clasen L, Gogtay N, Giedd JN (2011). How does your cortex grow? *Journal of Neuroscience* **31**, 7174–7177.

Rosenberg DR, Keshavan MS (1998). A.E. Bennett Research Award. Toward a neurodevelopmental model of of obsessive--compulsive disorder. *Biological Psychiatry* **43**, 623–640.

Saxena S, Rauch SL (2000). Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatric Clinics of North America* **23**, 563–586.

Schaer M, Cuadra MB, Schmansky N, Fischl B, Thiran JP, Eliez S (2012). How to measure cortical folding from MR images: a step-by-step tutorial to compute local gyrification index. *Journal of Visualized Experiments* **59**, e3417.

Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran JP (2008). A surface-based approach to quantify local cortical gyrification. *IEEE Transactions on Medical Imaging* **27**, 161–170.

Shim G, Jung WH, Choi JS, Jung MH, Jang JH, Park JY, Choi CH, Kang DH, Kwon JS (2009). Reduced cortical folding of the anterior cingulate cortex in obsessive-compulsive disorder. *Journal of Psychiatry and Neuroscience* **34**, 443–449.

Stahl R, Walcher T, De Juan Romero C, Pilz GA, Cappello S, Irmler M, Sanz-Aquela JM, Beckers J, Blum R, Borrell V, GotZ M (2013). Trnp1 regulates expansion and folding of the mammalian cerebral cortex by control of radial glial fate. *Cell* **153**, 535–549.

Tallinen T, Chung JY, Biggins JS, Mahadevan L (2014). Gyrification from constrained cortical expansion. *Proceedings of the National Academy of Sciences USA* **111**, 12667–12672.

Tallinen T, Chung JY, Rousseau F, Girard N, Lefevre J, Mahadevan L (2016). On the growth and form of cortical convolutions. *Nature Physics* **12**, 588–593.

Tibbo P, Warneke L (1999). Obsessive-compulsive disorder in schizophrenia: epidemiologic and biologic overlap. *Journal of Psychiatry and Neuroscience* **24**, 15–24.

Van Essen DC (1997). A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* **385**, 313–318.

Van Essen DC, Drury HA (1997). Structural and functional analyses of human cerebral cortex using a surface-based atlas. *Journal of Neuroscience* **17**, 7079–7102.

Venkatasubramanian G, Zutshi A, Jindal S, Srikanth SG, Kovoor JM, Kumar JK, Janardhan Reddy YC (2012). Comprehensive evaluation of cortical structure abnormalities in drug-naive, adult patients with obsessive-compulsive disorder: a surface-based morphometry study. *Journal of Psychiatric Research* **46**, 1161–1168.

Wobrock T, Gruber O, Mcintosh AM, Kraft S, Klinghardt A, Scherk H, Reith W, Schneider-Axmann T, Lawrie SM, Falkai P, Moorhead TW (2010). Reduced prefrontal gyrification in obsessive-compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience* **260**, 455–464.

Yoon S, Jun CS, Jeong HS, Lee S, Lim SM, Ma J, Ko E, Cho HB, Yeum TS, Lyoo IK (2013). Altered cortical gyrification patterns in panic disorder: deficits and potential compensation. *Journal of Psychiatric Research* **47**, 1446–1454.

Zhang Y, Yu C, Zhou Y, Li K, Li C, Jiang T (2009). Decreased gyrification in major depressive disorder. *Neuroreport* **20**, 378–380.

Zilles K, Palomero-Gallagher N, Amunts K (2013). Development of cortical folding during evolution and ontogeny. *Trends in Neuroscience* **36**, 275–284.

Part III.

General Discussion

10. Overall Key Results

Prior work has suggested that besides the involvement of the CSTC circuit in OCD, limbic areas such as the amygdala may play a crucial role in the neurobiological mechanism of the disorder (Milad & Rauch, 2012). Aberrant amygdala activation was mostly detected in the context of symptom provocation (Breiter & Rauch, 1996; Simon et al., 2014). Although overall findings suggested that in OCD aberrant activation could affect the connectivity within a broader network, almost no study has investigated the limbic connectivity during symptom provocation.

The first study presented in Chapter 7 (Rus et al., 2017a) explored this by analyzing the association between functional and structural connectivity of limbic areas in a multimodal way. This study results fulfilled one of the aims of this work by further elucidating the role of the amygdala during symptom provocation in OCD. In this first study, we found that while OCD patients were exposed to negative affective stimuli, the amygdala showed increased functional connectivity with parieto-occipital areas. Overall, results suggested a hyper-connectivity of emotional processing areas with areas mainly responsible for attention processing and control in OCD patients compared to healthy subjects. Most importantly, we detected an association between this altered functional connectivity in patients and the structural connectivity of underlying white matter tracts (i.e., parts of the ILF). The clinical relevance of these findings for OCD was moreover substantiated by a significant correlation between symptom severity and white matter tract integrity. In other words, an increase in symptom severity was associated with a reduced white matter tract integrity of these specific tracts.

Another aspect rendering the present thesis rather innovative is related to the fact that most of the structural OCD studies evaluating gray matter properties analyzed volume or thickness in a unimodal way, with partly inconsistent results. These studies used methods (e.g., VBM) which are known to have certain drawbacks (Helms, 2016; Piras et al., 2015). Thus, it has been suggested that changes in these measures could be influenced by changes in other properties of gray matter, such as surface area or cortical folding, making a clear interpretation of these results rather difficult.

Using a surface based approach, which allows for an independent measurement of different GM properties (e.g., by accounting for cortical surface convolutions when estimating volume), in the second study (Rus et al., 2017b) (Chapter 8) we analyzed various measures of GM

concurrently and created a cortical anatomical profile in a large sample of OCD patients. We found that in OCD patients, parieto-occipital regions were characterized by a significant reduction in both GM volume and surface area, and results indicated a potential link to different clinical symptoms. Remarkably, the surface area alterations seemed to affect a more extended network including rostral middle frontal, temporal and precuneus areas. Besides being one of the few studies using a surface based approach in a relatively large patient sample, these results highlight the relevance of parieto-occipital areas in OCD, by expanding the findings of the first study and providing new insights about their morphological properties. Thus, these findings fulfill the second aim of this thesis.

The third study presented in Chapter 9 focused on the frequent assumption that partly overlapping structural and functional brain alterations in OCD might be driven by early neurodevelopmental factors which might increase the vulnerability for the disorder (Rosenberg & Keshavan, 1998). Newer methods allow for an easy and economic evaluation of gyrification as a reliable indicator for early brain development. Alterations in gyrification have barely been explored in OCD up to now, although changes in this cortical measure were found in several other psychiatric disorders which share to some degree similar biological patterns (Hirjak et al., 2015; Nordahl et al., 2007; Shaw et al., 2012). Accordingly, our third study (Rus et al., 2016) thus evaluated gyrification in a big sample of OCD patients and found an overall "hypogyrified" brain, which was linked to an earlier age of onset. Affected regions involved mainly parietal areas, but they also included precentral motor areas and insula, temporal and middle frontal regions. These results further confirm the importance of parietal areas for OCD, reflected in an impaired cortical folding, which could, in turn, go along with an increased vulnerability for the disorder. Overall, the findings suggest that neurodevelopmental risk factors may play a role in OCD.

11. Integrating Results into the OCD Literature

Collectively, the contribution of the presented publications can be summarized in three main points.

First, from an anatomical perspective, there is one region that stands out from all three studies, namely, the parieto-occipital cortex. Alterations in these areas underscore their relevance for OCD and the often-proposed extension of the neurobiological disorder model.

Second, from a general brain pattern perspective visualized in the surface anatomical profile, all of our studies bring evidence for an overall alteration in brain morphology in OCD. This manifest itself in an overall reduction of gray matter, mirrored in various cortical measures.

Third, from a methodological perspective, using mostly multimodal approaches by concurrently analyzing various measures and associating them with each other, our results provide direct evidence for a link between functional and structural alterations in OCD. The observed connectivity disturbances in a broad circuit and on several levels (function, structure, connectivity), speak in favor of alterations at a network level in OCD.

These integrative results will be further discussed in the light of previous research findings.

11.1. Importance of Parietal Areas for the OCD Neurobiological Model

The first conclusion from this work is consistent with the indication of a previous systematic review by Menzies et al. (2008) and the meta-investigations by Eng et al. (2015), which also suggested a revision of the CSTC model in OCD (in terms of an extension by parietal areas).

With respect to the function of these apparently relevant brain areas for OCD, our results expand the findings of prior works (Menzies et al., 2008; Okasha et al., 2000). These previous studies suggested an involvement of these regions in attentional shifting, planning, and response inhibition and corresponding impairments in these processes in OCD. However, our results additionally indicate an aberrant functional connectivity between limbic and parietal areas during negative affective processing (i.e., symptom provocation) (Rus et al., 2017a).

A good overview over the altered areas found in the presented studies can be found in Figure 11.1, left boxes, study 1 in Section 11.3.3.

Therefore, it is important to note that in this symptom provocation context, parietal areas showed no regional activation disturbances. Instead, the disturbance was based on a malfunctioning interaction with limbic areas. Thus, it can be speculated that, by this erroneous communication, the initially isolated functions of these regions (i.e., emotional processing and attention processing), could have been affected. Consequently, these disruptions might as well be linked with the maladaptive behavior encountered in patients in such contexts (e.g., compulsions involving negative emotions such as anxiety or attentional biases such as a highly restricted cognitive focus on feared stimuli).

Interestingly, a recent review has pointed out that WM tracts that pass through parietal regions or terminate there (such as ILF and IFOF which connect relevant nodes of the OCD circuitry), also show structural alterations (Piras et al., 2013). These alterations could be represented by altered white matter integrity or connectivity. However, probably due to the restrictive analysis used in our first study (Rus et al., 2017a) in Chapter 7(i.e., the ROI based approach integrated in the sequential data analysis method), the results did not reveal this difference in WM. Nevertheless, some associations between increase in symptom severity and reduction in WM integrity did point out the clinical relevance of these structural characteristics.

A compelling result was found in our second study (Rus et al., 2017b)(Chapter 8), where parietal areas of patients were affected by reductions in surface area and volume, see also Figure 11.1, right boxes, study 2 in Section 11.3.3.

These results are consistent with similar studies in OCD, which were summarized in the review of Piras et al. (2015). In that review alterations in OCD were suggested to occur, among others, in the executive network including as well posterior brain regions such as parts of the parietal

cortex. Moreover, this review concluded that given that these morphometric alterations in parietal areas have been found to be related to symptom severity, they might also be considered as markers of disease severity or even progression. Our study results could not confirm these associations with clinical scores, i.e., there were associations only at an uncorrected threshold. When viewed as a whole, the first two studies (Rus et al., 2017a, 2017b)(Chapter 7, Chapter 8) indicate that if parietal areas do show functional as well as structural disturbances, these alterations on various levels might be linked. Hence, disturbances on a basic level (e.g., structure), might trigger or promote disturbances on higher levels (e.g., function), hence working as a self-potentiating system. As a consequence, this overall disrupted system might contribute to some degree to the manifestation of OCD symptoms.

Based on brain maturation or development of brain cortical structure, it is likely that an aberrant function might be linked to, or even caused by, an already altered structure. This conception would go in line with the assumption that these structural alterations occurred early in brain development. However, as there is evidence that some morphological properties can be affected by external factors also during the course of life, such as medication or environmental influences, the opposite interaction might also be possible.

Notably, as our analyses do not provide any directional information present results concur with evidence for both assumptions, especially with respect to specific brain areas such as parietal regions in OCD.

On the one hand, the results from our third study (Rus et al., 2016) (Chapter 9) seem to rather support the first hypothesis, given evidence of alterations in the gyrification index. The compelling finding that parts of superior and inferior parietal cortex were also affected by a reduction in gyrification allows the speculation that in OCD at least parts of these encountered structural alterations were already present in very early stages of brain development (see also Section 11.3.3, Figure 11.1, right boxes, study 3). This suggests that structural alterations in areas involving parietal regions may have occurred before disorder onset, and, thus, these alterations might even constitute a vulnerability marker for OCD.

On the other hand, both first studies (Rus et al., 2017a, 2017b)(Chapter 7, Chapter 8) add additional indicators for the influence of medication and comorbidities on functional connectivity on aberrant GM volume and surface area of parietal areas, albeit at uncorrected thresholds. These findings are not surprising as they are also supported by previous research (Piras et al., 2015). However, the extent or the exact mechanism in terms of how these brain characteristics may be influenced still remains unknown. Moreover, considering the hetero-chronous development of brain areas, posterior regions such as the parietal cortex are one of the first to develop after the occipital cortex (Zilles et al., 2013). It is striking that our results show precisely these relatively early developing areas to be affected in terms of function and structure.

In sum, the results from the three studies presented here highlight the importance of parietal

areas in OCD pathophysiology by revealing functional as well as structural alterations, and also by indicating probable links between these impairments. These results further suggest an implication of parietal areas in a more complex network of associated areas in the disorder model. However, the causal association between these interactions is still a matter of debate and needs further investigation.

11.2. Altered Cortical Morphology in OCD

The results of the second and third study in Chapter 8 and Chapter 9 (Rus et al., 2017b, 2016) provide compelling evidence for an overall reduced GM morphology in OCD, encountered in a widespread network of the cortical mantle (see also Section 11.3.3, Figure 11.1, boxes study 2 and study 3) and in various measures of GM, such as volume, surface area and gyrification. When comparing the findings to previous studies, however, several factors need to be considered, namely: *first*, the heterogeneity in terms of study design involving sample sizes, which tend to strongly vary; *second*, sample characteristics such as symptom dimensions and severity, presence of comorbidities or use of medication, which also tend to vary and which are known to influence, to a certain degree GM structure; *third*, methodological differences such as different analysis methods (e.g. VBM or SBA, ROI vs. whole brain analyses) or varying statistical correction approaches. These are only few of the major differences between existing studies, which make comparisons challenging.

11.2.1. Comparison with Methodological Different Studies

Compared to VBM studies, we confirmed the recent review by Piras et al. (2015) by showing overall GM reduction at the cortex level in parts of the executive circuitry (as already mentioned in the previous section). However, as we did not analyze subcortical regions, we could not replicate subcortical tissue expansions, as reported by Piras et al. (2015). Although these previous studies brought evidence for associations with clinical scores, the morphological alterations found in our study were associated with symptom severity on an uncorrected threshold only.

In contrast to a recent VBM mega-analysis (de Wit et al., 2014), our results revealed a rather focused volume reduction in the mentioned parietal regions, whereas the surface area reduction was more expanded, involving also rostral middle frontal regions. We could, however, not find any alterations in cerebellar and prefrontal areas as described in this mega-anaysis. Some of this divergence might be explained by methodological differences, i.e., as discussed before the volume measured by VBM could be confounded by alterations in other GM measures. Nevertheless, another important difference to our study is the large sample size of the mega-analysis which goes along with a significantly larger detection power.

With regard to VBM studies it is important to keep in mind that these studies evaluate mostly cortical volume or GM density, but rarely thickness. As it has been shown that these measures represent a conglomerate of surface area, gyrification and thickness (Hutton et al., 2008, 2009), it can be assumed that some of these previous studies cannot determine if differences in GM volume or density are influenced by alterations in the other GM properties. Hence, it is possible

that this methodological difference in estimating GM could have contributed, to a certain degree, to the deviation from our results.

11.2.2. Comparison with Methodological Similar Studies

Given the current state of the art it is difficult to make a clear statement about which of the GM measurements is most appropriate to detect changes in early brain development or during life time. Nevertheless, by employing an SBA approach the results from our two studies (Rus et al., 2017b, 2016) provide a detailed insight into various measurements of GM (see Chapter 8, Chapter 9). Hence, by collecting information about all measures concurrently and finding out which of them is affected in OCD, present results might enable future studies to restrict the localisation of GM alterations in OCD to specific brain regions. Accordingly, current results show links between various GM measures, and further stress the need for a combined evaluation of several GM measures to gain a more solid view on the encountered alterations (Palaniyappan & Liddle, 2012).

It is worth mentioning that the study (Rus et al., 2017b) in Chapter 8 is only the third SBA study to evaluate all measurable properties of GM in OCD concurrently. We partly confirmed the findings of the other two previously published studies (Q. Fan et al., 2013; Venkatasubramanian et al., 2012), specifically in terms of the affected regions. However, it should be noted that there are also inconsistencies between these previous studies with regard to the direction of alteration and the GM measure found to be affected. In this respect, we found similar regions to be affected as Q. Fan et al. (2013), i.e., rostral middle frontal, temporo-insular and inferior parietal areas. However, while they provided evidence for increased thickness and gyrification in these areas and no differences in surface area in OCD patients, we found a reduction in volume, surface area and gyrification in similar regions with no differences in thickness. Therefore, while the affected areas partly overlap, the affected GM measures and their exact direction of alterations clearly diverge between our study and this previous one.

As compared to the other study by Venkatasubramanian et al. (2012) which also assessed all GM measures concurrently, we could confirm the overall reduction in surface area and volume, although we found different regions to be affected. Moreover, we could not find any thickness differences. In contrast to this study we brought additionally evidence for reductions in gyrification presented in study three (Rus et al., 2016) from Chapter 9.

The partly distinct results among these three studies might be explained by the difference in sample characteristic between the studies. For example, whereas the majority of our patients were medicated, the other two studies included either medication-naive (Venkatasubramanian et al., 2012) or unmedicated patients (Q. Fan et al., 2013).

Another striking fact is that our results revealed differences in almost all GM measures, besides

thickness. In comparison, previous SBA studies mostly evaluated cortical thickness and found reductions in this specific GM measure in OCD patients (Fouche et al., 2017; Kuhn et al., 2013; Nakamae et al., 2014; Shaw et al., 2012; Shin et al., 2007).

In this respect, it is undeniable that it would be premature to derive a clear picture from existing findings on GM morphology in OCD. Even more, when looking at the literature about the exact development and interrelation of these GM measures in healthy individuals, it becomes clear that up to now very little is known. This makes a transfer to the clinical relevance of morphological alterations in psychiatric populations in general even more challenging.

11.2.3. The GM Measures and their Associations

Measures such as GM thickness and surface area are genetically and phenotypically independent and can influence GM volume to a significant degree (Panizzon et al., 2009; Winkler et al., 2010). Moreover, from longitudinal studies of brain development, there are indications that the potential interactions between these measures (i.e., developmental changes in GM volume) emerge through gender- and age - dependent interactions of changes in GM thickness and surface area (Raznahan et al., 2011). Further, these studies reveal as well that changes in surface area, reflect the complex interaction between the exposed cortical area during changes in brain size and the changes in the degree of cortical gyrification.

A more recent longitudinal study (Tamnes et al., 2017) revealed that during the course of life the cerebral cortex shows widespread and regionally variable nonlinear decreases in volume and thickness with increasing age, whereas the decrease in surface area is comparatively smaller and steadier. This study also showed that during adolescence, cortical thinning appears to be the main contributor to cortical volume reductions. Thus, they concluded that the regional and topological patterns in the interaction between long-term changes in thickness and surface area are very complex.

Overall, it seems that interactions among GM measures occur during brain maturation, but also later during the course of life. However, the exact interrelations are still unknown. Additionally, the cellular and molecular mechanisms behind these developmental changes in brain morphology remain unexplored. These gaps in knowledge might thus explain the yet heterogeneous literature, specifically when it comes to non-healthy populations. Unfortunately, there is little literature on how external factors (e.g., disorders or medication) affect brain morphology. This underlines the need of further longitudinal studies especially in the field of psychiatric illnesses to better understand the present results.

Importantly, findings on alteration of brain morphology in other psychiatric disorders such as anxiety disorders (Hilbert et al., 2015), depression (Schmaal et al., 2016) or schizophrenia (Dietsche, Kircher, & Falkenberg, 2017; Palaniyappan & Liddle, 2012) support, to some extent,

our results. Besides the fact that these disorders share, to a certain degree, clinical characteristics and often co-occur, studies have shown that these disorders also share some neural patterns, such as partly overlapping morphological alterations in cortical and subcortical structures (Jenkins et al., 2016; Kempton et al., 2011; Mataix-Cols & van den Heuvel, 2006; Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010). Thus, these findings support the idea that a better understanding of these morphological alterations and their role for the pathogenesis of these disorders is of increasing importance. However, shared neurobiological commonalities and the difficulty in disentangling the specificity of each disorder complicates this objective. Especially, in the case of our study findings, a certain confounding influence of these factors cannot be excluded, although we tried to statistically account for the effect of comorbidity. Therefore, the question which of these alterations is specific to OCD, remains unanswered and requires further evaluation by integrative studies based on large sample sizes and multimodal approaches such the one used by Palaniyappan and Liddle (2012).

11.2.4. Indicators for Alterations during Brain Development in OCD

It is important to be aware that, at this stage of research, we cannot specify or predict the exact onset time of the encountered GM changes in OCD. Similarly, no assumption can be made so far about which of the GM measures is related to disease progression and which to its onset (or, in other words, whether these changes are progressive across the course of the disorder or manifest even before disorder onset).

Nevertheless, previous findings showed that gyrification is a reliable indicator of changes occurring during brain development in early childhood. This period is critical, as the cortical folding of the brain reaches its final stage of development during this time (Zilles et al., 2013). Therefore, it is highly interesting that in the third study (Rus et al., 2016) of this thesis in Chapter 9 we provide evidence for a widespread decrease in gyrification in patients, which was associated with early age of disorder onset. These findings would suggest that alterations in these regions might have occurred already during a period of early brain development which, in turn, may have increased patients vulnerability to suffer from an early disorder onset and potentially subsequent disturbances in brain structure and function.

Our findings, however, only slightly overlap with the few studies conducted in OCD cortical folding so far (Q. Fan et al., 2013; Venkatasubramanian et al., 2012; Wobrock et al., 2010). These studies yielded somewhat opposite results in terms of direction of alteration or affected regions. Nevertheless, the existing literature is, in itself, strikingly heterogeneous - i.e., up to now gyrification was found to be decreased (Wobrock et al., 2010), increased (Venkatasubramanian et al., 2012) or unchanged (Q. Fan et al., 2013) in OCD patients compared to healthy individuals.

In general, our results fit well to studies of cortical folding in other related psychiatric disorders,

that overlap in either clinical symptoms, neurobiological concepts or sometimes also co-occur, such as anxiety disorders (Yoon et al., 2013), depression (Zhang et al., 2009) or schizophrenia (Hirjak et al., 2015). These studies also showed a reduced cortical folding in patients suffering from this associated psychiatric disorders.

Taken together, this evidence supports the assumption that a common pathway might exist between these disorders. Most probably, a certain vulnerability to these GM differences in volume, thickness and surface area might be present due to altered cortical folding in early brain development. As a consequence, the probability of an early disorder onset would be increased, as also supported by our findings showing an association with the age of onset.

In sum, assuming that an intact brain structure is the basis for an efficient brain function, the alterations in brain morphology encountered in OCD patients may be crucial for the often-reported functional alterations. Finally, these alterations speak in favour of further investigations on the specific interactions between these various measures of brain structure and function.

11.3. Reduced Brain Structure vs. Increased Brain Function in OCD

The results of the presented studies bring a remarkable contrast into light, namely, a decrease in structural measures encountered in studies (Rus et al., 2017b, 2016) of Chapter 8 and Chapter 9 versus an hyperactive circuitry in terms of an increase in functional connectivity, encountered in the study (Rus et al., 2017a) of Chapter 7 . The hyper-active circuitry postulated already in the OCD neurobiological model (Saxena & Rauch, 2000) was partly partly found in the first study of this work (Rus et al., 2017a) in Chapter 7 - where an increased interaction between emotional processing areas and areas involved in visual processing and attention during symptom provocation was found. Although the analysis of aberrant brain function in OCD evolving in the CSTC model has been in the research focus for many years, several gaps, such as the integrative view of function and structure remain unexplored.

11.3.1. Increased Functional Connectivity

The first study (Rus et al., 2017a) presented in this thesis in Chapter 7 analyzed functional connectivity as well as structural integrity and connectivity of underlying WM tracts in an innovative way. These results shed light on the relevance of the limbic regions in OCD during symptom provocation.

Symptom provocation is also a major constituent of CBT therapy. A better understanding of the neuronal processes occurring during this therapy step might help to elucidate the neural processes taking place during further therapeutic steps, such as during fear extinction in the context of habituation. Moreover, understanding the mechanistic processes of the disorder in each of the therapeutic steps could be beneficial for the complementation of the recent neurobiological model. As a broader goal, this could help developing better treatment options, given the clearer neurological targets.

Present results represent an important extension of previous findings by evaluating functional connectivity during symptom provocation, rather than studying only functional activation. The investigation of functional connectivity can give more insight about the interactions of various regions and thereby broader network processes, as compared to the restrictive observation of regional activation patterns. The functional connectivity results are consistent with the few functional connectivity studies conducted in OCD so far (Jhung et al., 2014; Jung et al., 2013). Specifically, we could confirm the patterns of limbic dysconnectivity with fronto-parietal areas which have often been discussed in the context of resting state studies (Gottlich et al., 2014; Posner et al., 2014). Our results complement and further expand, to some extent, the findings by Jhung et al. (2014), who conducted the first, and to our knowledge, the only

study, evaluating functional connectivity in a symptom provocation context. Their approach differs slightly from ours, as they focused on striatal connectivity alterations. Despite this, their overall results suggested that a limbic network dysfunction together with an emotionally salient error awareness, play a pivotal role in OCD patients with contamination fear. This was partly reflected in the encountered altered amygdala-parietal connection in OCD patients (Chapter 7).

Other symptom provocation studies or studies investigating the processing of negative emotions showed functional activation disruptions in areas such as OFC, ACC or dlPFC in patients (Adler et al., 2000; Breiter et al., 1996; Simon et al., 2014, 2010). What remains surprising is that in contrast to these studies, present results did not show any significant difference in regional activation patterns between patients and controls. Arguably, the fact that the task used in our first study (Rus et al., 2017a) of Chapter 7 did not show any activation differences might indicate that the task affected patients and controls in a similar way. However, other reasons may have also played a role. One of the reasons might have been that our patient sample was multi-symptomatic and the stimuli which they were exposed to contained primarily contamination-related pictures. These pictures may not have affected all patients in the same way. Nevertheless, the questionnaire and debriefing scores showed a significantly increased disgust sensitivity in patients compared to controls. These behavioral scores emphasize the relevance of this task for OCD patients. Nevertheless, we have to admit that a more careful selection of individualized stimuli or categorization of stimuli based on symptom dimensions as done by Simon et al. (2010), might have been more effective for the investigation of disorder-characteristic functional activation patterns.

11.3.2. Relevance of Amygdala for OCD

One of the main goals of our work was to detect the relevance of the amygdala and its interconnections during symptom provocation. The task was associated with a prominent bilateral amygdala activation in both groups. Given the fact that the amygdala is known to be strongly involved in the processing of negative emotions this activation clearly indicates that the task had the intended effect (i.e., a negative emotional impact). Importantly, in patients compared to controls this result was accompanied by a significantly stronger connectivity between this emotional processing area and areas responsible for visual processing and attention.

The present results suggest that during the perception of OCD relevant stimuli (i.e., stimuli associated with contamination and negative valence) patients could not disengage their attention from these stimuli and may have been drawn into the classical “vicious circle“ (i.e., anxiety caused by the stimuli, obsessions in terms of contamination-related thoughts, even more increased anxiety, see Figure 1.1 in Chapter 1). Speculatively, this vicious circle may have been

reinforced by this increased amydala-occipito/parietal connectivity reflecting increased attention or an intensive perception of these stimuli hence going along with a comparatively stronger experience of negative emotions.

Our results complement the findings of the meta-analytic review by Rotge et al. (2008). They concluded that subcortical activations might be responsible for mediation of symptoms, whereas dorsal fronto-parietal activations are more associated with the resistance to triggered symptoms. We complement their results by showing that the interaction between these areas, reflected in an increased connectivity, might be one mechanism underlying the experience of disgust, anxiety and accompanying obsessive thoughts (or, in a natural environment outside the MRI, compulsive behavior).

By evaluating the amygdala connections during negative affective processing in OCD, which previously has been shown to be of relevance in processes such as threat assessment and emotional memory (LeDoux, 2012), we substantiated the findings of Breiter and Rauch (1996), who emphasized the role of the amygdala for anxiety processing in this psychiatric disorder.

Previous studies evaluating negative affective processing in OCD (Britton et al., 2010; Cannistraro et al., 2004; Rotge et al., 2008) as well showed alterations in amygdala, although the inconsistencies relied on the direction of alteration. A more recent study by Simon et al. (2014) concluded that, given the amygdala hyperactivity during symptom provocation and the damping of its activation during distraction in patients with various OCD symptom types, this region could represent a common neural correlate that links OCD to other anxiety disorders. Our results lend some support to this theory. To completely confirm this assumption, a further control group with an anxiety or a related disorder is needed in a future study. Nevertheless, a gain in knowledge of present results represents the *amygdala connectivity* during task, which has not been evaluated and reported this way until now, while its *activation* has been often analyzed in previous similar studies.

Overall, our results about the exact role of the amygdala for OCD shed light into two major points that are relevant for further research.

First, the result of normal not aberrant activation vs. impaired amygdala connectivity reinforces the need of investigation of this brain area on various neural levels. This means that not only brain activation but also connectivity and its directionality should be measured in order to gain a better picture of the exact alterations in OCD.

Second, our results only show altered amygdala connectivity during direct symptom provocation, but little is known about how relevant this area is in the context of other disorder-relevant processes such as expectation of a feared stimulus or a feared situation, habituation to certain stimuli/states or fear extinction. All of these processes are also stages of therapy in which patients are mostly accompanied by the feeling of anxiety and uncertainty. We speculate that

the amygdala might have varying relevance in these stages.

Hence, specific investigations combining functional and structural imaging and focusing on the specific therapy stages are needed to elucidate the exact role that amygdala has in the psychopathology of OCD. Further the neurobiological OCD model needs then to be reconsidered, by inclusion of additional areas, such as this limbic region.

11.3.3. Integrative View of Functional and Structural Alterations

Besides the gained information on functional hyper-connectivity and structural alterations in OCD, the results of this work expand existing knowledge by relating the aberrant function with the underlying structure. Taken together, the three studies presented in this work (see Part II) outline an integrative view of several neuronal processes and patterns in OCD: from functional activation to functional connectivity (Rus et al., 2017a), as well as from structural connectivity of WM and its integrity (Rus et al., 2017a) to structural properties of GM (Rus et al., 2017b, 2016), and last their association with the clinical characteristics of the disorder.

Narrative and meta-analytic reviews (Eng et al., 2015; Menzies et al., 2008; Nakao et al., 2014; Pauls et al., 2014) have already emphasized the need of a more joint reflection of all the relevant findings associated with the disorder. They suggested the integration of neuropsychological perspectives, neuroimaging findings, but also genetic and basic research findings. With the advent of new methods and analysis approaches for exploring brain function, from simple brain activation analysis to more complex viewpoints, such as connectome based analyses or machine learning techniques, this integrative view of findings gains increasing importance. In this respect, results of the presented studies (Rus et al., 2017a, 2017b, 2016) in Part II fulfilled the broader aim of the thesis in showing that to some extent, certain linkages exist between function and structure. Furthermore, the findings re-opened the debate on questions about the directionality and exact mechanisms of these interactions.

The brain is able to recover in case of physical (e.g. brain injury) as well as functional (e.g. impairment of oxygenation in certain regions) trauma. This recovery usually takes place shortly after the traumatic event and can be seen as a form of reorganization and adaptation of its neural functions. With this in mind, it could be speculated that this ability of the brain to self-reorganize and -adapt could also take place in case of aberrant function or structure in OCD. Therefore, assuming that certain regions encounter structural losses already during early brain development, as indicated by the cortical folding differences in the third study (Rus et al., 2016)(see Chapter 9), it is conceivable that in the further course of development the brain function might adapt and re-modulate its communication pathways, and would be thus still able to maintain a certain network efficacy. However, if the opposite would happen, - e.g., certain events or traumata which favor maladaptive behavior and unfavorable brain function -

it might be possible that the structural changes occurring during life adapt to this abnormal function.

These various scenarios, although not tested in the present work, might explain the result heterogeneity (such as increased or decreased GM volume) to some degree. Nevertheless, to investigate the causal interaction of all these changes, longitudinal and multimodal studies employing multivariate analysis approaches are needed.

From an anatomical perspective, present results indicate the relevance of several regions for the psychopathology of OCD. These regions have been shown to be altered both in function and structure and involve, besides the discussed *parietal areas, parts of frontal, occipital, temporal, fusiform gyrus* and *precentral areas*. For a descriptive overview see Figure 11.1. Previous concepts of the OCD neurobiological model have suggested considering several of these areas in the OCD model. For example, Menzies et al. (2008) and (Eng et al., 2015) proposed to pay more attention to *parietal areas*. These regions are involved in various cognitive functions in which OCD patients showed impairments, such as attention, working memory or spatial perception. They were also often found to be altered in GM or WM structure. The review by Nakao et al. (2014) which proposed a multi-dimensional model for OCD based on the various symptom dimensions underscored the role of *temporal areas*, especially for washing compulsions. They also suggested that *occipital areas*, which are part of the visuospatial attention network, have often been shown to be impaired in patients according to neuropsychological studies. These impairments ameliorated with clinical symptom improvement.

Viewed as a whole, our study results show several of these previously proposed regions to be functionally as well as structurally altered (see Figure 11.1) . Hence, their relevance for the neurobiological model of OCD is undeniable. Furthermore, these results underline the need of more multimodal research to determine their exact role and involvement in the circuitry. In sum, more research is needed in all of these areas to be better able to validate findings and elucidate brain pathophysiology of OCD.

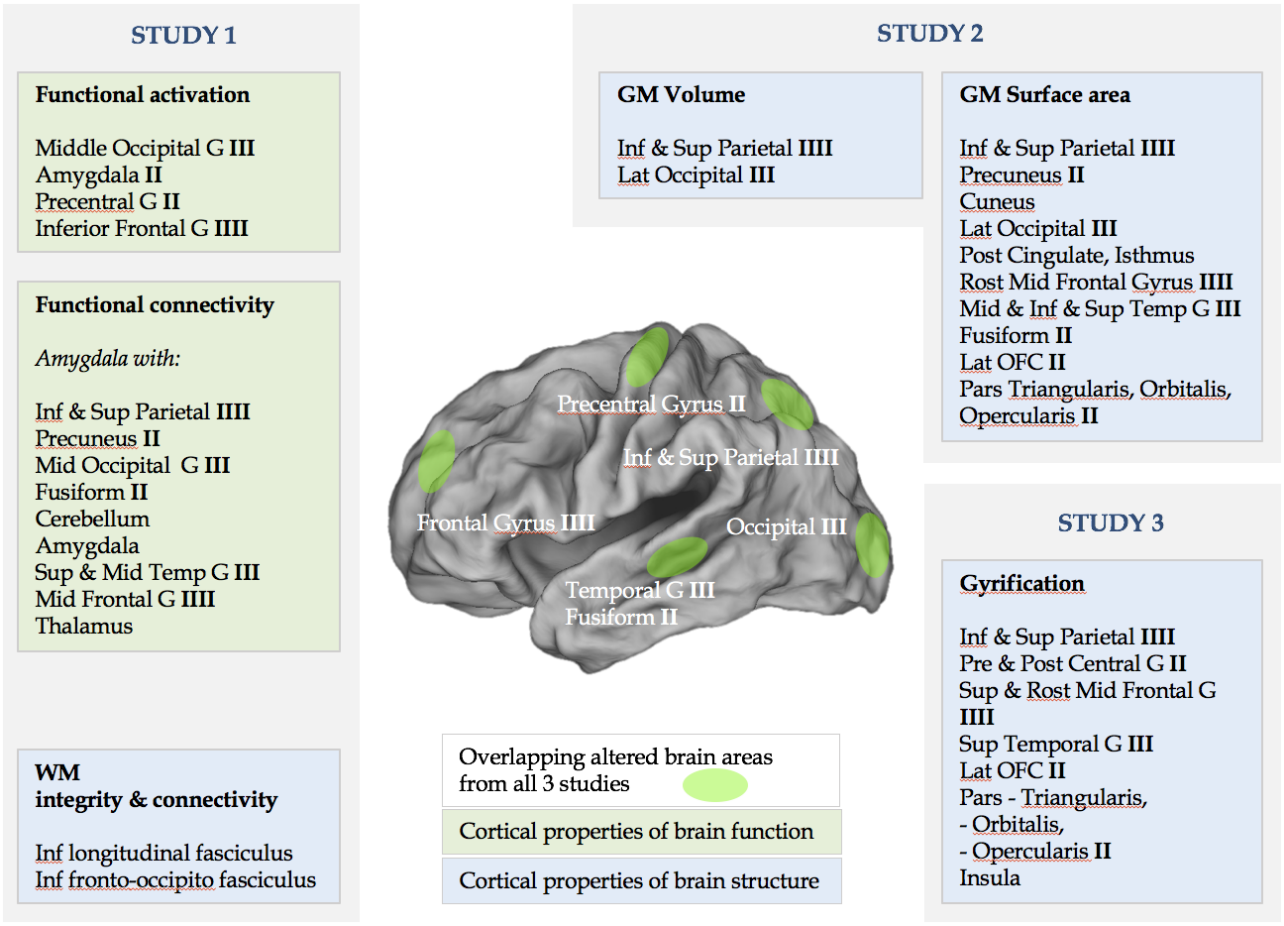

Figure 11.1.: Overview of brain areas found to be altered in OCD patients, resulted from the three studies.
Left boxes represent the brain areas that evolved to be altered in structure (WM) or impaired in function in OCD patients in study 1(Rus et al., 2017a) from Chapter 7.
Middle and Right boxes represent the brain areas that evolved to be altered in GM properties of the cortical mantle. Volume and surface area of study 2 (Rus et al., 2017b) from Chapter 8, Gyrification from study 3 (Rus et al., 2016) from Chapter 9.
The *brain template* in the *middle* presents the areas that were found altered in all three studies and in several cortical properties (function and structure).
The number of bars (e.g. III) represents how often this structure has been found to be impaired in function or structure in the three studies, it is a descriptive indicator of the frequency that this specific area was found to be altered in patients.

12. Thesis Achievements, Limitations and Future Work

Viewed as a whole, our work is encouraging and broadens the view about potential neuroimaging markers for OCD. This neural markers, which most probably relate to the clinical manifestation of OCD, are of relevance in elucidating the neuronal mechanistic processes of this psychiatric disorder. In the following, several achievements in light of their limitations and potential future work will be addressed.

First, the unique analysis framework embedding several neuroimaging analysis methods provided insight into various measurable neuronal parameters, both on a functional but also on a structural level (i.e. activation, connectivity, integrity). Furthermore, their linkages to each other and to symptomatology underlined the clinical relevance of the results. Nevertheless, knowing that the present results may be confounded by symptom heterogeneity and presence of comorbidities it would be of additional informative value if future studies considered the following: the use of multimodal approaches in evaluating larger samples and the presentation of individualized stimuli to better disentangle the specific neuronal patterns taking into account the symptom heterogeneity of the disorder. Furthermore, considering the relevance of the findings and their applicability for therapeutic purposes, this work gives insight into one specific part of therapy, i.e., symptom provocation. Therefore, it would be of great value to find out more about the neuronal patterns during all the other phases, such as anticipation of the feared situation or stimulus, exposition and extinction. It would be also a great achievement to use brain imaging for studying the neural activity related to therapeutic interventions as well as long term follow up investigations after these interventions. Knowing more about the exact neuronal mechanism underlying each of these significant therapy elements could contribute to the development of more tailored interventions depending on the symptom and disorder profile of the patients. This knowledge could also help disentangling potential target regions for specific noninvasive interventions, such as neurofeedback, which have proven to be effective in symptom reduction in other psychiatric disorders (e.g., post-traumatic stress disorder).

As a long-term goal, this type of neuroimaging results, in combination with other study findings investigating these processes at a cellular level in OCD, could help to focus the research on the disorder relevant areas. In the long run, this may constitute the basis for the development of

more effective pharmacological treatment.

Secondly, this thesis presents one of the few works in the existing OCD literature which gives insight into several measurable parameters of the cortical mantle concurrently (i.e. volume, surface area, thickness, gyrification) in a relatively large patient sample. One of the advantages of this work is the separate observation of each of these various measures, which allows to better rule out some of the confounding factors that might have contributed to changes in the other measures. For example, these confounding factors include cortical folding or surface area properties when estimating GM volume. Nevertheless, in light of the discussed limitations (e.g., influence of confounding factors such as medication, comorbidities or scanner type), future studies should examine the replicability of the existing findings in bigger samples using isolated analyses of the discussed confounding factors. Additionally, and in light of the considerable result heterogeneity in the literature, multimodal approaches in analyzing GM would be of great value, whereby the simultaneous use of different methods in analyzing brain morphology (e.g., VBM, SBA) and their results could be compared. Furthermore, the proportional contribution from each of these GM properties of the cortical mantle to the global brain changes in OCD, and their exact relationships, could be evaluated. This would be of major importance because it has been shown in other studies that the informative value of results increases when both methods are used concurrently (Palaniyappan et al., 2012).

Last, our results provide insights into potential vulnerability markers indicated by measures linked to processes that most probably happened early in brain development. However, these ideas are rather speculative, as the exact role of the several GM properties is still a matter of debate. Longitudinal studies are needed to elucidate the developmental progress and the interdependence of these morphological measures. Furthermore, little is known about the factors that contribute to the disorder onset, progression and symptom improvement and the exact interaction with brain morphology. Therefore, longitudinal studies that as well take into account these factors are needed to clarify the existing findings. The multiple factors that contribute to some extent to OCD indicate that future studies should integrate all these isolated findings into integrative approaches, i.e., by using computational modeling approaches (Stephan & Mathys, 2014). This would enable to infer mechanistically interpretable parameters (of computational or physiological processes) from the analyzed brain activity or behavior.

In sum, and in light of the existing limitations, the achievements of the presented studies strengthen our idea that the intricate picture of OCD will be much easier to clarify with the development of new methods, or the improvement of existing ones, but, especially, with the deliberate combination of these methods.

13. Conclusion

Taken together, it becomes clear that OCD is a psychiatric disorder with a well-defined and validated symptom profile and a well described cognitive-behavioural model. The neurobiological model, however, is still being revised and its adapted versions are a matter of ongoing debate. Hence, although several indicators for an aberrant neurobiology exist on various levels, these remain poorly replicated findings at the moment and are thus very hard to integrate into a homogeneous picture. This could be partly due to the fact that although the disorder has a comparably high prevalence, its insidious onset and often delayed diagnosis may have led to an underestimation of its impact. Therefore, OCD has received less attention in the neuroimaging field compared to other psychiatric disorders such as depression, anxiety, schizophrenia.

The present work provides valuable new insights into various measures of brain structure and function. It further reinforces the need of multimodal evaluation and integration of findings, by showing associations between the different neural parameters in OCD. Moreover, the results suggest significant clinical implications of these variations in brain morphology for the disorder and provide preliminary indication of potentially early vulnerability markers. Importantly, results showed that valuable information can be gained by the analysis of therapy-related processes such as symptom provocation, and further support the role of emotional processing brain areas during this specific therapy stage.

The present results should encourage the OCD research community to perform further integrative studies that evaluate various aspects of brain structure and function and their mutual associations in a multimodal way, as well as their link to neuropsychological but also genetic, cellular and clinical variables. We are convinced that this combined approach could help to unify the existing inconsistencies in OCD and help to disentangle the mechanisms behind its psychopathology.

List of Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
BDI	Beck Depression Inventory
bedpostX	Bayesian estimation of diffusion parameters obtained using sampling techniques
BOLD	blood oxygenation level dependant
CBT	cognitive behavioural therapy
CSTC	cortico-striato-thalamo-cortical circuit
df	degrees of freedom
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Version 5
DTI	Diffusion Tensor Imaging
EPI	echo-planar imaging
ERP	exposure and response prevention
FA	fractional anisotropy
FEE	Fragebogen zur Erfassung der Ekelempfindlichkeit,
fMRI	functional magnetic resonance imaging
FOV	field of view
FWE	familywise error correction
GABA	gamma-aminobutyric acid
GI	gyrification index
GLM	general linear model
GM	gray matter
Gpi, Gpe	globus pallidus internus/ externus
gPPI	generalized form of context-dependent psychophysiological interaction
HRF	hemodynamic response function
IAPS	International Affective Picture System
IFG	inferior frontal gyrus
IFOF	inferior frontal occipital fasciculus
lGI	local Gyrification Index
MD	mean diffusivity
MNI	Montreal Neurological Institute
MP-RAGE	magnetization-prepared rapid gradient-echo
MPRAGE	magnetization-prepared rapid acquisition gradient echo
MRI	Magnetic Resonance Imaging
(s)MRI	(structural) magnetic resonance imaging

(M)AN(C)OVA	(multiple) analysis of (co)variance
MRS	magnetic resonance spectroscopy
OCD	obsessive-compulsive disorder
OCDR	obsessive-compulsive and related disorders
OCI-R	Obsessive-Compulsive Inventory – Revised
OFC, alOFC	orbitofrontal cortex, anterolateral OFC
PCC	posterior cingulate cortex
PET	positron emission tomography
probFT	probabilistic fiber tracking
restFC	resting state functional connectivity
ROI	regions of interest
rs-fMRI	Resting state fMRI
SBA	surface based approach methods/ analysis
SC	structural connectivity
SN	substantia nigra
SPECT	single photon emission computed tomography
SPM	Statisticam Parametric Mapping
SPSS	Statistical Package for Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitors
STN	subthalamic nucleus
T	Tesla
t	from Students T test
taskFC	task dependent functional connect
TE	echo time
TI	inversion time
TMS	transcranial magnetic stimulation
TR	repetition time
VBM	voxel based morphometry
vlPFC, dlPFC	ventrolateral -, dorsolateral prefrontal cortex
vmCd	ventro medial caudate nucleus
WM	white matter
WM tracts	white matter fiber tracts
Y-BOCS	Yale-Brown Obsessive Compulsive Scale
χ^2	chi square test

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References

Abramovitch, A., Abramowitz, J. S., & Mittelman, A. (2013). The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis [Journal Article]. *Clin Psychol Rev*, *33*(8), 1163-71. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24128603 doi: 10.1016/j.cpr.2013.09.004 (cited on page 11)

Abramowitz, J. S. (2006a). The psychological treatment of obsessive-compulsive disorder [Journal Article]. *Can J Psychiatry*, *51*(7), 407-16. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16838822 doi: 10.1177/070674370605100702 (cited on page 5)

Abramowitz, J. S. (2006b). *Understanding and treating obsessive-compulsive disorder: A cognitive-behavioral approach* [Book]. New York, NY: Erlbaum. (cited on page 7)

Abramowitz, J. S., & Jacoby, R. J. (2014). Obsessive-compulsive disorder in the dsm-5 [Journal Article]. *Clinical Psychology Science and Practice*, 221-235. doi: DOI:10.1111/cpsp.12070 (cited on pages 5 and 8)

Abramowitz, J. S., Taylor, S., & McKay, D. (2009). Obsessive-compulsive disorder [Journal Article]. *Lancet*, *374*(9688), 491-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19665647 doi: 10.1016/S0140-6736(09)60240-3 (cited on page 8)

Adler, C. M., McDonough-Ryan, P., Sax, K. W., Holland, S. K., Arndt, S., & Strakowski, S. M. (2000). fmri of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder [Journal Article]. *J Psychiatr Res*, *34*(4-5), 317-24. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11104844 (cited on pages 14 and 89)

Admon, R., Bleich-Cohen, M., Weizmant, R., Poyurovsky, M., Faragian, S., & Hendler, T. (2012). Functional and structural neural indices of risk aversion in obsessive-compulsive disorder (ocd) [Journal Article]. *Psychiatry Res*, *203*(2-3), 207-13. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22959813 doi: 10.1016/j.pscychresns.2012.02.002 (cited on page 26)

Ahmari, S. E., Spellman, T., Douglass, N. L., Kheirbek, M. A., Simpson, H. B., Deisseroth, K., ... Hen, R. (2013). Repeated cortico-striatal stimulation generates persistent ocd-like behavior [Journal Article]. *Science*, *340*(6137), 1234-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23744948 doi: 10.1126/science.1234733 (cited on page 26)

Albelda, N., & Joel, D. (2012). Current animal models of obsessive compulsive disorder:

an update [Journal Article]. *Neuroscience*, *211*, 83-106. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21925243 doi: 10.1016/j.neuroscience.2011.08.070 (cited on page 26)

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex [Journal Article]. *Annu Rev Neurosci*, *9*, 357-81. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3085570 doi: 10.1146/annurev.ne.09.030186.002041 (cited on page 29)

Alonso, P., Cuadras, D., Gabriels, L., Denys, D., Goodman, W., Greenberg, B. D., ... Menchon, J. M. (2015). Deep brain stimulation for obsessive-compulsive disorder: A meta-analysis of treatment outcome and predictors of response [Journal Article]. *PLoS One*, *10*(7), e0133591. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26208305 doi: 10.1371/journal.pone.0133591 (cited on page 8)

Andersson, E., Hedman, E., Enander, J., Radu Djurfeldt, D., Ljotsson, B., Cervenka, S., ... Ruck, C. (2015). D-cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: A randomized clinical trial [Journal Article]. *JAMA Psychiatry*, *72*(7), 659-67. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25970252 doi: 10.1001/jamapsychiatry.2015.0546 (cited on page 8)

Anticevic, A., Hu, S., Zhang, S., Savic, A., Billingslea, E., Wasylink, S., ... Pittenger, C. (2014). Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *75*(8), 595-605. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24314349 doi: 10.1016/j.biopsych.2013.10.021 (cited on page 16)

APA, A. P. A. (2013). *Diagnostic and statistical manual of mental disorders (dsm-5): Chapter 6. obsessive-compulsive and related disorders* (5th ed.) [Book]. Washington, DC. (cited on page 5)

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., & Zilles, K. (1995). The ontogeny of human gyrification [Journal Article]. *Cereb Cortex*, *5*(1), 56-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7719130 (cited on page 22)

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry–the methods [Journal Article]. *Neuroimage*, *11*(6 Pt 1), 805-21. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10860804 doi: 10.1006/nimg.2000.0582 (cited on pages 18 and 19)

Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Moller, H. J., Wfsbp Task Force on Treatment Guidelines for Anxiety, O.-C., ... Vega, J. (2008). World federation of societies of biological psychiatry (wfsbp) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision [Journal Article]. *World J Biol Psychiatry*, *9*(4), 248-312. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18949648 doi: 10.1080/15622970802465807

(cited on page 7)

Bannon, S., Gonsalvez, C. J., Croft, R. J., & Boyce, P. M. (2002). Response inhibition deficits in obsessive-compulsive disorder [Journal Article]. *Psychiatry Res*, *110*(2), 165-74. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12057828 (cited on page 11)

Barr, L. C., Goodman, W. K., & Price, L. H. (1993). The serotonin hypothesis of obsessive compulsive disorder [Journal Article]. *Int Clin Psychopharmacol*, *8 Suppl 2*, 79-82. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8201248 (cited on page 8)

Baumgarten, H. G., & Grozdanovic, Z. (1998). Role of serotonin in obsessive-compulsive disorder [Journal Article]. *Br J Psychiatry Suppl*(35), 13-20. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9829022 (cited on page 8)

Baxter, J., L. R., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Schwartz, J. M., & Selin, C. E. (1987). Local cerebral glucose metabolic rates in obsessive-compulsive disorder. a comparison with rates in unipolar depression and in normal controls [Journal Article]. *Arch Gen Psychiatry*, *44*(3), 211-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3493749 (cited on page 13)

Beucke, J. C., Kaufmann, C., Linnman, C., Gruetzmann, R., Endrass, T., Deckersbach, T., ... Kathmann, N. (2012). Altered cingulostriatal coupling in obsessive-compulsive disorder [Journal Article]. *Brain Connect*, *2*(4), 191-202. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22823561 doi: 10.1089/brain.2012.0078 (cited on page 18)

Beucke, J. C., Sepulcre, J., Eldaief, M. C., Sebold, M., Kathmann, N., & Kaufmann, C. (2014). Default mode network subsystem alterations in obsessive-compulsive disorder [Journal Article]. *Br J Psychiatry*, *205*(5), 376-82. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25257066 doi: 10.1192/bjp.bp.113.137380 (cited on page 16)

Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., ... Kathmann, N. (2013). Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder [Journal Article]. *JAMA Psychiatry*, *70*(6), 619-29. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23740050 doi: 10.1001/jamapsychiatry.2013.173 (cited on page 16)

Bloch, M. H., Landeros-Weisenberger, A., Kelmendi, B., Coric, V., Bracken, M. B., & Leckman, J. F. (2006). A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder [Journal Article]. *Mol Psychiatry*, *11*(7), 622-32. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16585942 doi: 10.1038/sj.mp.4001823 (cited on page 8)

Bloch, M. H., Landeros-Weisenberger, A., Rosario, M. C., Pittenger, C., & Leckman, J. F. (2008). Meta-analysis of the symptom structure of obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *165*(12), 1532-42. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18923068 doi: 10.1176/appi.ajp.2008.08020320 (cited on page 6)

Boedhoe, P. S., Schmaal, L., Abe, Y., Ameis, S. H., Arnold, P. D., Batistuzzo, M. C., ...

van den Heuvel, O. A. (2016). Distinct subcortical volume alterations in pediatric and adult ocd: A worldwide meta- and mega-analysis [Journal Article]. *Am J Psychiatry*, appiajp201616020201. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27609241 doi: 10.1176/appi.ajp.2016.16020201 (cited on page 20)

Breiter, H. C., & Rauch, S. L. (1996). Functional mri and the study of ocd: from symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdala [Journal Article]. *Neuroimage*, *4*(3 Pt 3), S127-38. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9345537 doi: 10.1006/nimg.1996.0063 (cited on pages 15, 77, and 90)

Breiter, H. C., Rauch, S. L., Kwong, K. K., Baker, J. R., Weisskoff, R. M., Kennedy, D. N., ... Rosen, B. R. (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder [Journal Article]. *Arch Gen Psychiatry*, *53*(7), 595-606. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8660126 (cited on pages 14 and 89)

Britton, J. C., Stewart, S. E., Killgore, W. D., Rosso, I. M., Price, L. M., Gold, A. L., ... Rauch, S. L. (2010). Amygdala activation in response to facial expressions in pediatric obsessive-compulsive disorder [Journal Article]. *Depress Anxiety*, *27*(7), 643-51. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20602430 doi: 10.1002/da.20718 (cited on pages 15 and 90)

Buhlmann, U., Deckersbach, T., Engelhard, I., Cook, L. M., Rauch, S. L., Kathmann, N., ... Savage, C. R. (2006). Cognitive retraining for organizational impairment in obsessive-compulsive disorder [Journal Article]. *Psychiatry Res*, *144*(2-3), 109-16. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17007938 doi: 10.1016/j.psychres.2005.10.012 (cited on page 11)

Burguiere, E., Monteiro, P., Feng, G., & Graybiel, A. M. (2013). Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors [Journal Article]. *Science*, *340*(6137), 1243-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23744950 doi: 10.1126/science.1232380 (cited on pages 26 and 27)

Cannistraro, P. A., Wright, C. I., Wedig, M. M., Martis, B., Shin, L. M., Wilhelm, S., & Rauch, S. L. (2004). Amygdala responses to human faces in obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *56*(12), 916-20. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15601600 doi: 10.1016/j.biopsych.2004.09.029 (cited on pages 14, 15, and 90)

Cardoner, N., Harrison, B. J., Pujol, J., Soriano-Mas, C., Hernandez-Ribas, R., Lopez-Sola, M., ... Menchon, J. M. (2011). Enhanced brain responsiveness during active emotional face processing in obsessive compulsive disorder [Journal Article]. *World J Biol Psychiatry*, *12*(5), 349-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21781000 doi: 10.3109/15622975.2011.559268 (cited on page 17)

Cavedini, P., Riboldi, G., D'Annucci, A., Belotti, P., Cisima, M., & Bellodi, L. (2002). Decision-making heterogeneity in obsessive-compulsive disorder: ventromedial prefrontal cortex function predicts different treatment outcomes [Journal Article]. *Neuropsychologia*, *40*(2), 205-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11640942 (cited on page 11)

Cavedini, P., Zorzi, C., Piccinni, M., Cavallini, M. C., & Bellodi, L. (2010). Executive dysfunctions in obsessive-compulsive patients and unaffected relatives: searching for a new intermediate phenotype [Journal Article]. *Biol Psychiatry*, *67*(12), 1178-84. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20381015 doi: 10.1016/j.biopsych.2010.02.012 (cited on page 11)

Chamberlain, S. R., Blackwell, A. D., Fineberg, N. A., Robbins, T. W., & Sahakian, B. J. (2005). The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers [Journal Article]. *Neurosci Biobehav Rev*, *29*(3), 399-419. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15820546 doi: 10.1016/j.neubiorev.2004.11.006 (cited on page 11)

Chamberlain, S. R., Fineberg, N. A., Blackwell, A. D., Robbins, T. W., & Sahakian, B. J. (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania [Journal Article]. *Am J Psychiatry*, *163*(7), 1282-4. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16816237 doi: 10.1176/appi.ajp.163.7.1282 (cited on page 11)

Chamberlain, S. R., Fineberg, N. A., Menzies, L. A., Blackwell, A. D., Bullmore, E. T., Robbins, T. W., & Sahakian, B. J. (2007). Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *164*(2), 335-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17267798 doi: 10.1176/ajp.2007.164.2.335 (cited on page 11)

Clarkson, M. J., Cardoso, M. J., Ridgway, G. R., Modat, M., Leung, K. K., Rohrer, J. D., ... Ourselin, S. (2011). A comparison of voxel and surface based cortical thickness estimation methods [Journal Article]. *Neuroimage*, *57*(3), 856-65. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21640841 doi: 10.1016/j.neuroimage.2011.05.053 (cited on page 19)

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. i. segmentation and surface reconstruction [Journal Article]. *Neuroimage*, *9*(2), 179-94. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9931268 doi: 10.1006/nimg.1998.0395 (cited on page 19)

Delorme, R., Gousse, V., Roy, I., Trandafir, A., Mathieu, F., Mouren-Simeoni, M. C., ... Leboyer, M. (2007). Shared executive dysfunctions in unaffected relatives of patients with autism and obsessive-compulsive disorder [Journal Article]. *Eur Psychiatry*, *22*(1), 32-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17127035 doi: 10.1016/

j.eurpsy.2006.05.002 (cited on page 11)

de Vries, F. E., de Wit, S. J., Cath, D. C., van der Werf, Y. D., van der Borden, V., van Rossum, T. B., ... van den Heuvel, O. A. (2014). Compensatory frontoparietal activity during working memory: an endophenotype of obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *76*(11), 878-87. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24365484 doi: 10.1016/j.biopsych.2013.11.021 (cited on page 17)

de Wit, S. J., Alonso, P., Schweren, L., Mataix-Cols, D., Lochner, C., Menchon, J. M., ... van den Heuvel, O. A. (2014). Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *171*(3), 340-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24220667 doi: 10.1176/appi.ajp.2013.13040574 (cited on pages 20 and 83)

Dietsche, B., Kircher, T., & Falkenberg, I. (2017). Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies [Journal Article]. *Aust N Z J Psychiatry*, *51*(5), 500-508. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28415873 doi: 10.1177/0004867417699473 (cited on page 85)

Dougherty, D. D., Baer, L., Cosgrove, G. R., Cassem, E. H., Price, B. H., Nierenberg, A. A., ... Rauch, S. L. (2002). Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *159*(2), 269-75. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11823270 doi: 10.1176/appi.ajp.159.2.269 (cited on page 8)

Dougherty, D. D., Rauch, S. L., & Jenike, M. A. (2004). Pharmacotherapy for obsessive-compulsive disorder [Journal Article]. *J Clin Psychol*, *60*(11), 1195-202. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15389617 doi: 10.1002/jclp.20083 (cited on page 8)

Eddy, K. T., Dutra, L., Bradley, R., & Westen, D. (2004). A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder [Journal Article]. *Clin Psychol Rev*, *24*(8), 1011-30. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15533282 doi: 10.1016/j.cpr.2004.08.004 (cited on page 8)

Eng, G. K., Sim, K., & Chen, S. H. (2015). Meta-analytic investigations of structural grey matter, executive domain-related functional activations, and white matter diffusivity in obsessive compulsive disorder: an integrative review [Journal Article]. *Neurosci Biobehav Rev*, *52*, 233-57. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25766413 doi: 10.1016/j.neubiorev.2015.03.002 (cited on pages 18, 26, 80, 91, and 92)

Fan, Q., Palaniyappan, L., Tan, L., Wang, J., Wang, X., Li, C., ... Liddle, P. F. (2013). Surface anatomical profile of the cerebral cortex in obsessive-compulsive disorder: a study of cortical thickness, folding and surface area [Journal Article]. *Psychol Med*, *43*(5), 1081-91. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22935427 doi: 10.1017/

S0033291712001845 (cited on pages 21, 23, 84, and 86)

Fan, S., van den Heuvel, O. A., Cath, D. C., van der Werf, Y. D., de Wit, S. J., de Vries, F. E., ... Pouwels, P. J. (2015). Mild white matter changes in un-medicated obsessive-compulsive disorder patients and their unaffected siblings [Journal Article]. *Front Neurosci*, *9*, 495. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26793045 doi: 10.3389/fnins.2015.00495 (cited on page 24)

Fineberg, N. A., Chamberlain, S. R., Hollander, E., Boulougouris, V., & Robbins, T. W. (2011). Translational approaches to obsessive-compulsive disorder: from animal models to clinical treatment [Journal Article]. *Br J Pharmacol*, *164*(4), 1044-61. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21486280 doi: 10.1111/j.1476-5381.2011.01422.x (cited on page 27)

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. ii: Inflation, flattening, and a surface-based coordinate system [Journal Article]. *Neuroimage*, *9*(2), 195-207. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9931269 doi: 10.1006/nimg.1998.0396 (cited on pages 18 and 19)

Fitzgerald, K. D., Moore, G. J., Paulson, L. A., Stewart, C. M., & Rosenberg, D. R. (2000). Proton spectroscopic imaging of the thalamus in treatment-naive pediatric obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *47*(3), 174-82. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10682215 (cited on page 13)

Foa, E. B., Kozak, M. J., Goodman, W. K., Hollander, E., Jenike, M. A., & Rasmussen, S. A. (1995). Dsm-iv field trial: obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *152*(1), 90-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7802127 doi: 10.1176/ajp.152.1.90 (cited on page 5)

Foa, E. B., Liebowitz, M. R., Kozak, M. J., Davies, S., Campeas, R., Franklin, M. E., ... Tu, X. (2005). Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *162*(1), 151-61. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15625214 doi: 10.1176/appi.ajp.162.1.151 (cited on page 8)

Fontenelle, L. F., Harrison, B. J., Yucel, M., Pujol, J., Fujiwara, H., & Pantelis, C. (2009). Is there evidence of brain white-matter abnormalities in obsessive-compulsive disorder?: a narrative review [Journal Article]. *Top Magn Reson Imaging*, *20*(5), 291-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20859190 doi: 10.1097/RMR.0b013e3181e8f22c (cited on page 24)

Fouche, J. P., du Plessis, S., Hattingh, C., Roos, A., Lochner, C., Soriano-Mas, C., ... van den Heuvel, O. A. (2017). Cortical thickness in obsessive-compulsive disorder: multisite mega-analysis of 780 brain scans from six centres [Journal Article]. *Br J Psychiatry*, *210*(1), 67-74. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27198485 doi: 10.1192/bjp.bp.115.164020 (cited on page 85)

Franklin, M. E., Abramowitz, J. S., Kozak, M. J., Levitt, J. T., & Foa, E. B. (2000). Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples [Journal Article]. *J Consult Clin Psychol*, *68*(4), 594-602. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10965635 (cited on page 7)

Garibotto, V., Scifo, P., Gorini, A., Alonso, C. R., Brambati, S., Bellodi, L., & Perani, D. (2010). Disorganization of anatomical connectivity in obsessive compulsive disorder: a multi-parameter diffusion tensor imaging study in a subpopulation of patients [Journal Article]. *Neurobiol Dis*, *37*(2), 468-76. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19913616 doi: 10.1016/j.nbd.2009.11.003 (cited on page 25)

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N., Friston, K. J., & Frackowiak, R. S. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains [Journal Article]. *Neuroimage*, *14*(1 Pt 1), 21-36. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11525331 doi: 10.1006/nimg.2001.0786 (cited on page 19)

Gottlich, M., Kramer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. (2014). Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder [Journal Article]. *Hum Brain Mapp*, *35*(11), 5617-32. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25044747 doi: 10.1002/hbm.22574 (cited on pages 16 and 88)

Gottlich, M., Kramer, U. M., Kordon, A., Hohagen, F., & Zurowski, B. (2015). Resting-state connectivity of the amygdala predicts response to cognitive behavioral therapy in obsessive compulsive disorder [Journal Article]. *Biol Psychol*, *111*, 100-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26388257 doi: 10.1016/j.biopsycho.2015.09.004 (cited on page 16)

Greenberg, B. D., Benjamin, J., Martin, J. D., Keuler, D., Huang, S. J., Altemus, M., & Murphy, D. L. (1998). Delayed obsessive-compulsive disorder symptom exacerbation after a single dose of a serotonin antagonist in fluoxetine-treated but not untreated patients [Journal Article]. *Psychopharmacology (Berl)*, *140*(4), 434-44. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9888619 (cited on page 8)

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis [Journal Article]. *Proc Natl Acad Sci U S A*, *100*(1), 253-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12506194 doi: 10.1073/pnas.0135058100 (cited on page 16)

Gruner, P., & Pittenger, C. (2017). Cognitive inflexibility in obsessive-compulsive disorder [Journal Article]. *Neuroscience*, *345*, 243-255. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27491478 doi: 10.1016/j.neuroscience.2016.07.030 (cited on page 11)

Gürsel, D., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2017). Salience, frontoparietal, and default mode network alterations in obsessive-compulsive disorder: A meta-analysis of

resting-state functional connectivity [Journal Article].
(in preparation) (cited on page 17)

Harrison, B. J., Pujol, J., Cardoner, N., Deus, J., Alonso, P., Lopez-Sola, M., ... Soriano-Mas, C. (2013). Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *73*(4), 321-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23200527 doi: 10.1016/j.biopsych.2012.10.006 (cited on page 16)

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., Lopez-Sola, M., Hernandez-Ribas, R., ... Cardoner, N. (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder [Journal Article]. *Arch Gen Psychiatry*, *66*(11), 1189-200. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19884607 doi: 10.1001/archgenpsychiatry.2009.152 (cited on page 16)

Helms, G. (2016). Segmentation of human brain using structural mri [Journal Article]. *MAGMA*, *29*(2), 111-24. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26739264 doi: 10.1007/s10334-015-0518-z (cited on pages 19 and 77)

Hilbert, K., Pine, D. S., Muehlhan, M., Lueken, U., Steudte-Schmiedgen, S., & Beesdo-Baum, K. (2015). Gray and white matter volume abnormalities in generalized anxiety disorder by categorical and dimensional characterization [Journal Article]. *Psychiatry Res*, *234*(3), 314-20. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26490569 doi: 10.1016/j.pscychresns.2015.10.009 (cited on page 85)

Hirjak, D., Kubera, K. M., Wolf, R. C., Thomann, A. K., Hell, S. K., Seidl, U., & Thomann, P. A. (2015). Local brain gyrification as a marker of neurological soft signs in schizophrenia [Journal Article]. *Behav Brain Res*, *292*, 19-25. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26031380 doi: 10.1016/j.bbr.2015.05.048 (cited on pages 21, 78, and 87)

Hou, J. M., Zhao, M., Zhang, W., Song, L. H., Wu, W. J., Wang, J., ... Li, H. T. (2014). Resting-state functional connectivity abnormalities in patients with obsessive-compulsive disorder and their healthy first-degree relatives [Journal Article]. *J Psychiatry Neurosci*, *39*(5), 304-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24866415 (cited on page 16)

Husted, D. S., Shapira, N. A., & Goodman, W. K. (2006). The neurocircuitry of obsessive-compulsive disorder and disgust [Journal Article]. *Prog Neuropsychopharmacol Biol Psychiatry*, *30*(3), 389-99. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16443315 doi: 10.1016/j.pnpbp.2005.11.024 (cited on page 14)

Hutton, C., De Vita, E., Ashburner, J., Deichmann, R., & Turner, R. (2008). Voxel-based cortical thickness measurements in mri [Journal Article]. *Neuroimage*, *40*(4), 1701-10. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18325790 doi: 10.1016/j.neuroimage.2008.01.027 (cited on pages 19 and 83)

Hutton, C., Draganski, B., Ashburner, J., & Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging [Journal Article]. *Neuroimage*, *48*(2), 371-80. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19559801 doi: 10.1016/j.neuroimage.2009.06.043 (cited on pages 19 and 83)

Jenkins, L. M., Barba, A., Campbell, M., Lamar, M., Shankman, S. A., Leow, A. D., ... Langenecker, S. A. (2016). Shared white matter alterations across emotional disorders: A voxel-based meta-analysis of fractional anisotropy [Journal Article]. *Neuroimage Clin*, *12*, 1022-1034. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27995068 doi: 10.1016/j.nicl.2016.09.001 (cited on page 86)

Jhung, K., Ku, J., Kim, S. J., Lee, H., Kim, K. R., An, S. K., ... Lee, E. (2014). Distinct functional connectivity of limbic network in the washing type obsessive-compulsive disorder [Journal Article]. *Prog Neuropsychopharmacol Biol Psychiatry*, *53*, 149-55. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24768985 doi: 10.1016/j.pnpbp.2014.04.007 (cited on pages 18 and 88)

Jung, W. H., Kang, D. H., Kim, E., Shin, K. S., Jang, J. H., & Kwon, J. S. (2013). Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing and resting-state [Journal Article]. *Neuroimage Clin*, *3*, 27-38. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24179846 doi: 10.1016/j.nicl.2013.06.013 (cited on pages 17 and 88)

Kariuki-Nyuthe, C., Gomez-Mancilla, B., & Stein, D. J. (2014). Obsessive compulsive disorder and the glutamatergic system [Journal Article]. *Curr Opin Psychiatry*, *27*(1), 32-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24270485 doi: 10.1097/YCO.0000000000000017 (cited on page 8)

Kempton, M. J., Salvador, Z., Munafo, M. R., Geddes, J. R., Simmons, A., Frangou, S., & Williams, S. C. (2011). Structural neuroimaging studies in major depressive disorder. meta-analysis and comparison with bipolar disorder [Journal Article]. *Arch Gen Psychiatry*, *68*(7), 675-90. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21727252 doi: 10.1001/archgenpsychiatry.2011.60 (cited on page 86)

Koch, K., Reess, T. J., Rus, O. G., Zimmer, C., & Zaudig, M. (2014). Diffusion tensor imaging (dti) studies in patients with obsessive-compulsive disorder (ocd): a review [Journal Article]. *J Psychiatr Res*, *54*, 26-35. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24694669 doi: 10.1016/j.jpsychires.2014.03.006 (cited on page 24)

Koran, L. M., Hanna, G. L., Hollander, E., Nestadt, G., Simpson, H. B., & American Psychiatric, A. (2007). Practice guideline for the treatment of patients with obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *164*(7 Suppl), 5-53. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17849776 (cited on pages 7 and 8)

Kuhn, S., Kaufmann, C., Simon, D., Endrass, T., Gallinat, J., & Kathmann, N. (2013). Reduced thickness of anterior cingulate cortex in obsessive-compulsive disorder [Jour-

nal Article]. *Cortex*, *49*(8), 2178-85. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23067727 doi: 10.1016/j.cortex.2012.09.001 (cited on pages 20 and 85)

LeDoux, J. (2012). Rethinking the emotional brain [Journal Article]. *Neuron*, *73*(4), 653-76. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22365542 doi: 10.1016/j.neuron.2012.02.004 (cited on page 90)

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fmri signal [Journal Article]. *Nature*, *412*(6843), 150-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11449264 doi: 10.1038/35084005 (cited on page 13)

Lucey, J. V., Costa, D. C., Blanes, T., Busatto, G. F., Pilowsky, L. S., Takei, N., ... Kerwin, R. W. (1995). Regional cerebral blood flow in obsessive-compulsive disordered patients at rest. differential correlates with obsessive-compulsive and anxious-avoidant dimensions [Journal Article]. *Br J Psychiatry*, *167*(5), 629-34. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8564319 (cited on page 13)

Magioncalda, P., Martino, M., Ely, B. A., Inglese, M., & Stern, E. R. (2016). Microstructural white-matter abnormalities and their relationship with cognitive dysfunction in obsessive-compulsive disorder [Journal Article]. *Brain Behav*, *6*(3), e00442. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27099803 doi: 10.1002/brb3.442 (cited on page 25)

Mataix-Cols, D., Fernandez de la Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Perez-Vigil, A., ... Consortium, D. C. S. A. (2017). D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and post-traumatic stress disorders: A systematic review and meta-analysis [Journal Article]. *JAMA Psychiatry*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28122091 doi: 10.1001/jamapsychiatry.2016.3955 (cited on page 8)

Mataix-Cols, D., Rosario-Campos, M. C., & Leckman, J. F. (2005). A multidimensional model of obsessive-compulsive disorder [Journal Article]. *Am J Psychiatry*, *162*(2), 228-38. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15677583 doi: 10.1176/appi.ajp.162.2.228 (cited on page 6)

Mataix-Cols, D., & van den Heuvel, O. A. (2006). Common and distinct neural correlates of obsessive-compulsive and related disorders [Journal Article]. *Psychiatr Clin North Am*, *29*(2), 391-410, viii. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16650715 doi: 10.1016/j.psc.2006.02.006 (cited on page 86)

McKay, D., Abramowitz, J. S., Calamari, J. E., Kyrios, M., Radomsky, A., Sookman, D., ... Wilhelm, S. (2004). A critical evaluation of obsessive-compulsive disorder subtypes: symptoms versus mechanisms [Journal Article]. *Clin Psychol Rev*, *24*(3), 283-313. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15245833 doi: 10.1016/j.cpr.2004.04.003 (cited on page 6)

Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited [Journal Article]. *Neurosci Biobehav Rev*, *32*(3), 525-49. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18061263 doi: 10.1016/j.neubiorev.2007.09.005 (cited on pages 11, 14, 26, 30, 32, 80, 91, and 92)

Milad, M. R., & Rauch, S. L. (2012). Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways [Journal Article]. *Trends Cogn Sci*, *16*(1), 43-51. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22138231 doi: 10.1016/j.tics.2011.11.003 (cited on pages 26, 30, 31, and 77)

Mills, K. L., & Tamnes, C. K. (2014). Methods and considerations for longitudinal structural brain imaging analysis across development [Journal Article]. *Dev Cogn Neurosci*, *9*, 172-90. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24879112 doi: 10.1016/j.dcn.2014.04.004 (cited on page 22)

Moorhead, T. W., Harris, J. M., Stanfield, A. C., Job, D. E., Best, J. J., Johnstone, E. C., & Lawrie, S. M. (2006). Automated computation of the gyrification index in prefrontal lobes: methods and comparison with manual implementation [Journal Article]. *Neuroimage*, *31*(4), 1560-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16600639 doi: 10.1016/j.neuroimage.2006.02.025 (cited on page 22)

Mori, S., & Zhang, J. (2006). Principles of diffusion tensor imaging and its applications to basic neuroscience research [Journal Article]. *Neuron*, *51*(5), 527-39. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16950152 doi: 10.1016/j.neuron.2006.08.012 (cited on page 23)

Murayama, K., Nakao, T., Sanematsu, H., Okada, K., Yoshiura, T., Tomita, M., ... Kanba, S. (2013). Differential neural network of checking versus washing symptoms in obsessive-compulsive disorder [Journal Article]. *Prog Neuropsychopharmacol Biol Psychiatry*, *40*, 160-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22996045 doi: 10.1016/j.pnpbp.2012.09.002 (cited on page 14)

Nakamae, T., Narumoto, J., Sakai, Y., Nishida, S., Yamada, K., Kubota, M., ... Fukui, K. (2012). Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder [Journal Article]. *Prog Neuropsychopharmacol Biol Psychiatry*, *37*(1), 90-5. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22251565 doi: 10.1016/j.pnpbp.2012.01.001 (cited on page 20)

Nakamae, T., Sakai, Y., Abe, Y., Nishida, S., Fukui, K., Yamada, K., ... Narumoto, J. (2014). Altered fronto-striatal fiber topography and connectivity in obsessive-compulsive disorder [Journal Article]. *PLoS One*, *9*(11), e112075. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25375933 doi: 10.1371/journal.pone.0112075 (cited on pages 25 and 85)

Nakao, T., Nakagawa, A., Nakatani, E., Nabeyama, M., Sanematsu, H., Yoshiura, T., ... Kanba, S. (2009). Working memory dysfunction in obsessive-compulsive disorder: a neuropsychological and functional mri study [Journal Article]. *J Psychiatr Res*, *43*(8), 784-91. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19081580 doi: 10.1016/j.jpsychires.2008.10.013 (cited on page 25)

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., ... Kanba, S. (2005). Brain activation of patients with obsessive-compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study [Journal Article]. *Biol Psychiatry*, *57*(8), 901-10. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15820711 doi: 10.1016/j.biopsych.2004.12.039 (cited on page 14)

Nakao, T., Okada, K., & Kanba, S. (2014). Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings [Journal Article]. *Psychiatry Clin Neurosci*, *68*(8), 587-605. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24762196 doi: 10.1111/pcn.12195 (cited on pages 11, 14, 30, 91, and 92)

Narr, K. L., Bilder, R. M., Toga, A. W., Woods, R. P., Rex, D. E., Szeszko, P. R., ... Thompson, P. M. (2005). Mapping cortical thickness and gray matter concentration in first episode schizophrenia [Journal Article]. *Cereb Cortex*, *15*(6), 708-19. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15371291 doi: 10.1093/cercor/bhh172 (cited on page 19)

Nestadt, G., Samuels, J., Riddle, M. A., Liang, K. Y., Bienvenu, O. J., Hoehn-Saric, R., ... Cullen, B. (2001). The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the johns hopkins ocd family study [Journal Article]. *Psychol Med*, *31*(3), 481-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11305856 (cited on page 7)

Nordahl, C. W., Dierker, D., Mostafavi, I., Schumann, C. M., Rivera, S. M., Amaral, D. G., & Van Essen, D. C. (2007). Cortical folding abnormalities in autism revealed by surface-based morphometry [Journal Article]. *J Neurosci*, *27*(43), 11725-35. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17959814 doi: 10.1523/JNEUROSCI.0777-07.2007 (cited on pages 21 and 78)

Okasha, A., Rafaat, M., Mahallawy, N., El Nahas, G., El Dawla, A. S., Sayed, M., & El Kholi, S. (2000). Cognitive dysfunction in obsessive-compulsive disorder [Journal Article]. *Acta Psychiatr Scand*, *101*(4), 281-5. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10782547 (cited on pages 11 and 80)

Olatunji, B. O., Ferreira-Garcia, R., Caseras, X., Fullana, M. A., Wooderson, S., Speckens, A., ... Mataix-Cols, D. (2014). Predicting response to cognitive behavioral therapy in contamination-based obsessive-compulsive disorder from functional magnetic resonance

imaging [Journal Article]. *Psychol Med*, *44*(10), 2125-37. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24229474 doi: 10.1017/S0033291713002766 (cited on pages 14 and 15)

Otto, M. W., Kredlow, M. A., Smits, J. A., Hofmann, S. G., Tolin, D. F., de Kleine, R. A., ... Pollack, M. H. (2016). Enhancement of psychosocial treatment with d-cycloserine: Models, moderators, and future directions [Journal Article]. *Biol Psychiatry*, *80*(4), 274-83. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26520240 doi: 10.1016/j.biopsych.2015.09.007 (cited on page 8)

Palaniyappan, L., & Liddle, P. F. (2012). Differential effects of surface area, gyrification and cortical thickness on voxel based morphometric deficits in schizophrenia [Journal Article]. *Neuroimage*, *60*(1), 693-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22227049 doi: 10.1016/j.neuroimage.2011.12.058 (cited on pages 19, 84, 85, and 86)

Panizzon, M. S., Fennema-Notestine, C., Eyler, L. T., Jernigan, T. L., Prom-Wormley, E., Neale, M., ... Kremen, W. S. (2009). Distinct genetic influences on cortical surface area and cortical thickness [Journal Article]. *Cereb Cortex*, *19*(11), 2728-35. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19299253 doi: 10.1093/cercor/bhp026 (cited on pages 21 and 85)

Pauls, D. L. (2010). The genetics of obsessive-compulsive disorder: a review [Journal Article]. *Dialogues Clin Neurosci*, *12*(2), 149-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20623920 (cited on page 7)

Pauls, D. L., Abramovitch, A., Rauch, S. L., & Geller, D. A. (2014). Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective [Journal Article]. *Nat Rev Neurosci*, *15*(6), 410-24. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24840803 doi: 10.1038/nrn3746 (cited on pages 26, 27, and 91)

Penades, R., Catalan, R., Rubia, K., Andres, S., Salamero, M., & Gasto, C. (2007). Impaired response inhibition in obsessive compulsive disorder [Journal Article]. *Eur Psychiatry*, *22*(6), 404-10. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17127038 doi: 10.1016/j.eurpsy.2006.05.001 (cited on page 11)

Peng, Z., Shi, F., Shi, C., Miao, G., Yang, Q., Gao, W., ... Shen, D. (2014). Structural and diffusion property alterations in unaffected siblings of patients with obsessive-compulsive disorder [Journal Article]. *PLoS One*, *9*(1), e85663. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24489665 doi: 10.1371/journal.pone.0085663 (cited on page 26)

Perani, D., Garibotto, V., Gorini, A., Moresco, R. M., Henin, M., Panzacchi, A., ... Fazio, F. (2008). In vivo pet study of 5ht(2a) serotonin and d(2) dopamine dysfunction in drug-naive obsessive-compulsive disorder [Journal Article]. *Neuroimage*, *42*(1), 306-14. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18511303 doi: 10.1016/j.neuroimage.2008.04.233 (cited on page 8)

Piras, F., Piras, F., Caltagirone, C., & Spalletta, G. (2013). Brain circuitries of obsessive

compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies [Journal Article]. *Neurosci Biobehav Rev*, *37*(10 Pt 2), 2856-77. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24177038 doi: 10.1016/j.neubiorev.2013.10.008 (cited on pages 24 and 80)

Piras, F., Piras, F., Chiapponi, C., Girardi, P., Caltagirone, C., & Spalletta, G. (2015). Widespread structural brain changes in ocd: a systematic review of voxel-based morphometry studies [Journal Article]. *Cortex*, *62*, 89-108. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23582297 doi: 10.1016/j.cortex.2013.01.016 (cited on pages 19, 26, 77, 80, 81, and 83)

Pittenger, C., & Bloch, M. H. (2014). Pharmacological treatment of obsessive-compulsive disorder [Journal Article]. *Psychiatr Clin North Am*, *37*(3), 375-91. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25150568 doi: 10.1016/j.psc.2014.05.006 (cited on page 8)

Posner, J., Marsh, R., Maia, T. V., Peterson, B. S., Gruber, A., & Simpson, H. B. (2014). Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder [Journal Article]. *Hum Brain Mapp*, *35*(6), 2852-60. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24123377 doi: 10.1002/hbm.22371 (cited on pages 16 and 88)

Radua, J., Grau, M., van den Heuvel, O. A., Thiebaut de Schotten, M., Stein, D. J., Canales-Rodriguez, E. J., ... Mataix-Cols, D. (2014). Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder [Journal Article]. *Neuropsychopharmacology*, *39*(7), 1547-57. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24407265 doi: 10.1038/npp.2014.5 (cited on page 24)

Radua, J., van den Heuvel, O. A., Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders [Journal Article]. *Arch Gen Psychiatry*, *67*(7), 701-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20603451 doi: 10.1001/archgenpsychiatry.2010.70 (cited on page 86)

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G. L., Greenstein, D., ... Giedd, J. N. (2011). How does your cortex grow? [Journal Article]. *J Neurosci*, *31*(19), 7174-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21562281 doi: 10.1523/JNEUROSCI.0054-11.2011 (cited on pages 19, 21, and 85)

Reess, T. J., Rus, O. G., Schmidt, R., de Reus, M. A., Zaudig, M., Wagner, G., ... Koch, K. (2016). Connectomics-based structural network alterations in obsessive - compulsive disorder [Journal Article]. *Transl Psychiatry*, *6*(9), e882. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27598966 doi: 10.1038/tp.2016.163 (cited on page 25)

Rosenberg, D. R., & Keshavan, M. S. (1998). A.e. bennett research award. toward a neurodevelopmental model of of obsessive–compulsive disorder [Journal Article]. *Biol Psychiatry*,

43(9), 623-40. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9582996 (cited on pages 21, 22, and 78)

Rotge, J. Y., Guehl, D., Dilharreguy, B., Cuny, E., Tignol, J., Bioulac, B., ... Aouizerate, B. (2008). Provocation of obsessive-compulsive symptoms: a quantitative voxel-based meta-analysis of functional neuroimaging studies [Journal Article]. *J Psychiatry Neurosci*, *33*(5), 405-12. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18787662 (cited on pages 15 and 90)

Rus, O. G., Reess, T. J., Wagner, G., Zaudig, M., Zimmer, C., & Koch, K. (2016). Hypogyrification in obsessive-compulsive disorder [Journal Article]. *Psychol Med*, 1-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27938423 doi: 10.1017/S0033291716003202 (cited on pages 78, 81, 83, 84, 86, 88, 91, and 93)

Rus, O. G., Reess, T. J., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K. (2017a). Functional and structural connectivity of the amygdala in obsessive-compulsive disorder [Journal Article]. *Neuroimage Clin*, *13*, 246-255. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28018851 doi: 10.1016/j.nicl.2016.12.007 (cited on pages 26, 77, 80, 81, 88, 89, 91, and 93)

Rus, O. G., Reess, T. J., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K. (2017b). Structural alterations in obsessive-compulsive disorder: A surface based analysis of cortical volume, surface area and thickness [Journal Article]. *Journal of Psychiatry & Neuroscience*. (cited on pages 77, 80, 81, 83, 84, 88, 91, and 93)

Ruscio, A. M., Stein, D. J., Chiu, W. T., & Kessler, R. C. (2010). The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication [Journal Article]. *Mol Psychiatry*, *15*(1), 53-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18725912 doi: 10.1038/mp.2008.94 (cited on page 3)

Sachdev, P. S., Loo, C. K., Mitchell, P. B., McFarquhar, T. F., & Malhi, G. S. (2007). Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation [Journal Article]. *Psychol Med*, *37*(11), 1645-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17655805 doi: 10.1017/S0033291707001092 (cited on page 8)

Sachdev, P. S., & Malhi, G. S. (2005). Obsessive-compulsive behaviour: a disorder of decision-making [Journal Article]. *Aust N Z J Psychiatry*, *39*(9), 757-63. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16168033 doi: 10.1080/j.1440-1614.2005.01680.x (cited on page 11)

Saxena, S., & Rauch, S. L. (2000). Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder [Journal Article]. *Psychiatr Clin North Am*, *23*(3), 563-86. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10986728 (cited on pages 13, 29, 30, and 88)

Schaer, M., Cuadra, M. B., Schmansky, N., Fischl, B., Thiran, J. P., & Eliez, S. (2012). How to measure cortical folding from mr images: a step-by-step tutorial to compute local

gyrification index [Journal Article]. *J Vis Exp*(59), e3417. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22230945 doi: 10.3791/3417 (cited on page 22)

Schaer, M., Cuadra, M. B., Tamarit, L., Lazeyras, F., Eliez, S., & Thiran, J. P. (2008). A surface-based approach to quantify local cortical gyrification [Journal Article]. *IEEE Trans Med Imaging*, *27*(2), 161-70. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18334438 doi: 10.1109/TMI.2007.903576 (cited on page 22)

Schmaal, L., Hibar, D. P., Samann, P. G., Hall, G. B., Baune, B. T., Jahanshad, N., ... Veltman, D. J. (2016). Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the enigma major depressive disorder working group [Journal Article]. *Mol Psychiatry*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27137745 doi: 10.1038/mp.2016.60 (cited on page 85)

Shapira, N. A., Liu, Y., He, A. G., Bradley, M. M., Lessig, M. C., James, G. A., ... Goodman, W. K. (2003). Brain activation by disgust-inducing pictures in obsessive-compulsive disorder [Journal Article]. *Biol Psychiatry*, *54*(7), 751-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14512216 (cited on page 14)

Shaw, P., Malek, M., Watson, B., Sharp, W., Evans, A., & Greenstein, D. (2012). Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder [Journal Article]. *Biol Psychiatry*, *72*(3), 191-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22418014 doi: 10.1016/j.biopsych.2012.01.031 (cited on pages 21, 78, and 85)

Shaw, P., Sharp, W., Sudre, G., Wharton, A., Greenstein, D., Raznahan, A., ... Rapoport, J. (2015). Subcortical and cortical morphological anomalies as an endophenotype in obsessive-compulsive disorder [Journal Article]. *Mol Psychiatry*, *20*(2), 224-31. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24514568 doi: 10.1038/mp.2014.3 (cited on page 20)

Shin, Y. W., Yoo, S. Y., Lee, J. K., Ha, T. H., Lee, K. J., Lee, J. M., ... Kwon, J. S. (2007). Cortical thinning in obsessive compulsive disorder [Journal Article]. *Hum Brain Mapp*, *28*(11), 1128-35. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17525985 doi: 10.1002/hbm.20338 (cited on page 85)

Simon, D., Adler, N., Kaufmann, C., & Kathmann, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction [Journal Article]. *Neuroimage Clin*, *4*, 549-57. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24818080 doi: 10.1016/j.nicl.2014.03.011 (cited on pages 15, 77, 89, and 90)

Simon, D., Kaufmann, C., Musch, K., Kischkel, E., & Kathmann, N. (2010). Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation [Journal Article]. *Psychophysiology*, *47*(4), 728-38. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20158678 doi: 10.1111/j.1469-8986.2010.00980.x (cited on pages 14 and 89)

Simon, D., Kischkel, E., Spielberg, R., & Kathmann, N. (2012). A pilot study on the validity of using pictures and videos for individualized symptom provocation in obsessive-compulsive disorder [Journal Article]. *Psychiatry Res*, *198*(1), 81-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22414659 doi: 10.1016/j.psychres.2011.12.022 (cited on page 14)

Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging [Journal Article]. *Front Neurosci*, *7*, 31. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23486659 doi: 10.3389/fnins.2013.00031 (cited on pages 23 and 24)

Spalletta, G., Piras, F., Fagioli, S., Caltagirone, C., & Piras, F. (2014). Brain microstructural changes and cognitive correlates in patients with pure obsessive compulsive disorder [Journal Article]. *Brain Behav*, *4*(2), 261-77. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24683518 doi: 10.1002/brb3.212 (cited on pages 25 and 26)

Stephan, K. E., & Mathys, C. (2014). Computational approaches to psychiatry [Journal Article]. *Curr Opin Neurobiol*, *25*, 85-92. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24709605 doi: 10.1016/j.conb.2013.12.007 (cited on page 96)

Storch, E. A., Wilhelm, S., Sprich, S., Henin, A., Micco, J., Small, B. J., ... Geller, D. A. (2016). Efficacy of augmentation of cognitive behavior therapy with weight-adjusted d-cycloserine vs placebo in pediatric obsessive-compulsive disorder: A randomized clinical trial [Journal Article]. *JAMA Psychiatry*, *73*(8), 779-88. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27367832 doi: 10.1001/jamapsychiatry.2016.1128 (cited on page 8)

Szechtman, H., Ahmari, S. E., Beninger, R. J., Eilam, D., Harvey, B. H., Edemann-Callesen, H., & Winter, C. (2016). Obsessive-compulsive disorder: Insights from animal models [Journal Article]. *Neurosci Biobehav Rev*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27168347 doi: 10.1016/j.neubiorev.2016.04.019 (cited on page 26)

Tallinen, T., Chung, J. Y., Biggins, J. S., & Mahadevan, L. (2014). Gyrification from constrained cortical expansion [Journal Article]. *Proc Natl Acad Sci U S A*, *111*(35), 12667-72. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25136099 doi: 10.1073/pnas.1406015111 (cited on page 22)

Tamnes, C. K., Herting, M. M., Goddings, A. L., Meuwese, R., Blakemore, S. J., Dahl, R. E., ... Mills, K. L. (2017). Development of the cerebral cortex across adolescence: A multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness [Journal Article]. *J Neurosci*, *37*(12), 3402-3412. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28242797 doi: 10.1523/JNEUROSCI.3302-16.2017 (cited on page 85)

Taylor, S. (2011). Etiology of obsessions and compulsions: a meta-analysis and narrative review of twin studies [Journal Article]. *Clin Psychol Rev*, *31*(8), 1361-72. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22024245 doi: 10.1016/j.cpr.2011.09

.008 (cited on page 7)

Taylor, S. (2013). Molecular genetics of obsessive-compulsive disorder: a comprehensive meta-analysis of genetic association studies [Journal Article]. *Mol Psychiatry*, *18*(7), 799-805. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22665263 doi: 10.1038/mp.2012.76 (cited on page 8)

Torres, A. R., Prince, M. J., Bebbington, P. E., Bhugra, D., Brugha, T. S., Farrell, M., ... Singleton, N. (2006). Obsessive-compulsive disorder: prevalence, comorbidity, impact, and help-seeking in the british national psychiatric morbidity survey of 2000 [Journal Article]. *Am J Psychiatry*, *163*(11), 1978-85. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17074950 doi: 10.1176/ajp.2006.163.11.1978 (cited on page 3)

Trevizol, A. P., Shiozawa, P., Cook, I. A., Sato, I. A., Kaku, C. B., Guimaraes, F. B., ... Cordeiro, Q. (2016). Transcranial magnetic stimulation for obsessive-compulsive disorder: An updated systematic review and meta-analysis [Journal Article]. *J ECT*, *32*(4), 262-266. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27327557 doi: 10.1097/YCT.0000000000000335 (cited on page 8)

Vaghi, M. M., Vertes, P. E., Kitzbichler, M. G., Apergis-Schoute, A. M., van der Flier, F. E., Fineberg, N. A., ... Robbins, T. W. (2016). Specific frontostriatal circuits for impaired cognitive flexibility and goal-directed planning in obsessive-compulsive disorder: Evidence from resting-state functional connectivity [Journal Article]. *Biol Psychiatry*. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27769568 doi: 10.1016/j.biopsych.2016.08.009 (cited on page 16)

van den Heuvel, O. A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S. R., Nakamae, T., ... Veltman, D. J. (2016). Brain circuitry of compulsivity [Journal Article]. *Eur Neuropsychopharmacol*, *26*(5), 810-27. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26711687 doi: 10.1016/j.euroneuro.2015.12.005 (cited on pages 30, 31, and 32)

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2005). Twin studies on obsessive-compulsive disorder: a review [Journal Article]. *Twin Res Hum Genet*, *8*(5), 450-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16212834 doi: 10.1375/183242705774310060 (cited on page 7)

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2007). Genetic and environmental influences on obsessive-compulsive symptoms in adults: a population-based twin-family study [Journal Article]. *Psychol Med*, *37*(11), 1635-44. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17592667 doi: 10.1017/S0033291707000980 (cited on page 7)

van Velzen, L. S., de Wit, S. J., Curcic-Blake, B., Cath, D. C., de Vries, F. E., Veltman, D. J., ... van den Heuvel, O. A. (2015). Altered inhibition-related frontolimbic connectivity in obsessive-compulsive disorder [Journal Article]. *Hum Brain Mapp*, *36*(10), 4064-75. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26183689 doi: 10.1002/hbm

.22898 (cited on page 17)

Venkatasubramanian, G., Zutshi, A., Jindal, S., Srikanth, S. G., Kovoor, J. M., Kumar, J. K., & Janardhan Reddy, Y. C. (2012). Comprehensive evaluation of cortical structure abnormalities in drug-naive, adult patients with obsessive-compulsive disorder: a surface-based morphometry study [Journal Article]. *J Psychiatr Res*, *46*(9), 1161-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22770508 doi: 10.1016/j.jpsychires.2012.06.003 (cited on pages 21, 23, 84, and 86)

Via, E., Cardoner, N., Pujol, J., Alonso, P., Lopez-Sola, M., Real, E., ... Harrison, B. J. (2014). Amygdala activation and symptom dimensions in obsessive-compulsive disorder [Journal Article]. *Br J Psychiatry*, *204*(1), 61-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24262816 doi: 10.1192/bjp.bp.112.123364 (cited on pages 14 and 15)

Watkins, L. H., Sahakian, B. J., Robertson, M. M., Veale, D. M., Rogers, R. D., Pickard, K. M., ... Robbins, T. W. (2005). Executive function in tourette's syndrome and obsessive-compulsive disorder [Journal Article]. *Psychol Med*, *35*(4), 571-82. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15856727 (cited on page 11)

Whiteside, S. P., Port, J. D., & Abramowitz, J. S. (2004). A meta-analysis of functional neuroimaging in obsessive-compulsive disorder [Journal Article]. *Psychiatry Res*, *132*(1), 69-79. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15546704 doi: 10.1016/j.pscychresns.2004.07.001 (cited on page 13)

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., ... Glahn, D. C. (2010). Cortical thickness or grey matter volume? the importance of selecting the phenotype for imaging genetics studies [Journal Article]. *Neuroimage*, *53*(3), 1135-46. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20006715 doi: 10.1016/j.neuroimage.2009.12.028 (cited on pages 21 and 85)

Wobrock, T., Gruber, O., McIntosh, A. M., Kraft, S., Klinghardt, A., Scherk, H., ... Moorhead, T. W. (2010). Reduced prefrontal gyrification in obsessive-compulsive disorder [Journal Article]. *Eur Arch Psychiatry Clin Neurosci*, *260*(6), 455-64. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20112027 doi: 10.1007/s00406-009-0096-z (cited on pages 21, 22, and 86)

Yoon, S., Jun, C. S., Jeong, H. S., Lee, S., Lim, S. M., Ma, J., ... Lyoo, I. K. (2013). Altered cortical gyrification patterns in panic disorder: deficits and potential compensation [Journal Article]. *J Psychiatr Res*, *47*(10), 1446-54. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23871448 doi: 10.1016/j.jpsychires.2013.06.015 (cited on page 87)

Zhang, Y., Yu, C., Zhou, Y., Li, K., Li, C., & Jiang, T. (2009). Decreased gyrification in major depressive disorder [Journal Article]. *Neuroreport*, *20*(4), 378-80. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19218876 doi: 10.1097/WNR.0b013e3283249b34 (cited on page 87)

Zilles, K., Palomero-Gallagher, N., & Amunts, K. (2013). Development of cortical folding during evolution and ontogeny [Journal Article]. *Trends Neurosci*, *36*(5), 275-84. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23415112 doi: 10.1016/j.tins.2013.01.006 (cited on pages 21, 22, 81, and 86)

Zohar, J., Chopra, M., Sasson, Y., Amiaz, R., & Amital, D. (2000). Obsessive compulsive disorder: serotonin and beyond [Journal Article]. *World J Biol Psychiatry*, *1*(2), 92-100. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12607204 (cited on page 8)

Own Publications

Alves-Pinto, A., Rus, O. G., Reess, T. J., A., W., Wagner, G., Zaudig, M., & Koch, K. (2017). Altered connectivity of reward-related neuronal dynamics in obsessive - compulsive disorder [Journal Article].
(in preparation)

Koch, K., Reess, T. J., Rus, O. G., Gürsel, D., Wagner, G., Zaudig, M., & Zimmer, C. (n.d.). Increased default mode network connectivity in obsessive–compulsive disorder during reward processing [Journal Article]. *J Psychiatr Res*. (submitted)

Koch, K., Reess, T. J., Rus, O. G., & Zimmer, C. (2016). Extensive learning is associated with gray matter changes in the right hippocampus. *NeuroImage*, *125*, 627 - 632. Retrieved from http://www.sciencedirect.com/science/article/pii/S1053811915009672 doi: http://dx.doi.org/10.1016/j.neuroimage.2015.10.056

Koch, K., Reess, T. J., Rus, O. G., Zimmer, C., & Zaudig, M. (2014). Diffusion tensor imaging (dti) studies in patients with obsessive-compulsive disorder (ocd): a review [Journal Article]. *J Psychiatr Res*, *54*, 26-35. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24694669 doi: 10.1016/j.jpsychires.2014.03.006 (cited on page 24)

Koch, K., Rus, O. G., Reess, T. J., Schachtzabel, C., Schultz, C., Sorg, C., & Schlösser, R. (2014). Functional connectivity and grey matter volume of the striatum in schizophrenia [Journal Article]. *Br J Psychiatry*, *205*, 204-213. Retrieved from http://bjp.rcpsych.org/content/205/3/204.long doi: doi:10.1192/bjp.bp.113.138099

Reess, T. J., Rus, O. G., Gürsel, D. A., Schmitz-Koepa, B., Wagner, B. G., G., & Koch, K. (2017). Association between hippocampus volume and symptom profiles in obsessive -compulsive disorder [Journal Article]. *Neuroimage Clin*. (in review)

Reess, T. J., Rus, O. G., Schmidt, R., de Reus, M. A., Zaudig, M., Wagner, G., ... Koch, K. (2016). Connectomics-based structural network alterations in obsessive - compulsive disorder [Journal Article]. *Transl Psychiatry*, *6*(9), e882. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27598966 doi: 10.1038/tp.2016.163 (cited on page 25)

Reess, T. J., Rus, O. G., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K. (2017). Neural correlates of risk aversion in obsessive-compulsive disorder [Journal Article].
(in preparation)

Rus, O. G., Reess, T. J., Wagner, G., Zaudig, M., Zimmer, C., & Koch, K. (2016). Hypogyrifica-

tion in obsessive-compulsive disorder [Journal Article]. *Psychol Med*, 1-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27938423 doi: 10.1017/S0033291716003202 (cited on pages 78, 81, 83, 84, 86, 88, 91, and 93)

Rus, O. G., Reess, T. J., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K. (2017a). Functional and structural connectivity of the amygdala in obsessive-compulsive disorder [Journal Article]. *Neuroimage Clin*, *13*, 246-255. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28018851 doi: 10.1016/j.nicl.2016.12.007 (cited on pages 26, 77, 80, 81, 88, 89, 91, and 93)

Rus, O. G., Reess, T. J., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K. (2017b). Structural alterations in obsessive-compulsive disorder: A surface based analysis of cortical volume, surface area and thickness [Journal Article]. *Journal of Psychiatry & Neuroscience*. (cited on pages 77, 80, 81, 83, 84, 88, 91, and 93)

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Affidavit - Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation “The obsessed brain - Functional and structural neural correlates in obsessive-compulsive disorder“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kentlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “The obsessed brain - Functional and structural neural correlates in obsessive-compulsive disorder“ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 21.07.2017 Oana Georgiana Rus

Declaration of Author Contributions

1.Publication: Functional and structural connectivity of the amygdala in obsessive-compulsive disorder Rus, O. G., Reess, T. J., Wagner, G., Zimmer, C., Zaudig, M., & Koch, K., (2017), Neuroimage: Clinical

The author of the thesis is the first author of the research article; O.G.R, T.J.R. and K.K. - conception and design, acquisition of data, analysis and interpretation of data, manuscript revision; O.G.R. - drafted the article; G.W. - conception of data, revision manuscript; C.Z. - data acquisition. M.Z. - patient collection; all authors - final approval of published version.

2.Publication: Structural alterations in patients with obsessive-compulsive disorder: A surface based analysis of cortical volume, surface area and thickness Rus, O. G., Reess, T. J., Wagner, G., Zaudig, M., Zimmer, C., & Koch, K., submitted at Journal of Psychiatry and Neuroscience

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Herby I confirm that the contributions to each publication are correct.

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