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Altered Cortico-Striatal Functional Connectivity During Resting State in Obsessive-Compulsive Disorder

Benita Magdalena Maria Schmitz-Koep

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1. Prof. Dr. Claus Zimmer
2. apl. Prof. Dr. Kathrin Koch

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Contents

1. Preliminary remarks

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Authors: Jessica Calzà, Deniz A. Gürsel, Benita Schmitz-Koep, Benno Bremer, Lena Reinholz, Götz Berberich, Kathrin Koch

Study design: Kathrin Koch and Götz Berberich

Data acquisition: Deniz A. Gürsel, Benita Schmitz-Koep, Benno Bremer and Lena Reinholz

Data analyses: Jessica Calzà

Manuscript writing: Jessica Calzà, Deniz A. Gürsel, Benita Schmitz-Koep, Benno Bremer, Lena Reinholz, Götz Berberich and Kathrin Koch

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2. Abstract

Obsessive-compulsive disorder (OCD) is a seriously impairing psychiatric disorder. It has long been associated with alterations in the cortico-striato-thalamo-cortical pathway (CSTC). More specifically, an imbalance between the direct and the indirect pathway has been proposed as a pathophysiological mechanism behind OCD symptoms. Functional connectivity (FC) studies using resting state functional magnetic resonance imaging (fMRI) have given more evidence for the disruption of the CSTC. However, results are heterogeneous.

Since FC within the CSTC as a whole has not been investigated yet, the present study aimed at exploring FC within all relevant nodes of the direct and indirect pathway of the CSTC in 44 OCD patients and 40 healthy controls.

Analyses showed an increased FC between the left subthalamic nucleus (STN) and the left external globus pallidus (GPe), as well as an increased FC between the left GPe and the left internal globus pallidus (GPi) in patients with OCD compared to healthy controls.

The results further support CSTC involvement in OCD pathology. However, our findings showing increased FC between relevant structures of the indirect pathway contradict the current hypothesis and could introduce an altered interpretation of the classical model of the CSTC. The results highlight the role of the STN, which is a relevant target region of deep brain stimulation (DBS) in patients with treatment-refractory OCD. Hence, our findings could contribute a neurobiological framework to a better comprehension of the fundamental processes underlying DBS. They could provide a basis for future investigations improving the accurate choice of DBS targets and thus increasing clinical outcome for patients as well as reducing the probability of adverse events.

3. Zusammenfassung

Die Zwangserkrankung ist eine psychiatrische Erkrankung mit hohem Leidensdruck. Schon früh konnte sie mit Veränderungen im kortiko-striato-thalamo-kortikalen Regelkreis in Verbindung gebracht werden. Als zugrunde liegende Pathophysiologie der Zwangserkrankung wird ein Ungleichgewicht zwischen dem direkten und dem indirekten Weg dieses Regelkreises angenommen. Die These der Störung des kortiko-striato-thalamo-kortikalen Regelkreises wird unterstützt durch Untersuchungen der funktionellen Konnektivität im Ruhezustand mittels funktioneller Magnetresonanztomographie, Ergebnisse dieser Studien sind jedoch heterogen.

Da die funktionelle Konnektivität innerhalb des kortiko-striato-thalamo-kortikalen Regelkreises in seiner Gesamtheit bisher noch nicht beleuchtet wurde, untersucht die hier beschriebene Studie die funktionelle Konnektivität zwischen allen relevanten Knotenpunkten des direkten und indirekten Weges dieses Regelkreises an 44 Patienten mit Zwangserkrankung im Vergleich zu 40 gesunden Probanden.

Hierbei zeigte sich bei Patienten mit Zwangserkrankung eine erhöhte funktionelle Konnektivität zwischen dem linken Nucleus subthalamicus und Globus pallidus externus sowie zwischen dem linken Globus pallidus externus und internus.

Diese Ergebnisse heben die Relevanz des indirekten Weges, insbesondere des Nucleus subthalamicus, hervor und lassen möglicherweise die Funktion des kortiko-striato-thalamo-kortikalen Regelkreises in einem neuen Licht erscheinen. Darüber hinaus könnten die Ergebnisse das Verständnis der Tiefenhirnstimulation als Therapieoption für schwere Zwangsstörungen verbessern.

4. Abbreviations

ACC	- Anterior cingulate cortex
ADHD	- Attention deficit hyperactivity disorder
BOLD	- Blood oxygenation level dependent
CBT	- Cognitive-behavioural therapy
CSTC	- Cortico-striato-thalamo-cortical pathway
DBS	- Deep brain stimulation
DSM-V	- Diagnostic and Statistical Manual of Mental Disorders
EPI	- Echo planar imaging
FC	- Functional connectivity
FD	- Framewise displacement
FDR	- False discovery rate
FID	- Free induction decay
fMRI	- Functional magnetic resonance imaging
FOV	- Field of view
GE	- Gradient echo
GPe	- External globus pallidus
GPi	- Internal globus pallidus
HAM-D	- Hamilton Depression rating scale
ICD-10	- International Statistical Classification of Diseases and Related Health Problems, 10th Revision
MPRAGE	- Magnetisation prepared rapid acquisition by gradient echo
OCD	- Obsessive-compulsive disorder
OCI-R	- Obsessive-Compulsive Inventory – Revised
OFC	- Orbitofrontal cortex
PET	- Positron emission tomography
RF	- Radiofrequency
ROI	- Region of interest
SD	- Standard deviation
SNr	- Substantia nigra
SPECT	- Single photon emission computed tomography
SRI	- Serotonin reuptake inhibitors
SSNRI	- Selective serotonin-norepinephrine reuptake inhibitor

SSRI	- Selective serotonin reuptake inhibitor
STN	- Subthalamic nucleus
TCA	- Tricyclic antidepressants
TE	- Echo time
TR	- Repetition time
Y-BOCS	- Yale-Brown Obsessive Compulsive Scale

5. Introduction

Obsessive compulsive disorder

Definition

Obsessive-compulsive disorder (OCD) is a psychiatric disorder defined by recurrent obsessive thoughts, which are hardly or not at all controllable, and resulting repetitive compulsive actions, which are meant to attenuate distressful obsessive thoughts. Actions cause a temporary relief, which leads to reinforcement (Figure 1). Also forms of obsession-only or compulsion-only OCD occur.

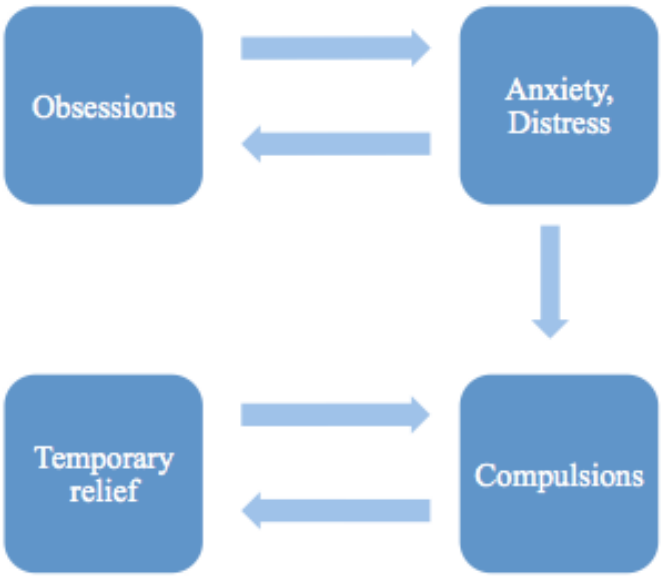

Figure 1: Cycles of reinforcement in OCD.

Modified from Pauls, Abramovitch, Rauch and Geller (2014).

Symptoms and diagnosis

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) by the American Psychiatric Association defines obsessions as "recurrent and persistent thoughts, urges or images". Obsessions are encountered as "intrusive and unwanted, and […] cause marked anxiety or distress" in most individuals. Patients attempt "to ignore or supress […], or to neutralise them with some other thought or action (i.e., by performing a compulsion)." Compulsions are "repetitive behaviours […] or mental acts" performed "in response to an obsession or according to rules that must be applied rigidly" to reduce anxiety or distress and to prevent a dreaded event or situation. The diagnosis of OCD requires the

presence of obsessions, compulsions or both. Obsessions and/or compulsions are required to be time-consuming, cause significant distress or functional impairment and must not be attributable to the effects of substances or other medical conditions. The quality of insight (good/fair vs. poor vs. absent-delusional) is also taken into account by the DSM-V (American Psychiatric Association, 2013). The International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) further specifies compulsions as not inherently enjoyable and not resulting in the completion of a useful task. ICD-10 diagnostic criteria are outlined in figure 2. OCD symptoms include a very broad variety of dimensions. Obsessions may involve aggression, sexuality, religion, somatic symptoms, symmetry, contamination and hoarding, to mention the most common topics. They result in compulsions such as checking, ordering, counting, rituals, cleaning and collecting (Leckman et al., 1997). This heterogeneity makes it challenging to diagnose as well as to treat. OCD particularly interferes with relationships, social functioning and home management (Ruscio, Stein, Chiu, & Kessler, 2010). A recent study revealed that patients with OCD have an increased risk of both dying by suicide as well as attempting suicide even after adjusting for psychiatric comorbidities (Fernández de la Cruz et al., 2017). This further highlights the need for thorough monitoring of patients with OCD and adequate therapy.

ICD-10 Diagnostic Criteria
F42 Obsessive-compulsive disorder

- A. Obsessions, compulsions or both; present on most days for ≥ 2 weeks
- B. All of the following features must be present for obsessions an compulsions:
  - 1) acknowledged as orignated in mind of patient, not imposed by outside person or influences
  - 2) repetitive and unpleasant, at least one obsession or compulsion is acknowledged as excessive or unreasonable
  - 3) patient tries to resist, at least one obsession or compulsion which is unsuccesfully resisted
  - 4) Obsession or compulsion is not in itself pleasurable
- C. Obsessions or compulsions cause distress or interfere with social or individual functioning
- D. Exclusion criteria: not the result of other mental disorders

Figure 2: ICD-10 diagnostic criteria for OCD.

Adapted from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

Epidemiology

Ruscio et al. (2010) estimate a lifetime prevalence of 2.3% and a 12-month prevalence of 1.2 %. It has been suggested that age of onset can be divided into two subgroups, one representing early onset with a mean of 11 years, the other one representing late onset with a mean of 23 years, the cut-off being 21 years (Taylor, 2011a). Ruscio et al. (2010) found significantly higher odds of onset for females compared to males (odds ratio 2.1). However, males seem more likely to have early onset (Ruscio et al., 2010; Taylor, 2011a). OCD often is a seriously impairing disorder with patients spending a mean of nearly 9 years suffering from it (Ruscio et al., 2010).

Aetiology

Family and twin studies have been investigated in meta-analyses and reviews suggesting familial predisposition of OCD and proposing genetic as well as environmental factors to play an important role in the development of OCD (Pauls, 2010; Taylor, 2011b).

Comorbidities

OCD is very often associated with other psychiatric conditions (Ruscio et al., 2010; Torres et al., 2006). This further complicates diagnosis and treatment of OCD. Most common comorbidities are anxiety disorders, mood disorders, impulse control disorders and substance use disorders and, typically, these mental disorders predate the onset of OCD (Ruscio et al., 2010).

Therapy

The American Psychiatric Association recommends cognitive-behavioural therapy (CBT) and serotonin reuptake inhibitors (SRIs) as first-line treatments. Depending on individual patient factors either monotherapy with CBT or SRIs or combined treatment can be effective. CBT including exposure and response prevention has the best evidentiary support. As pharmacological treatment clomipramine, fluoxetine, fluvoxamine, paroxetine and sertraline are recommended. Regarding side effects, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, fluvoxamine, paroxetine and sertraline are preferred over the tricyclic antidepressant clomipramine (Koran et al., 2007). However, even with best available treatment applied, about 10% of the patients with OCD do not have a clinically meaningful response and suffer from treatment-refractory OCD (Denys, 2006). In these cases there are alternative treatments to be considered including neuroleptic augmentation and neurosurgical techniques, such as ablative procedures and deep brain stimulation (DBS) (Hirschtritt, Bloch, & Mathews, 2017).

Cortico-striato-thalamo-cortical pathway (CSTC)

Neurobiological model

It has long been suggested by Alexander, DeLong and Strick (1986) that the basal ganglia are part of multiple parallel, segregated circuits forming closed loops. Distinct areas of the cortex project to corresponding parts of the thalamus via specific regions of the basal ganglia. The thalamus then projects back to the cortex, as illustrated in Figure 3. However, as these pathways have been reviewed, it has been shown that not only parallel but also integrative processing occurs (Haber & Knutson, 2010).

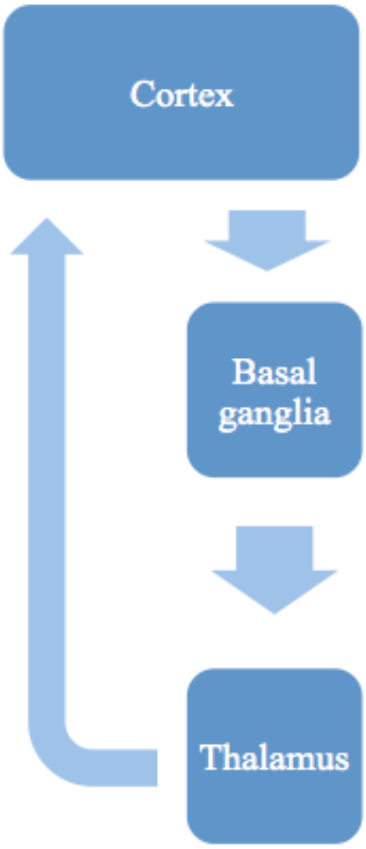

Figure 3: The generalised basal ganglia-thalamocortical circuit.

The cortex projects to the thalamus via the basal ganglia. The thalamus then projects back to the cortex.
Modified from Alexander et al. (1986).

Alexander and Crutcher (1990) furthermore proposed that within these loops two pathways could be discriminated: The direct and the indirect pathway. The direct pathway involves excitatory signals from the cortex to the striatum. The striatum inhibits the internal globus pallidus (GPi) and pars reticulata of substantia nigra (SNr). This decreases inhibitory signalling from GPi and SNr to the thalamus resulting in higher activation of the thalamus.

The thalamus then projects back to the cortex via excitatory neurons. Thus, the direct pathway results in overall excitation of the cortex. It is therefore considered a positive feedback loop. The indirect pathway also involves excitatory signals from the cortex to the striatum. The striatum inhibits the external globus pallidus (GPe), which then exerts less inhibition on the subthalamic nucleus (STN). This increases the excitatory signalling from the STN to the GPi and SNr, which inhibit the thalamus. Therefore, the indirect pathway results in an overall inhibition of the cortex. It is considered a negative-feedback loop (Alexander & Crutcher, 1990; Saxena & Rauch, 2000). Excitatory projections are mainly glutamatergic, whereas inhibitory projections predominantly use gamma aminobutyric acid as a neurotransmitter (Graybiel, 1990). The direct pathway and the indirect pathway are illustrated in Figure 4. Various cognitive processes and motor functions have been associated to the CSTC (Alexander et al., 1986; Middleton & Strick, 2000). These include reward-based learning, decision making, goal directed behaviour, procedural and habit learning, action selection and execution, action inhibition and control of impulsivity (Baxter et al., 1996; Fitzgerald et al., 2011; Graybiel & Rauch, 2000; Saxena & Rauch, 2000).

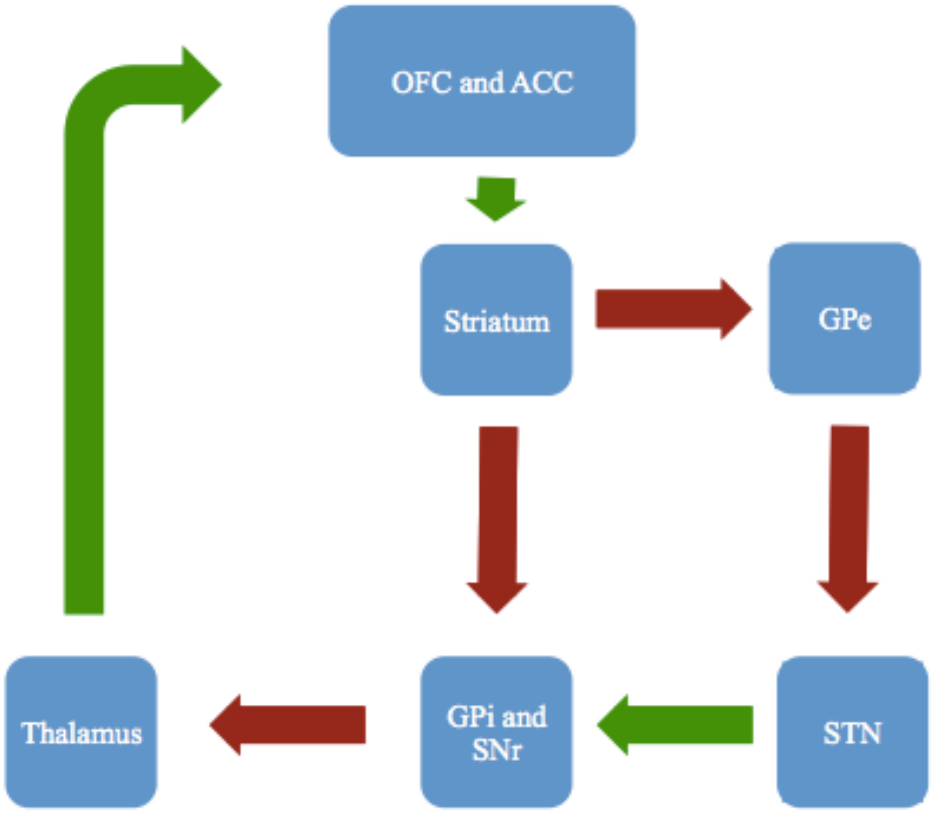

Figure 4: The CSTC.

Green arrows indicate excitatory pathways, whereas red arrows indicate inhibitory pathways. The direct pathway involves excitatory signals from the cortex to the striatum. The striatum inhibits the internal globus pallidus (GPi) and pars reticulate of substantia nigra (SNr). This decreases inhibitory signalling from GPi and SNr to the thalamus resulting in higher activation of the thalamus. The thalamus then projects back to the cortex via excitatory neurons. Thus, the direct pathway results in overall excitation of the cortex. It is therefore considered a positive feedback loop. The indirect pathway also involves excitatory signals from the cortex to the striatum. The striatum inhibits the external globus pallidus (GPe), which then exerts less inhibition on the subthalamic nucleus (STN). This increases the excitatory signalling from the STN to the GPi and SNr, which inhibit the thalamus. Therefore, the indirect pathway results in an overall inhibition of the cortex. It is considered a negative-feedback loop.

Abbreviations: OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, GPe = external globus pallidus, STN = subthalamic nucleus, GPi = internal globus pallidus, SNr = substantia nigra.

Modified from Pauls et al. (2014).

Pathophysiology of OCD

As reviewed by Saxena and Rauch (2000), functional neuroimaging studies have long identified abnormalities in the activity of the orbitofrontal cortex (OFC), the anterior cingulate

cortex (ACC), the basal ganglia and the thalamus in patients with OCD. More specifically, these parts of the CSTC showed elevated activity in baseline neuroimaging studies. Activity was further increased in symptom-provocation studies and decreased with successful treatment (Saxena & Rauch, 2000). Based on these findings, a neurobiological model of the pathophysiology of OCD has been proposed: In healthy individuals, inhibition from the indirect pathway modulates activation of the direct pathway. Since the direct pathway is thought to result in action execution, whereas the indirect pathway leads to action inhibition and the stop of impulsive behaviour, a balance between direct and indirect pathway is of crucial importance for adaption of behaviour. In patients with OCD, stimuli, such as perceived threats (for example concerns about hygiene), lead to excess activation of the direct pathway relative to the indirect pathway via the orbitofrontal cortex, resulting in an overall hyperactivity of the CSTC. As shown in Figure 5, elevated activity of the cortex leads to increased activation of the striatum. The striatum then exerts more inhibition on the GPi and SNr, which then have less ability to inhibit the thalamus. Higher activation of the thalamus loops back to higher activation of the cortex. Obsessive thoughts and compulsive behaviour follow (Baxter et al., 1996; Saxena & Rauch, 2000; Saxena, Bota, & Brody, 2001).

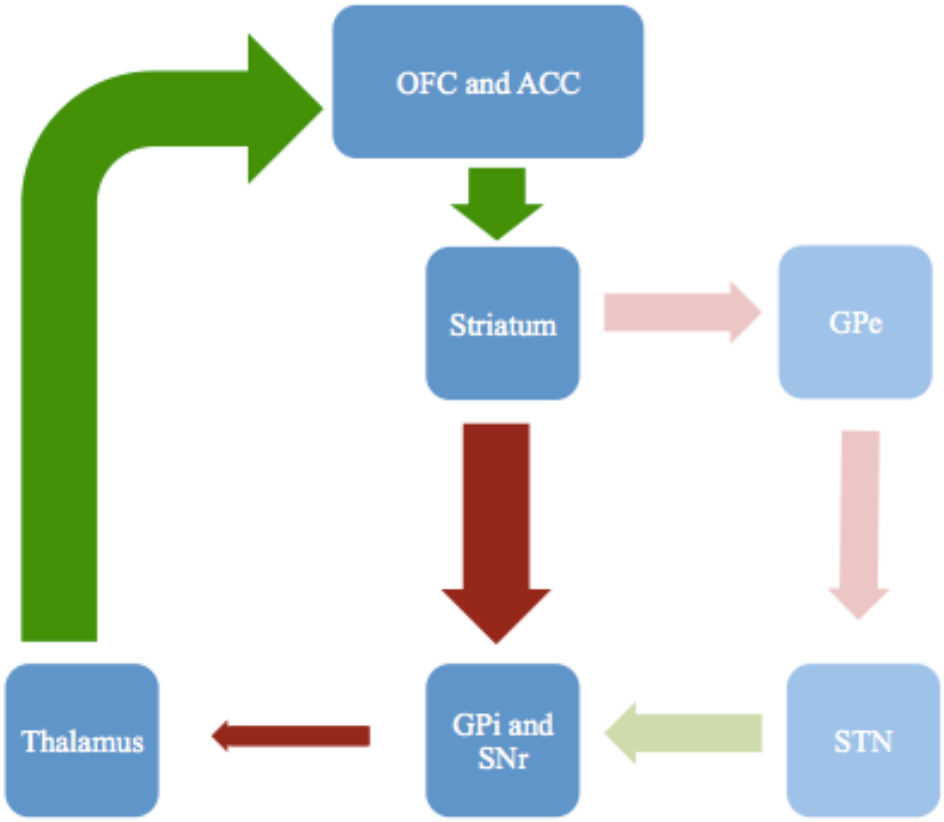

Figure 5: Imbalance of the CSTC in patients with OCD.

Green arrows indicate excitatory pathways, whereas red arrows indicate inhibitory pathways. The dark arrow shows the direct pathway, lighter colours show the indirect pathway. In patients with OCD, stimuli, such as perceived threats (for example concerns about hygiene), are thought to lead to excess activation of the direct pathway via the orbitofrontal cortex relative to the indirect pathway, resulting in an overall hyperactivity of the CSTC. Elevated activity of the cortex leads to increased activation of the striatum. The striatum then exerts more inhibition on the GPi and SNr, which then have less ability to inhibit the thalamus. Higher activation of the thalamus loops back to higher activation of the cortex. Abbreviations: OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, GPe = external globus pallidus, STN = subthalamic nucleus, GPi = internal globus pallidus, SNr = substantia nigra.
Modified from Pauls et al. (2014) .

As mentioned above, changes in activity of regions within the CSTC have given more insight into the pathophysiology of OCD and have laid the groundwork for the neurobiological model described. Furthermore, these regions have repeatedly been investigated to show structural alterations, both with regard to white as well as gray matter abnormalities (Piras, Piras, Caltagirone, & Spalletta, 2013; Piras et al., 2015). It has been indicated that microstructural changes in long-range connections within the CSTC might constitute the basis of its aberrant functional activity, as systematic meta-analyses reported alterations in fronto-basal white

matter pathways targeting the orbitofrontal cortex and the anterior cingulate cortex (Koch, Reeß, Rus, Zimmer, & Zaudig, 2014; Piras et al., 2013). The most important facts about the relevant elements of the CSTC are briefly summarised in the following chapters.

Orbitofrontal cortex

Possibly the first evidence for the specific function of the OFC was described by Harlow in 1868: Phineas Gage showed grave changes in behaviour after injury to the ventromedial prefrontal cortex by an iron rod (Harlow, 1868). Similarly, Eslinger and Damasio studied a patient in 1985 with damage to the frontal lobe after resection of an orbitofrontal meningioma (Eslinger & Damasio, 1985). Comparable to Gage, this patient had intact cognitive abilities such as solving abstract problems, however, appropriate emotion processing and social behaviour were lost (H. Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Furthermore, the OFC has been associated with reward-related and punishment-related learning and reversal learning as well as with decision-making (Bechara, Damasio, Damasio, & Anderson, 1994; Kringelbach & Rolls, 2004; Rolls, 1996; Tremblay & Schultz, 1999). Glucose hypermetabolism of the orbital gyri in OCD patients has early been identified by Baxter et al. (1987; 1988) using positron emission tomography (PET). Since then the OFC has repeatedly shown elevated metabolism in baseline PET studies (Sawle, Hymas, Lees, & Frackowiak, 1991; Swedo et al., 1989). Concordantly, OFC glucose uptake was further increased during symptom-provocation and decreased after treatment (Benkelfat et al., 1990; Cottraux et al., 1996; McGuire et al., 1994; Rauch et al., 1994; Swedo et al., 1992). For a review, see Saxena and Rauch (2000). Also functional magnetic-resonance imaging (fMRI) studies have shown hyperactivity of the OFC in patients with OCD during symptom provocation and during resting state (Adler et al., 2000; Breiter et al., 1996; Hou et al., 2012). The OFC is particularly active in situations of high uncertainty or unpredictability (Elliott, Dolan, & Frith, 2000). This is in line with findings by Ursu and Carter (2009), which showed fMRI hyperactivity of the OFC in anticipation of aversive events, independently of OCD-specific stimuli, in OCD patients. All of these studies underline that the OFC plays a crucial role in OCD pathophysiology.

Anterior cingulate cortex

It has long been suggested that the ACC is involved in executive functions (D'Esposito et al., 1995; Posner, 1994). The ACC monitors response competition in situations of conflict, shows error related activity and is therefore also termed as the error monitoring system of the brain (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Botvinick, Nystrom, Fissell, Carter, &

Cohen, 1999; Carter, Botvinick, & Cohen, 1999; Carter et al., 1998; van Veen & Carter, 2002). Dorsal ACC has also been proposed to play a role in reward-based decision making (Bush et al., 2002). Glucose metabolism in the cingulate cortex has been found to be increased in patients with OCD (Perani et al., 1995; Swedo et al., 1989) and decreased after treatment (Perani et al., 1995). Symptom provocation showed higher activation using PET and fMRI (Breiter et al., 1996; Rauch et al., 1994). For a review, see Saxena and Rauch (2000). Task performance fMRI studies have identified alterations in ACC activity in patients with OCD compared to healthy controls: The rostral ACC showed greater error-related activation in OCD patients than in healthy controls (Fitzgerald et al., 2005). Ursu, Stenger, Shear, Jones and Carter (2003) demonstrated increased error-related activity as well as increased conflict-related activity during correct trials in the ACC in patients with OCD. Furthermore, they related this increased activity to repetitive actions in OCD as a consequence of critical self-evaluation and the inappropriate need for correction (Ursu et al., 2003). Rostral and caudal ACC were hyperactive in OCD patients in a speeded reaction time task during both error and correctly rejected high-conflict trials, possibly representing a failure in response inhibition in OCD patients as well as an excessive error monitoring (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005). Furthermore, during a working memory task, with increasing task demands decreased activation in the dorsal ACC was observed in OCD patients compared to healthy controls (Koch et al., 2012). These task performance studies document the involvement of ACC activity alterations in OCD pathology. Moreover, cingulotomy led to clinical improvement in some patients with severe, treatment-refractory OCD, further highlighting the importance of the ACC in the pathophysiology of the illness (Dougherty et al., 2002).

Striatum

The striatum is part of the basal ganglia and is considered its main input structure (Alexander et al., 1986). It includes caudate nucleus, putamen and nucleus accumbens. The striatum is involved in the learning of motor skills (Seitz, Roland, Bohm, Greitz, & Stone-Elander, 1990). Furthermore, it shows activation when reward is anticipated (O'Doherty, Deichmann, Critchley, & Dolan, 2002). Specifically the ventral striatal nucleus accumbens reacts proportionally to increasing rewards but not punishments (Knutson, Adams, Fong, & Hommer, 2001a). Activation subsides when reward is received and is even suppressed when expected reward does not occur (Knutson, Fong, Adams, Varner, & Hommer, 2001b). Beyond that, it plays a role in numerous other kinds of behavioural processes, such as learning and memory (reviewed by Schultz, Tremblay and Hollerman (2003)). As illustrated

in Figure 5, the traditional neurobiological model of OCD pathophysiology suggests increased activation of the striatum. In patients with OCD, studies using PET have found hypermetabolism in the caudate nucleus (Baxter et al., 1987; 1988), which decreased after treatment (Baxter et al., 1992; Benkelfat et al., 1990; Saxena et al., 1999; Schwartz, 1996). Symptom-provocation elevated activity in the caudate/striatum, as shown using PET (McGuire et al., 1994; Rauch et al., 1994) and using fMRI (Breiter et al., 1996). For a review, see Saxena and Rauch (2000). However, structural and functional findings in the caudate nucleus are heterogeneous and could not consistently verify a dysfunction (Aylward et al., 1996). On the other hand, there have been studies investigating focal lesions of the basal ganglia which found obsessive-compulsive behaviour in patients with lesions in the caudate nucleus (Berthier, Kulisevsky, Gironell, & Heras, 1996; Laplane et al., 1989). Furthermore, a meta-analysis conducted by Whiteside, Port and Abramowitz (2004) including PET and single photon emission computed tomography (SPECT) studies reported consistent differences in radiotracer uptake between patients with OCD and healthy controls in the head of the caudate nucleus. Lastly, especially the ventral striatum has been investigated to be a promising target of DBS in highly treatment-resistant patients (Denys et al., 2010; Greenberg et al., 2010).

Subthalamic nucleus

The STN belongs to the basal ganglia and is considered to be part of the indirect pathway of the CSTC (Alexander et al., 1986; Saxena & Rauch, 2000). It is involved in various cognitive, affective and motor functions, including decision making, reward processing and emotional aspects of behaviour (Bonnevie & Zaghloul, 2018; Darbaky, Baunez, Arecchi, Legallet, & Apicella, 2005; Frank, 2006; Mallet et al., 2007). However, most importantly it plays a role in control of impulsivity and action inhibition (Aron & Poldrack, 2006; Bari & Robbins, 2013; Bastin et al., 2014; Chabardès et al., 2013; Frank, 2006). Frank (2006) suggested activity of the STN to be dynamic, degree and duration being directly driven by the amount of response conflict present. He proposed that STN activity must be well balanced, as it is important for preventing premature choices, on the other hand, hyperactivity may impair cognitive function (Frank, 2006). In patients with OCD the indirect pathway of the CSTC may be underactive in comparison to the direct pathway (Saxena & Rauch, 2000). As part of the indirect pathway, the STN plays an important role in the neurobiological model of OCD pathophysiology. This is further highlighted as DBS of the STN leads to improvement of OCD symptoms (Chabardès et al., 2013; Mallet et al., 2002; 2008; Mulders et al., 2016).

Internal and external globus pallidus

GPi and GPe are part of the basal ganglia. Whereas GPe is part of the indirect pathway of the CSTC, GPi and SNr are the mutual output of direct and indirect pathway as illustrated in Figure 4 (Alexander & Crutcher, 1990). However, also direct structural connections between GPi and GPe have been reported in animal studies (DeLong, 1990; Hazrati, Parent, Mitchell, & Haber, 1990; Kincaid, Penney, Young, & Newman, 1991; Parent & Hazrati, 1995b). As it plays an important role in the CSTC, it is involved in numerous cognitive processes and motor functions associated to CSTC activity (Alexander et al., 1986; Middleton & Strick, 2000). In patients with OCD, Perani et al. (1995) found increased glucose metabolism in the lenticular nuclei (putamen and globus pallidus) at rest using PET. McGuire et al. (1994) observed activation in the globus pallidus during symptom provocation. FMRI during symptom provocation revealed activation of the lenticular nuclei (Breiter et al., 1996). A meta-analysis of PET and fMRI studies by Rotge et al. (2008) suggested GPe to possibly play a direct role in the production of OCD symptoms. The importance of the globus pallidus in the pathophysiology of OCD is further highlighted by studies reporting obsessive-compulsive behaviour in patients with globus pallidus lesions (Laplane et al., 1989; Rodrigo Escalona, Adair, Roberts, & Graeber, 1997). More recently, this importance was confirmed by a worldwide meta- and mega-analysis investigating subcortical volume alterations in OCD, which described larger pallidum volumes in adult OCD patients compared to adult controls (Boedhoe et al., 2017).

Thalamus

Almost all input to the cortex passes through the thalamus with only few exceptions. Therefore, the thalamus has been described as the gateway to the cortex. It plays a crucial role in sensory and motor control as well as in sleep and arousal and in cognitive functions (Ward, 2013). PET studies in OCD patients have found increased glucose metabolism in the thalamus compared to healthy controls (Perani et al., 1995; Swedo et al., 1989). McGuire et al. (1994) reported activation to be increased during symptom provocation. A SPECT study identified significantly higher resting state regional cerebral blood flow in the thalami (Lacerda et al., 2003). However, a meta-analysis of PET and SPECT studies could not demonstrate consistent differences between OCD patients and healthy controls (Whiteside et al., 2004).

Functional connectivity

Functional connectivity (FC) is generally defined as a temporal correlation of neurophysiological measurements acquired in spatially separated brain areas at the same time (Aertsen, Gerstein, Habib, & Palm, 1989; Friston, Frith, Liddle, & Frackowiak, 1993). Using fMRI these neurophysiological measurements are neuronal activity patterns visualised by the blood oxygenation level dependent (BOLD) effect. Hence, FC reflects functional communication between regions (van den Heuvel & Hulshoff Pol, 2010). In OCD, this approach has been used to study the CSTC during resting state. Altered FC has been found within structures of the CSTC including cortex, striatum and thalamus (Fitzgerald et al., 2011; Harrison et al., 2009; Jung et al., 2017; Posner et al., 2014; Sakai et al., 2011). More specifically, Fitzgerald et al. (2011) observed increased FC between the dorsal striatum and the frontal pole using fMRI during resting state. Similarly, Harrison et al. (2009) described increased FC between the ventral caudate/nucleus accumbens and the OFC and ACC. Increased FC in these structures of the direct pathway may support the neurobiological model of an imbalance between the direct and indirect pathway with hyperactivity of the direct pathway. However, FC investigations have not only produced consistent results. Jung et al. (2017) published decreased FC between OFC and striatum and increased FC between striatal areas and thalamus. Chen et al. (2016) reported a generally decreased FC within the CSTC, with decreased connectivity between left caudate nucleus and thalamus being positively correlated with illness duration of OCD. Beucke et al. (2013) found greater distant and local FC of the OFC, greater distant FC of the STN and greater local FC of the putamen in unmedicated OCD patients compared to healthy controls. Furthermore, distant FC of the OFC and putamen was positively correlated with global OCD symptom severity. Anticevic et al. (2014) observed increased global brain FC in dorsal striatum and anterior thalamus but decreased global FC in ventral striatum/nucleus accumbens. However, specific FC between ventral striatum/nucleus accumbens and ventral ACC was increased in OCD patients. While these studies consistently highlight the importance of the CSTC in OCD pathophysiology, controversy of the individual results is evident. A possible reason for this result heterogeneity could be that methodological approaches differ between the studies. Some studies use data-driven, model-free methods investigating whole-brain FC (Anticevic et al., 2014; Beucke et al., 2013; Chen et al., 2016; Moreira et al., 2017; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). Other studies utilise a seed-based approach to explore FC, either without direct relation to the CSTC or using selected nodes of the CSTC (Fitzgerald et al., 2011; Gürsel, Avram, Sorg, Brandl, & Koch, 2018; Harrison et al., 2009; Jung et al., 2017). However, none of these

studies studied FC within the CSTC as a whole, which means between all nodes that have been identified to play relevant anatomical roles in the direct and indirect pathway. These nodes are OFC, ACC, striatum, STN, GPi, GPe and thalamus (Alexander et al., 1986; Parent & Hazrati, 1995a; 1995b; Pauls et al., 2014; Saxena et al., 2001; Saxena & Rauch, 2000).

6. Objectives

As mentioned above, although FC has been identified as a valuable tool to investigate OCD pathology and findings of the studies described above contributed considerably to understanding the mechanism behind altered connectivity in OCD, none of these studies have explored connectivity within all relevant nodes of the CSTC as a whole. To fill this gap and shed more light on the functional communication between these regions of interest (ROIs), the present investigation was conducted. ROI-to-ROI connectivity within all nodes of the direct and indirect CSTC pathway was studied in a relatively large sample of OCD patients and healthy controls using resting-state fMRI. The selected nodes are, as outlined above, known to play important roles in OCD pathology.

7. Methods

Participants

Forty-four OCD patients (14 males, 30 females) and 40 healthy controls (19 males, 21 females) participated in the study (Table 1). Subjects were recruited from Klinik Windach Institute and Hospital of Neurobehavioural Research and Therapy (WINTR), Germany, with primary diagnosis of OCD. An experienced psychiatrist performed the assessment of the disorder based on the DSM-V criteria for OCD diagnosis. Additionally, severity of OCD symptoms was determined in this study using the self-report Yale-Brown Obsessive Compulsive Scale (Y-BOCS) version (see appendix). The Y-BOCS consists of 5 obsession and 5 compulsion related items (time spent, interference with normal functioning, distress, resistance and control). All items are rated from 0 (None/Definitely resists/Complete control) to 4 (Extreme/Completely yields/No control) based on the last 7 days. This adds up to a score of maximum 20 for each obsession and compulsion and a total score of 40 (Goodman, 1989). To assess the main OCD symptom dimensions, the Obsessive-Compulsive Inventory – Revised (OCI-R) was used (see appendix). The OCI-R is the short version of the Obsessive-Compulsive Inventory (OCI). It includes 6 subscales: Hoarding, Checking, Ordering, Neutralising, Washing and Obsessing. There are 3 items per subscale, which leads to a total item number of 18. Items are rated from 0 (not at all) to 4 (extremely) based on the distress or bother they caused during the past month (Foa et al., 2002; Gönner, Leonhart, & Ecker, 2007). In order to detect possible symptoms of depression, the Hamilton Depression rating scale (HAM-D) was conducted (see appendix). The HAM-D is an interview based on 21 items: Depressed mood, suicide, guilt, insomnia (initial, middle, delayed), work and interests, retardation, agitation, anxiety (psychic, somatic), somatic symptoms (gastrointestinal, general), genital symptoms, hypochondriasis, loss of insight, loss of weight, diurnal variation (morning, evening), depersonalisation, paranoid symptoms, obsessive symptoms. Items are either rated from 0 (absent) to 4 (severe) or 0 (absent) to 2 (clearly present) adding up to the highest possible score of 66 (Hamilton, 1960). Schizophrenia, autism, substance and alcohol abuse/dependency, mental retardation, pregnancy, and severe medical conditions were exclusion criteria for patients. At the time of scanning, 17 patients were under medication, the other 27 were medication-naïve or had stopped medication at least 1 week before scanning. Healthy controls had no history of psychiatric disorders. Exclusion criteria for both OCD patients and healthy controls were a history of clinically important head injuries, seizures or

neurological diseases. For demographic and clinical data of all subjects see Table 1. After a detailed description of the study, all patients had to give written informed consent to the study protocol to be included. The study protocol was in accordance with the Declaration of Helsinki and was validated by the Ethics Committee of the Klinikum rechts der Isar, Technische Universität München.

Table 1: Demographic and clinical data.

Note: Multiple medications and comorbidities can be present in a single subject

Abbreviations: OCD = obsessive-compulsive disorder, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, TCA = tricyclic antidepressant, ADHD = attention deficit hyperactivity disorder, Y-BOCS = Yale-Brown Obsessive Compulsive Scale, HAM-D = Hamilton Depression score.

	OCD patients	**Healthy controls**	**Group difference**
Number of participants	44	40	
Sex (male : female)	14 : 30	19 : 21	not significant
Mean age at scanning (in years)	33.32 (SD = 11.35)	34.12 (SD = 8.81)	not significant
Duration of OCD (in years)	14.93 (SD = 11.84)		
Age of onset	17.34 (SD = 8.14)		
Medication (yes : no)	17 : 27		
SSRI	15		
SNRI	2		
Methylphenidate	1		
Neuroleptic	1		
TCA	2		
Comorbidities (yes : no)	19 : 25		
Depression	12		
Anxiety disorder	5		
ADHD	2		
Personality disorder	1		
Y-BOCS			
Mean total	21.41 (SD = 5.94)		
Obsessions	10.88 (SD = 3.42)		
Compulsions	10.52 (SD = 3.84)		
OCI-R			
Mean total	27.73 (SD = 10.15)		
Washing	5.00 (SD = 4.25)		
Checking	5.34 (SD = 3.48)		
Neutralising	2.70 (SD = 3.27)		
Obsessing	7.43 (SD = 3.40)		
Ordering	4.45 (SD = 3.63)		
Hoarding	2.80 (SD = 2.72)		
HAM-D mean score	13.14 (SD = 5.56)	0.70 (SD = 1.08)	

Functional magnetic-resonance imaging

The following paragraphs are based on books by McRobbie, Moore, Graves & Prince (2006) and Poldrack, Mumford & Nichols (2011). Magnetic resonance images result from nuclear magnetic resonance. The nucleus of a hydrogen atom is a single positively charged proton with associated spin on its own axis. This rotating positive charge generates a magnetic moment which, put in a strong external magnetic field, precesses around the direction of the field (Figure 6). The frequency of its precession is known as the Larmor frequency, ω, which is proportional to the field strength, B ($\omega = \gamma B$, where γ = gyromagnetic ratio). There are two possible states of orientation for precession: parallel/spin-up or anti-parallel/spin-down. The transition between the two states requires electromagnetic radiation of the Larmor frequency. As the anti-parallel orientation demands more energy, there will be more protons spinning parallel, causing a net longitudinal magnetisation in the order of microtesla in the direction of the field. In equilibrium the precession of the protons is out-of-phase, so there will be no net magnetisation in the transverse plane. As, however, longitudinal magnetisation caused by the spin is very small compared to the strong external magnetic field, only transverse magnetisation is measured by the receiver coil. A radiofrequency (RF) pulse of Larmor frequency tilts net longitudinal magnetisation into the transverse plane and brings precession into phase. Thus, it can create a detectable signal, free induction decay (FID) which is illustrated in Figure 7. Because of the protons dephasing, FID decays to zero exponentially within milliseconds. After the RF pulse two forms of relaxation take place: Firstly, the spins dephase. FID happens due to inhomogeneity in the main magnetic field. The spins interact with each other, causing spin-spin relaxation. Transverse magnetisation decays exponentially within milliseconds, the spin-spin relaxation time, T_2. As T_2 does not take any field disturbance into account, the relaxation time combining T_2, field inhomogeneity, tissue susceptibility and diffusion of the protons, known as T_2*, is shorter. Secondly, the spins interact with tissue surrounding them, lattice. The spin-lattice relaxation causes the spins to lose energy and therefore restores longitudinal net magnetisation. This process takes several seconds known as spin-lattice relaxation time, T_1.

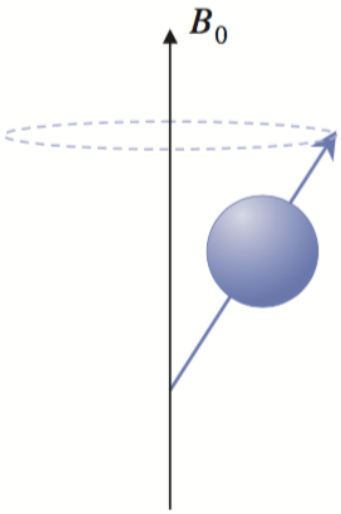

Figure 6: Precession of the magnetic moment.

Figure from McRobbie et al. (2006), p.139.

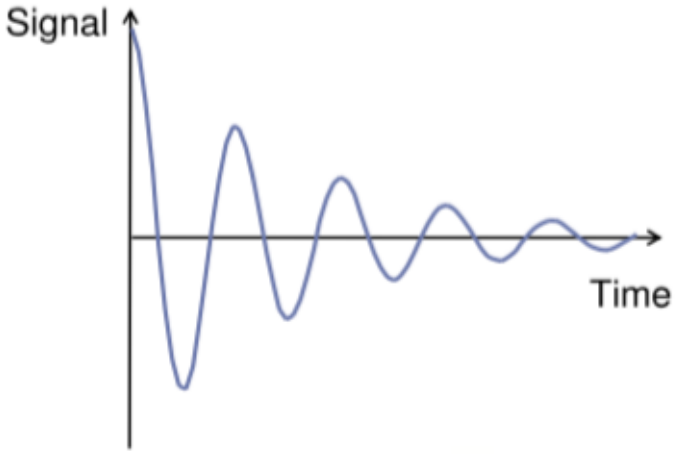

Figure 7: FID – signal induced in the receiver coil.

Figure from McRobbie et al. (2006), p.143.

In this project images were acquired using a gradient echo (GE) sequence. Scan time is very short using a GE due to short echo time (TE). After the RF pulse, a negative gradient is applied, resulting in faster dephasing than with FID. Then a positive gradient is applied, causing rephasing. An echo is generated. The gradient pulse does not compensate for field disturbances, therefore, the GE signal depends on T_2*. Magnetisation prepared rapid acquisition by gradient echo (MPRAGE) is a sequence that gives detailed anatomical information. Repetition time (TR) is very short and the flip angle low. This would usually compromise T_1 contrast, however, an inversion pre-pulse followed by delay generates T_1 weighting. For functional imaging a GE echo planar imaging (EPI) sequence was used.

Applying an oscillating readout gradient, a train of echoes is generated within T_2* of the FID. Thus, the EPI sequence is extremely fast and especially convenient for acquiring dynamic images such as in fMRI.

To visualise activation of the brain in fMRI the blood oxygenation level dependent (BOLD) effect can be used. Different oxygenation levels of haemoglobin have different magnetic susceptibility. Oxygenated blood has a longer T_2* than deoxygenated blood. Thus, oxygenated blood has higher MR signal. In areas of change of neuronal activity blood flow will change slowly within several seconds (Figure 8), causing a change in the MR signal as an indirect representation of neuronal activation. After an initial dip due to higher oxygen consumption, an increase in blood flow will raise the level of oxygenated blood, enhancing the MR signal. As the GE EPI sequences has strong T_2* weighting it is particularly suitable for functional imaging using the BOLD effect.

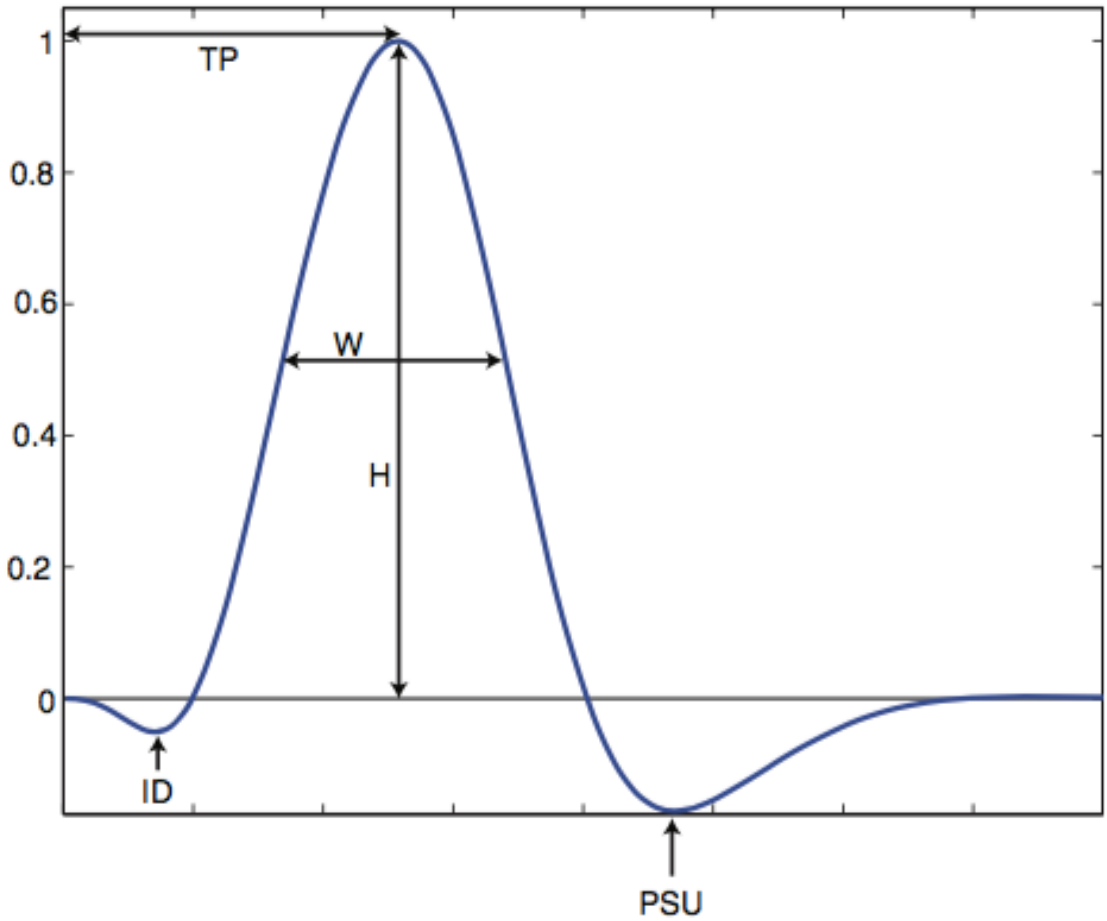

Figure 8: Hemodynamic response.

Abbreviations: TP = time from stimulus until peak, H = height of response, W = width of response at half the height, PSU = poststimulus undershoot, ID = initial dip.

Figure from Poldrack et al. (2011), p72.

The present study used resting-state fMRI to investigate FC. The following paragraph is based on a review of this technique by van den Heuvel and Hulshoff Pol (2010). Resting-state fMRI measures spontaneous low frequency fluctuations in the BOLD signal. That these low frequency fluctuations correlate in functionally related brain regions was first observed by Biswal, Zerrin Yetkin, Haughton and Hyde (1995). Since then FC has been investigated not only to identify functional networks in healthy subjects but also to detect possible alterations in neurological and psychiatric brain disorders, such as OCD. As mentioned above, there are different methodological approaches to processing resting-state fMRI data. There are data-driven, model-free methods as well as model-dependent designs. Model-free methods investigate whole brain FC without prior definition of a brain region. Model-dependent designs, on the other hand, use previously defined brain regions, called seeds (van den Heuvel & Hulshoff Pol, 2010). Figure 9 illustrates the correlation of time-series of the selected brain regions. In this case a seed to voxel approach is shown. Spontaneous low frequency fluctuations in the BOLD signal are measured during rest (panel a). BOLD fMRI signal can also be measured task-dependently to select a seed ROI (panel b). The resting-state time-series of the seed voxel is correlated with the resting-state time-series of a voxel j to investigate FC (panel c). High correlation means high FC between seed voxel and voxel j. The time-series of the seed voxel can then be correlated with the time-series of all other voxels in the brain. The result of the correlation analyses can be illustrated in a FC map (panel d) (van den Heuvel & Hulshoff Pol, 2010). In the present study, the time-series of one seed voxel (for example STN) was correlated with the time-series of another seed voxel (for example GPe).

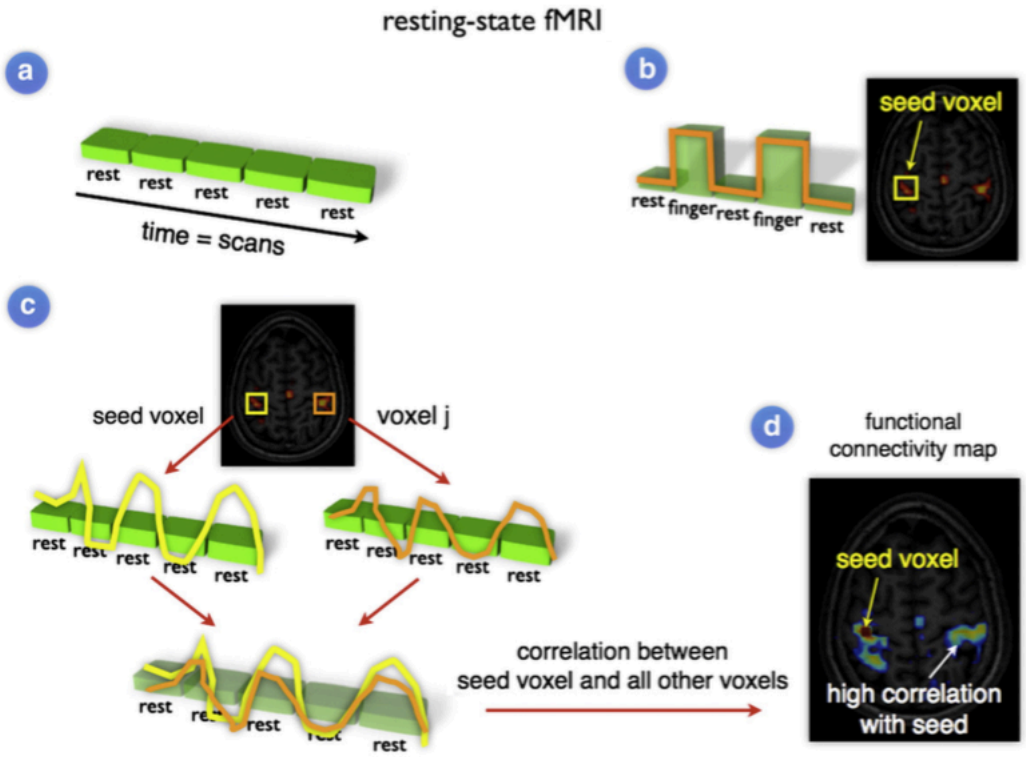

Figure 9: Correlation of time-series of selected brain regions to measure FC.

Spontaneous low frequency fluctuations in the BOLD signal are measured during rest (panel a). BOLD fMRI signal can also be measured task-dependently to select a seed ROI (panel b). The resting-state time-series of the seed voxel is correlated with the resting-state time-series of a voxel j to investigate FC (panel c). High correlation means high FC between seed voxel and voxel j. The time-series of the seed voxel can then be correlated with the time-series of all other voxels in the brain. The result of the correlation analyses can be illustrated in a FC map (panel d).
Figure from van den Heuvel and Hulshoff Pol (2010).

fMRI data acquisition

Functional Magnetic-Resonance images were acquired using a 3.0 Tesla Philips Ingenia whole body system (Philips Healthcare, Best, The Netherlands) with a 32-channel head coil. FMRI data was collected during resting state. Firstly a survey sequence was run. After planning the resting state fMRI using the survey images, a test fMRI scan was conducted to secure image quality and optimised field of view. We instructed participants to close their eyes, relax, to avoid any movement and not to fall asleep. A gradient-echo EPI sequence was used (scan parameters: scan duration = 551 sec, TE = 33 ms, TR = 2700 ms, flip angle = 90°, FOV = 192x192x141 mm, matrix = 96x94, 64 slices, transverse orientation, slice thickness = 2 mm, inter-slice gap = 0.2 mm, number of volumes = 200). Anatomical information was collected using a T1-weighted 3D MPRAGE sequence (scan parameters: scan duration = 299

sec, TE = 5.09 ms, flip angle = 8°, FOV = 239x256x161 mm, pixel matrix = 384x384, slice thickness = 0.7 mm).

fMRI preprocessing and analysis

FMRI data were preprocessed using the default preprocessing parameters of CONN Functional Connectivity toolbox conn v.17.f for Statistical Parametric Mapping (https://www.nitrc.org/projects/conn). Slice timing correction was performed based on slice order. Subjects' motion correction was conducted and all data were inspected for movement artefacts. Subjects with movement parameters exceeding 3 mm of translation on the x-, y-, or z-axis or 3° of rotation were excluded. This was not the case, hence no subject had to be excluded (n = 0). In addition, excessive head motion was established with framewise displacement (FD). FD is calculated by summing the absolute values of the derivatives of the 6 motion parameters derived from SPM12 (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). There were no significant differences found in mean FD (p = 0.83) between OCD patients (mean = 0.11, SD = 0.04) and healthy controls (mean = 0.11, SD = 0.03). Normalisation to a standard template in Montreal Neurological Institute space was carried out. Images were then smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. To detect and regress out possible outliers and artefacts due to head movement, ART software procedure was used. A band-pass filter (0.008-0.09 Hz) was applied. At a first level correlation analysis, confounding white matter, cerebrospinal fluid components and the six head motion parameters, generated during realignment, were entered as nuisance covariates.

For each subject ROI-to-ROI analyses were conducted. This means, using time-series information, bivariate correlation analyses were computed between each pair of ROIs. The resulting correlation matrices of each subject were Fisher z-transformed and entered into the second level analysis. To evaluate differences in FC between patients with OCD and healthy controls, a two-sample t-test, corrected for age and gender, was performed. For the ROI-to ROI analysis, bidirectional FC results were analysed. These results were corrected for multiple comparisons using analysis level FDR (false discovery rate) correction provided by the CONN toolbox. This means results were corrected for having multiple targets as well as for using multiple seeds. Only extremely robust results that survived at a peak level threshold of $p < 0.05$ using analysis level FDR correction were considered significant. Furthermore, a correlation analysis between ROI-to-ROI FC and OCD symptom severity, as assessed using the Y-BOCS, was conducted. Correlation analysis was also performed between ROI-to-ROI FC and medication in OCD patients. FC beta-values of the ROIs showing significant difference in FC between OCD patients and healthy controls were extracted and correlated

with the relevant measure. In correlation with symptom severity, these measures were Y-BOCS total scores, Y-BOCS obsession scores and Y-BOCS compulsion scores. In correlation with medication in OCD patients, this measure was medication, which was entered as a covariate specifying state of medication as either present or absent in patients. Medication was specified as absent if they were medication-naïve or had stopped medication at least one week before scanning.

In this analysis 7 bilateral seeds, resulting in a total of 14 seeds, were selected carefully as corresponding to the relevant nodes of the direct and indirect CSTC pathway (Pauls et al., 2014). As explored in more detail above, these ROIs are the OFC, ACC, striatum, STN, GPi, GPe and thalamus. OFC, ACC, striatum and thalamus ROIs correspond to the ROIs provided by the AAL2 atlas. STN, GPi and GPe were selected from the ROIs provided by the 7T ATAG atlas of Basal Ganglia. The 14 ROIs are illustrated in figure 10. The STN is shown in red, the GPi in cyan, the GPe in violet, the OFC in yellow, the striatum in blue, the Thalamus in green and the ACC in light blue.

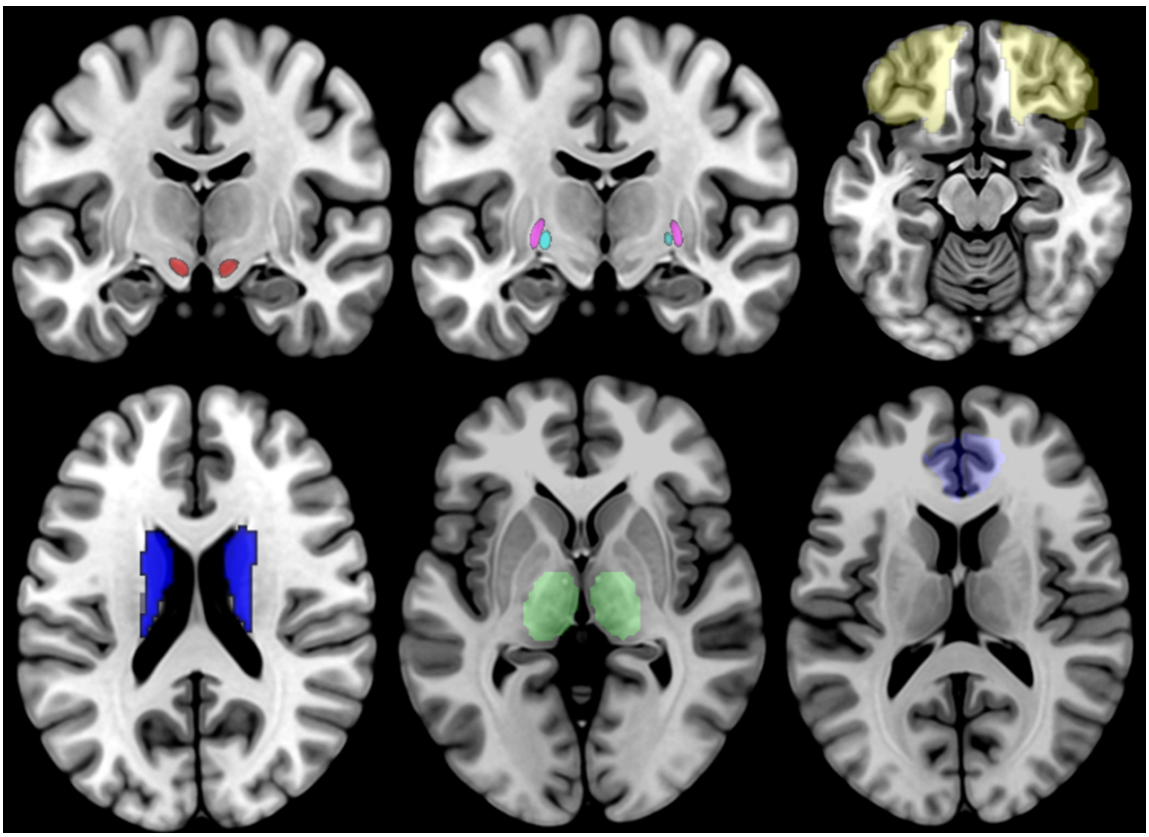

Figure 10: Illustration of the 14 ROIs.

The STN is shown in red, the GPi in cyan, the GPe in violet, the OFC in yellow, the striatum in blue, the Thalamus in green and the ACC in light blue.

8. Results

ROI-to-ROI analysis

We found significantly increased FC ($p < 0.05$, FDR analysis level corrected) between left STN and left GPe ($t = 4.29$) as well as significantly increased FC ($p < 0.05$, FDR analysis level corrected) FC between left GPe and left GPi ($t = 3.66$) in patients with OCD compared to healthy controls (table 2). The results are illustrated in figure 11.

Table 2: Significant results of ROI-to-ROI analysis.

Abbreviations: ROI = region of interest, STN = subthalamic nucleus, GPe = external globus pallidus, GPi = internal globus pallidus.

ROI-to-ROI	T-value	p-value (FDR corrected)
Left STN – Left GPe	4.29	0.0046
Left GPe – Left GPi	3.66	0.0203

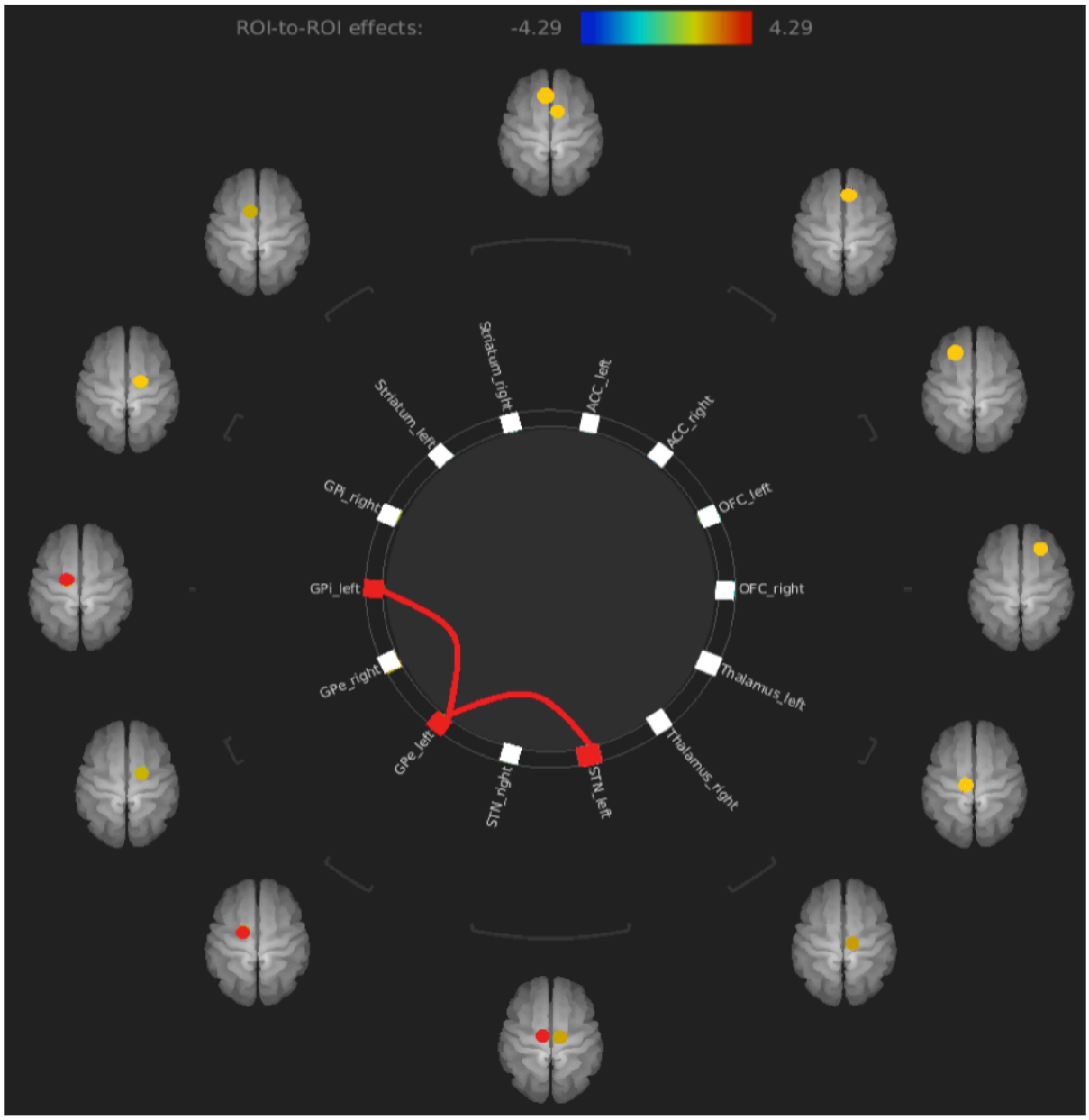

Figure 11: Increased FC between left STN and left GPe and increased FC between left GPe and left GPi in OCD patients compared to healthy controls.

The 14 selected seed regions are arranged in the inner circle and the corresponding brain regions are depicted in yellow in the outer circle. Significantly increased FC in OCD patients compared to healthy controls is marked in red.

Abbreviations: ACC = anterior cingulate cortex, OFC = orbitofrontal cortex, STN = subthalamic nucleus, GPe = external globus pallidus, GPi = internal globus pallidus.

Correlation with symptom severity

Correlation analysis between ROI-to-ROI FC and OCD symptom severity measures, Y-BOCS total scores, Y-BOCS obsession scores and Y-BOCS compulsion scores, did not yield any significant results.

Correlation with medication

Correlation analysis between ROI-to-ROI FC and medication in OCD patients did not yield any significant results either.

9. Discussion

Support for CSTC involvement in OCD pathology

In the present study ROI-to-ROI connectivity within all nodes of the direct and indirect CSTC pathway was investigated in a relatively large sample of OCD patients and healthy controls using resting-state fMRI. Aim of the study was to improve understanding of the mechanisms behind OCD pathology.

The analysis showed an increased FC between left STN and left GPe and an increased FC between left GPe and left GPi in patients with OCD compared to healthy controls. These results further support the widely accepted neurobiological model of OCD outlined above which suggests alterations within the CSTC.

However, comprehensive meta-analyses analysing gray/white matter structural alterations in OCD described changes not only in regions of the CSTC, such as the pallidum, but also in areas and networks not directly pertaining to the CSTC, such as dorsomedial, dorsolateral, ventrolateral, frontopolar prefrontal cortices, temporal and parietal regions (Abe et al., 2018; Boedhoe et al., 2017; Piras et al., 2015). Furthermore, functional alterations within the default mode network were reported in a meta-analysis of resting-state FC in OCD (Gürsel et al., 2018).

Nevertheless, alterations within the classic CTSC are still regarded as a central psychopathological mechanism in OCD. In more detail, the predominant view of OCD pathology is that symptoms might occur due to hyperactivity of the CSTC. As illustrated in figure 5, activity of the direct pathway is thought to be increased as compared to the indirect pathway as FC might be increased within the direct pathway, and more specifically between cortex and striatum, striatum and GPi/SNr and between thalamus and cortex. However, as discussed above, whereas the importance of the CSTC in OCD pathology has been validated in many studies, the results of past studies investigating FC within the CSTC vary greatly and are controversial. To the best of our knowledge, not many studies could yet give confirmation of the predominant hypothesis of increased FC within the direct pathway.

The present investigation sheds more light on CSTC involvement and could allow a new understanding of CSTC function in OCD. This is the first study exploring connectivity within all relevant nodes of the direct and indirect pathway of the CSTC as a whole. Its results showing increased FC between relevant structures of the indirect pathway contradict the

current hypothesis of increased FC within the direct pathway. However, as will be outlined in detail below, in the context of an altered CSTC model they are very plausible, indeed.

Introduction to a new perspective on CSTC function in OCD

Firstly, increased FC between left GPe and left GPi in patients with OCD compared to healthy controls was found. This is further evidence for the importance of the CSTC in OCD pathology and support for the hypothesis that the CSTC model and the connectivity within its relevant structures are more complex than initially thought. Whereas in the classical view of the indirect pathway of the CSTC, as shown in figure 3, GPe and and GPi are connected via the STN, also a direct structural connection between GPe and GPi has been reported in animal studies (DeLong, 1990; Hazrati et al., 1990; Kincaid et al., 1991; Parent & Hazrati, 1995b). Furthermore, the existence of multiple indirect pathways has been proposed, suggesting a direct projection from the GPe to GPi/SNr, the output structures of the basal ganglia (Smith, Bevan, Shink, & Bolam, 1998). The increased FC between external and internal GP found in the present study might support that proposition.

Secondly, increased FC between left STN and left GPe was found. This also highlights the importance of the CSTC in OCD pathology, as GPe and STN are the main structures of the indirect pathway of the CSTC (see figure 3). Furthermore, together with the finding of increased FC between GPe and GPi, this result might suggest that GPe plays a major role in OCD pathophysiology. This hypothesis is supported by Rotge et al. (2008) proposing the GPe to possibly play a direct role in the production of OCD symptoms. Moreover, the STN is involved in control of impulsivity and action inhibition and acute OCD symptoms have been suggested to be related to abnormally high oscillatory activity in the STN (Aron & Poldrack, 2006; Bari & Robbins, 2013; Bastin et al., 2014; Chabardès et al., 2013). Thus, altered FC between STN and GPe might lead to an imbalance between the direct and indirect pathway of the CSTC and the resulting modification of cortex excitation might be responsible for the characteristic cognitive and motor symptoms of OCD.

The relationships between GPe, GPi and STN as explored above are illustrated in figure 12.

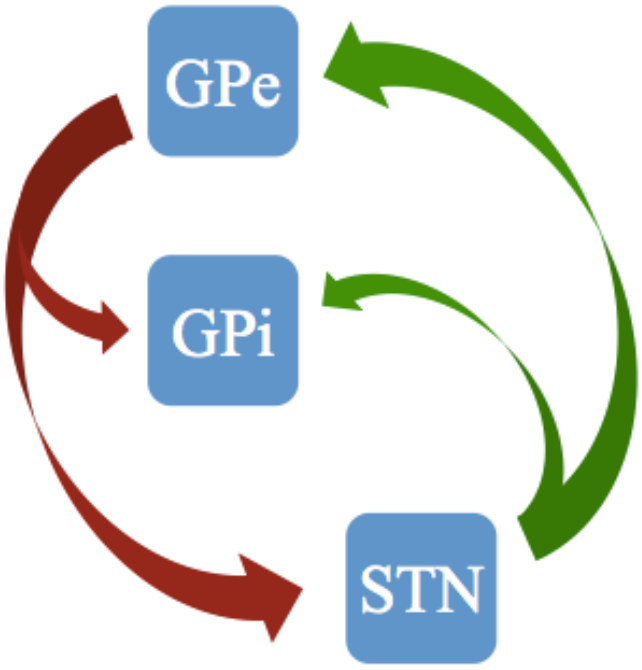

Figure 12: Relationships between GPe, GPi and STN.

Green arrows indicate excitatory pathways, whereas red arrows indicate inhibitory pathways.
Abbreviations: GPe = external globus pallidus, GPi = internal globus pallidus, STN = subthalamic nucleus.
Modified from Shink, Bevan, Bolam and Smith (1996).

The findings of the present study suggest a more important role for the indirect pathway, and especially for the STN, compared to the classical model of OCD pathophysiology. Figure 13 visualises the results in the context of the CSTC model. There is increased FC between GPe and GPi and between GPe and STN.

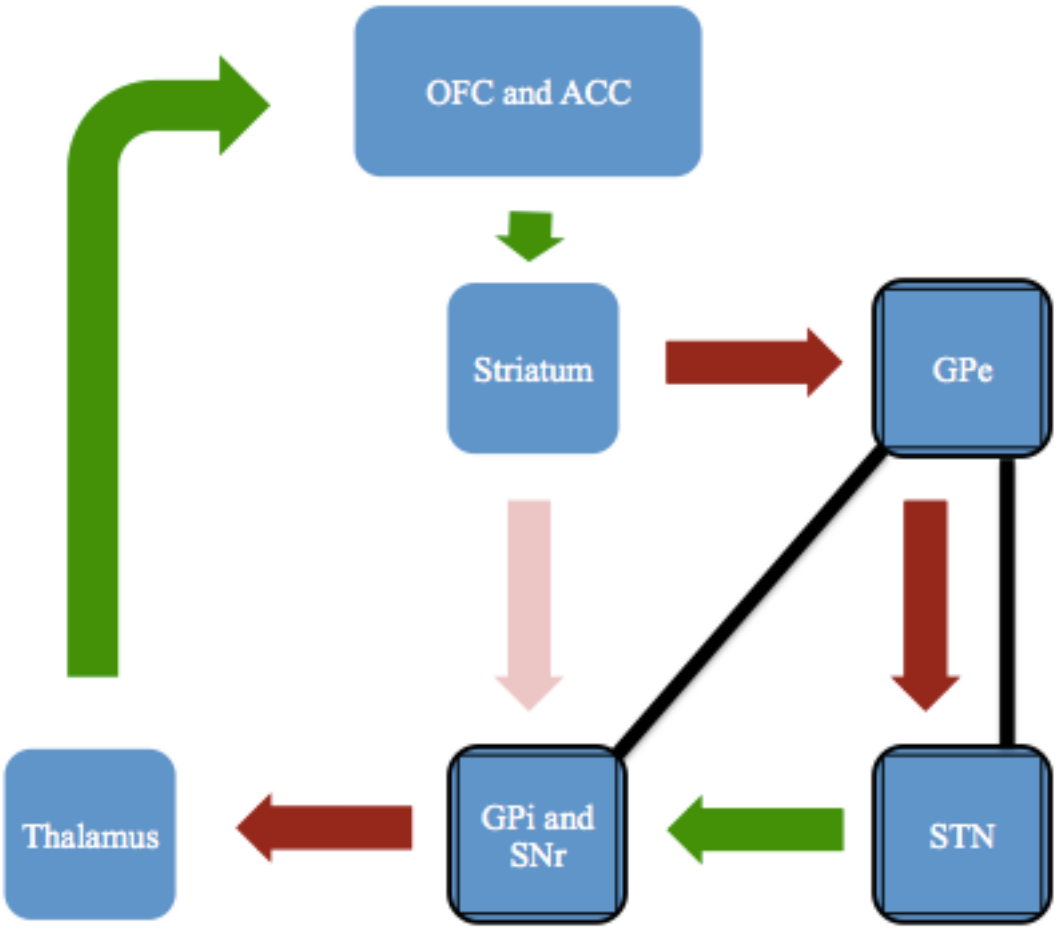

Figure 13: The results in the context of the CSTC model.

Green arrows indicate excitatory pathways, whereas red arrows indicate inhibitory pathways. The dark arrow shows the indirect pathway, lighter colours show the direct pathway. The results highlight the importance of the indirect pathway. The black lines illustrate increased FC between GPe and GPi and between GPe and STN.
Abbreviations: OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, GPe = external globus pallidus, STN = subthalamic nucleus, GPi = internal globus pallidus, SNr = substantia nigra.
Modified from Pauls et al. (2014).

The results introduce a new perspective on CSTC function in OCD pathophysiology. Consequent altered interpretation of the classical model of the CSTC is shown in Figure 14. Higher FC between GPe and GPi might mean more signalling through inhibitory projections. As a result GPi might be less active to inhibit the thalamus, leading to higher activation of the cortex and, consequently, OCD symptoms. Similarly, higher FC between GPe and the STN might mean more inhibition of the STN. This might lead to less activation of the GPi and result in less inhibition of the thalamus, also inducing higher activation of the cortex, which then causes OCD symptoms. Increased FC between GPe and STN might also mean more

excitatory signalling from the STN to GPe, leading to amplification of these pathways and, hence, likewise to the expression of OCD symptoms.

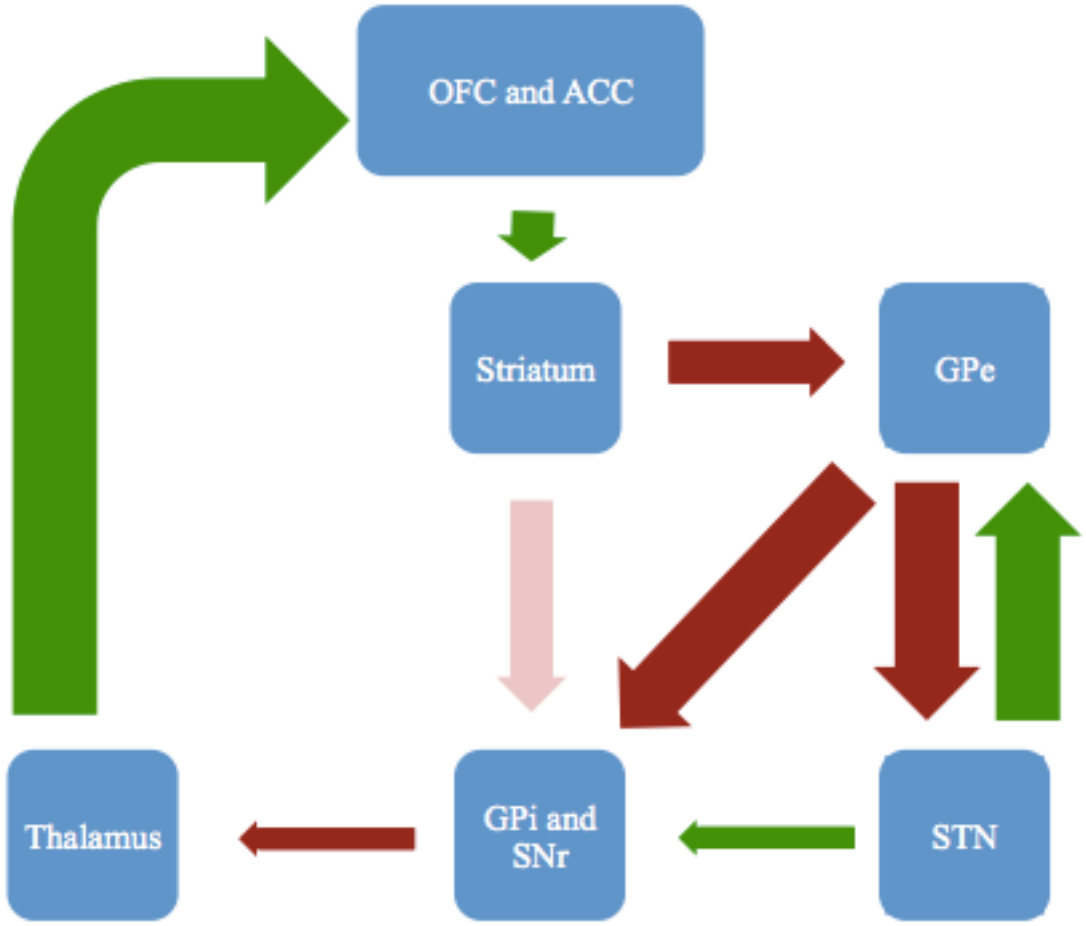

Figure 14: Altered model of the CSTC.

Green arrows indicate excitatory pathways, whereas red arrows indicate inhibitory pathways. As GPe exerts more inhibition on GPi, GPi exerts less inhibition on the thalamus. Higher activity of the thalamus loops back to higher activation of the cortex. As GPe exerts more inhibition on the STN, the STN has less ability to activate GPi. Again GPi exerts less inhibition on the thalamus and higher activity of the thalamus loops back to higher activation of the cortex. The STN activating GPe will amplify the inhibition exerted.
Abbreviations: OFC = orbitofrontal cortex, ACC = anterior cingulate cortex, GPe = external globus pallidus, STN = subthalamic nucleus, GPi = internal globus pallidus, SNr = substantia nigra.
Modified from Pauls et al. (2014).

The explanations above emphasise not only the importance of the GPe in OCD pathophysiology, but also highlight the role of the STN. Recent FC studies have investigated alterations in the connectivity of the STN in patients with OCD, increasing attention for its role in OCD pathology. Using resting-state fMRI, Beucke et al. (2013) observed that patients

with OCD showed significantly greater distant connectivity (defined as correlation to voxels exclusively outside a 12 mm sphere) in the STN compared to healthy controls. Also using resting-state fMRI, Morris, Baek and Voon (2017) found an association of perseveration to reduced connectivity between STN and premotor cortex. Furthermore, they found obsessive-compulsive inventory scores to be negatively correlated with connectivity between STN and dorsolateral prefrontal cortex (Morris et al., 2017). More recently, Cano et al. (2018) reported altered FC of the STN during resting state in patients with OCD as well. Specifically, their results showed increased FC with the premotor cortex and decreased FC between with the lenticular nucleus (including putamen and GP) (Cano et al., 2018). Although these findings regarding the STN are heterogeneous, together with our results they underline the hypothesis that the STN might be a key structure in OCD pathology.

Implications for the treatment of OCD

This hypothesis is supported by the fact that the STN is a relevant target region of DBS in patients with treatment-refractory OCD (Chabardès et al., 2013; Mallet et al., 2002; 2008; Mulders et al., 2016). DBS involves the implantation of electrodes that send electrical impulses to specific brain areas. Electrical stimulation via implanted electrodes as a treatment of patients with severe OCD was first applied by Nuttin, Cosyns, Demeulemeester, Gybels and Meyerson (1999) as an alternative to irreversible lesions. Since then especially ventral striatum/ventral capsule, nucleus accumbens and nucleus subthalamicus (STN) have been suggested as promising DBS targets in OCD treatment (de Koning, Figee, van den Munckhof, Schuurman, & Denys, 2011; Denys et al., 2010; Greenberg et al., 2010; 2006). DBS leads to sustained improvement of symptoms in the majority of patients and has been reviewed to potentially be a promising and safe therapy in treatment-refractory cases of OCD (de Koning et al., 2011; Denys et al., 2010; Greenberg et al., 2006; Islam, Franzini, Messina, Scarone, & Gambini, 2015; Mallet et al., 2002; Nair, Evans, Bear, Velakoulis, & Bittar, 2014; Voon et al., 2018). A meta-analysis of DBS in striatal areas such as ventral striatum/ventral capsule, anterior limb of the internal capsule, nucleus accumbens and caudate nucleus, as well as in the STN and in the inferior thalamic peduncle in 116 subjects with OCD has reported a global percentage of Y-BOCS score reduction of 45.1% and a global percentage of responders, defined as a reduction on Y-BOCS scores > 35%, of 60.0% (Alonso et al., 2015). Not only Y-BOCS scores change with DBS, patients experience complex, global changes during DBS, described as a changed way of being in the world (de Haan, Rietveld, Stokhof, & Denys, 2013). The exact mechanisms underlying DBS are not yet fully understood. It has been suggested that DBS interrupts disturbed CSTC signalling and changes connectivity, restoring

balance between direct and indirect pathway of the CSTC and thus leading to symptom reduction (Chiken & Nambu, 2016; Figee et al., 2013; Mulders et al., 2016; van Westen, Rietveld, Figee, & Denys, 2015).

The STN as a DBS target in OCD therapy has been identified by serendipity. In 2002, Mallet et al. implanted subthalamic electrodes in two patients with Parkinson's disease, who had a history of severe OCD. They observed dramatic reductions in Y-BOCS scores, by 81% and by 83%, and especially compulsions disappeared. Thus, they were the first to suggest high-frequency stimulation as a possible treatment in OCD (Mallet et al., 2002). These findings were replicated by Fontaine et al. in 2004, who also reported on a patient with Parkinson's disease and severe OCD. After STN stimulation, the Y-BOCS score had improved by 97% (31 points) 6 months after DBS (Fontaine et al., 2004). Following these case studies, Mallet et al. (2008) conducted the first controlled, double-blinded study investigating the STN as a target of stimulation in patients with highly refractory OCD. They included 17 patients in their analysis of which 16 (electrodes and stimulator were removed from one patient before randomisation due to infection) were randomly assigned to either undergo active stimulation followed by sham stimulation or to undergo sham stimulation followed by active stimulation. After active stimulation the Y-BOCS score was significantly lower than after sham stimulation (mean 19 vs. mean 28). However, they also reported serious adverse advents, such as intracerebral haemorrhage, infection and transient side effects. They concluded that STN stimulation may reduce severity of OCD symptoms and improve global functioning of patients with treatment-refractory OCD, however, they also suggested an association with the substantial risk of serious adverse events (Mallet et al., 2008). Other research groups have further investigated this sample of OCD patients: Using PET, Le Jeune et al. (2010) observed decreased metabolism of the anterior cingulate gyrus after STN DBS, as well as a correlation of the therapeutic effect (assessed by Y-BOCS scores) to decreased metabolism of the OFC. Also Welter et al. (2011) examined patients included in the study of Mallet et al. in 2008, reporting that both OCD severity as well as clinical improvement after STN stimulation were correlated with STN neuronal activity. Chabardès et al. (2013) investigated 4 OCD patients, two of which were included in Mallet et al. in 2008, with at least 6 months of follow-up after STN DBS and estimated a benefit that can reach up to 50-75% on the Y-BOCS score. For a summary of the main findings of studies with STN DBS in OCD, see Mulders et al. (2016).

As illustrated in figure 14, the present study introduces an altered model of the CSTC. Based on this model, increased FC between the STN and GPe, reflecting an increased concerted activity of these areas, might disrupt balance within the CSTC. Since the mechanisms

underlying DBS treatment are not yet fully understood, our findings could contribute a neurobiological framework to a better comprehension of the fundamental processes. High-frequency stimulation and pharmacological inactivation of the STN was demonstrated to reduce quinpirole-induced compulsive behaviour in rats (Winter et al., 2008). On a neuronal level, a study of high-frequency stimulation in patients with Parkinson's disease showed an inhibition of many STN neurons (Filali, Hutchison, Palter, Lozano, & Dostrovsky, 2004). Furthermore, stimulation of the subthalamic area at high frequencies in patients with Parkinson's disease suppressed abnormal synchronised oscillation of the GPi at lower frequencies (Brown et al., 2004). Evidence from human studies suggests simultaneous local and distal effects as mechanisms of DBS of specific brain regions, including local inhibition, local excitation, modulation of neural firing patterns and neurogenesis, likely being a complex combination of these (Benazzouz, Piallat, Pollak, & Benabid, 1995; Bourne, Eckhardt, Sheth, & Eskandar, 2012; Filali et al., 2004; Vitek, 2002). Furthermore, a modulation of connectivity by DBS in patients with OCD has been suggested, as well as a correlation between this modulation and changes in Y-BOCS score (Figee et al., 2013). Recently, Horn et al. (2017) used connectivity profiles to predict DBS treatment outcome in patients with Parkinson's disease. Elaborating on those findings from Figee et al. (2013) and Horn et al. (2017), most recently Balderman et al. (2019) could replicate these results for OCD and concluded that specific connectivity profiles can predict the clinical outcome of DBS in patients with OCD. The findings of the present study could provide a basis for future investigations improving the accurate choice of DBS targets and thus increasing clinical outcome for patients as well as reducing the probability of adverse events.

The discussion above might make it seem surprising that the present study did not find a correlation between altered FC and OCD symptom severity. However, it is possible that the alteration in FC found might still represent a core psychopathological mechanism, which, although not directly correlated with clinical severity, might to some degree normalise under DBS treatment. This assumption could be explored in future research.

10. Limitations

Finally, some limitations of the present study must be highlighted. Firstly, comorbidities may have affected the results to some degree. Although OCD was the primary diagnosis in all patients, 19 patients had comorbidities, including depression, anxiety disorder, ADHD and personality disorder. A possible influence on the results cannot be eliminated. Secondly, 17 patients were medicated at the time of scanning. A correlation analysis between ROI-to-ROI FC and medication in OCD patients did not find any significant results. However, a possible influence of SSRI medication on the FC alterations found in the present study cannot be fully excluded, as SSRIs are considered to have a neuroprotective effect and to promote brain-derived neurotrophic factor (BDNF) activation, thus directly increasing central nervous system myelination (D'Sa & Duman, 2002; Duman, 1997; Gervasoni et al., 2005; Gonul et al., 2005; Xiao et al., 2010). Furthermore, imaging studies firstly indicate that structural abnormalities in OCD patients are responsive to SSRIs and secondly report changes in FC induced by SSRIs (Arnone et al., 2018; Fan et al., 2012). Moreover, it has been suggested that the clinical efficacy of SSRIs may be related to a normalisation of FC in fronto-striatal networks and/or thalamo-cortical pathways connected to posterior brain regions after treatment (Piras et al., 2013). Hence, against the background of these findings and assumptions, the fact that 17 patients in the present study were receiving antidepressant treatment must, despite the lack of a statistically significant effect, be regarded a major limitation.

11. Conclusion

In conclusion, the present study investigated FC within all nodes of the direct and indirect CSTC pathway in patients with OCD and healthy controls using resting-state fMRI. The results showed an increased FC between left STN and left GPe and an increased FC between left GPe and left GPi in patients with OCD compared to healthy controls. These findings imply central nodes of the indirect pathway of the CSTC to be involved in OCD pathology and hint towards a new perspective on CSTC function in OCD. Furthermore, they suggest the STN to play a major role in OCD pathophysiology. Hence, the results of the present study may contribute to a better understanding of the general mechanisms underlying STN DBS as a treatment for severe OCD, creating the foundation for future investigations that may improve the treatment of OCD.

12. List of tables

13. List of figures

14. References

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15. Appendix

Y-BOCS

Y-BOCS (Zwangsgedanken/Zwangshandlungen)

Datum:_____

Fragebogen zur Selbsteinschätzung Name: _____

Zwangsgedanken

... sind unerwünschte und belastende Ideen, Gedanken, bildliche Vorstellungen oder Impulse, die sich immer wieder Ihrem Bewußtsein aufdrängen. Sie scheinen gegen Ihren Willen aufzutreten, und oft finden Sie si abstoßend. Vielleicht erkennen Sie ihre Sinnlosigkeit, und vielleicht vertragen sich Zwangsgedanken nicht mit dem Bild, das Sie von Ihrer Persönlichkeit haben.

Anleitung

Denken Sie beim Beantworten der Fragen bitte an die **letzten sieben Tage** (einschließlich des heutigen), und markieren Sie **eine** Antwort pro Frage.

1. Ein wie großer Teil Ihrer Zeit ist durch Zwangsgedanken ausgefüllt? Wie häufig treten Zwangsgedanken auf?

- ☐ 0 Habe keine Zwangsgedanken
- ☐ 1 weniger als eine Stunde am Tag bzw. gelegentliches Auftreten (nicht mehr als 8x /Tag)
- ☐ 2 Eine bis drei Stunden am Tag bzw. häufiges Auftreten (mehr als 8x/Tag, aber die meisten Stunden des Tages sind frei von Zwangsgedanken)
- ☐ 3 mehr als drei Stunden und bis zu acht Stunden am Tag bzw. sehr häufiges Auftreten (mehr als 8x/Tag und in den meisten Stunden des Tages)
- ☐ 4 Mehr als acht Stunden am Tag bzw. ständige Anwesenheit (zu oft, um sie zählen zu können, und es vergeht kaum eine Stunde ohne mehrfaches Auftreten von Zwangsgedanken)

2. Wie stark beeinträchtigen Sie die Zwangsgedanken in Ihrem Privat- und Berufsleben? (wenn Sie momentan keine Arbeitsstelle haben, überlegen Sie bitte, wie sehr die Zwangsgedanken Sie bei Ihren täglichen Aktivitäten einschränken – denken Sie bitte zur Beantwortung dieser Frage bitte an Dinge, die Sie wegen der Zwangsgedanken nicht tun oder weniger tun)

- ☐ 0 keine Beeinträchtigung
- ☐ 1 Geringe Beeinträchtigung bei beruflichen oder privaten Aktivitäten, insgesamt aber keine Einschränkung der Lebensführung
- ☐ 2 Mäßige Beeinträchtigung in bestimmten Bereichen des beruflichen oder privaten Lebens, aber noch zu verkraften
- ☐ 3 Schwere Beeinträchtigung, führt zu starken Einschränkungen der beruflichen oder privaten Lebensführung
- ☐ 4 Extreme, lähmende Beeinträchtigung

3. Wie stark fühlen Sie sich durch die Zwangsgedanken belastet?

- ☐ 0 Gar nicht
- ☐ 1 Gelegentliche, schwache Belastung
- ☐ 2 Häufige, mäßig starke Belastung, aber noch zu verkraften
- ☐ 3 Sehr häufige, schwere und nur schwer zu ertragende Belastung
- ☐ 4 Beinahe ständige, extreme und unerträgliche Belastung

4. Wie groß sind Ihre Bemühungen, gegen die Zwangsgedanken anzugehen? Wie oft versuchen Sie, Ihnen keine Beachtung zu schenken oder sich auf etwas anderes zu konzentrieren, wenn diese Gedanken in Ihr Bewußtsein dringen? (es geht hier nicht darum, wie erfolgreich Sie dabei sind, die Gedanken in den Griff zu bekommen, sondern nur, wie sehr und wie oft Sie es versuchen)

- ☐ 0 Ich versuche jedesmal, dagegen anzugehen (oder die Zwangsgedanken sind so schwach, dass es nicht nötig ist, aktiv dagegen anzugehen)
- ☐ 1 Ich versuche meistens (d.h. in mehr als der Hälfte aller Fälle) dagegen anzugehen
- ☐ 2 Ich versuche manchmal dagegen anzugehen
- ☐ 3 Es widerstrebt mir zwar ein wenig, aber ich lasse alle Zwangsgedanken zu, ohne zu versuchen, sie unter Kontrolle zu bekommen
- ☐ 4 Ich lasse den Gedanken freien Lauf

5. Wieviel Kontrolle haben Sie über Ihre Zwangsgedanken? Wie gut gelingt es Ihnen, sie zu stoppen oder sich auf etwas anderes zu konzentrieren? (wenn Sie nur selten versuchen, die Gedanken zu kontrollieren, denken Sie zur Beantwortung dieser Frage bitte an eine der wenigen Gelegenheiten zurück, bei denen Sie es versucht haben – Anmerkung: diese Frage bezieht sich nicht auf Zwangsgedanken, die Sie durch die Ausführung von Zwangshandlungen stoppen!)

- ☐ 0 Völlige Kontrolle
- ☐ 1 Große Kontrolle – meist gelingt es mir, die Zwangsgedanken mit einiger Anstrengung und Konzentration zu stoppen oder mich abzulenken
- ☐ 2 Etwas Kontrolle – manchmal gelingt es mir, die Zwangsgedanken zu stoppen oder mich auf etwas anderes zu konzentrieren
- ☐ 3 Wenig Kontrolle – ich schaffe es nur selten und mur mit großen Schwierigkeiten, mich auf etwas anderes zu konzentrieren
- ☐ 4 Keine Kontrolle – ich bin kaum in der Lage, meine Zwangsgedanken auch nur für einen kurzen Augenblick zu ignorieren

Zwangshandlungen

... sind Verhaltensweisen oder Handlungen, zu denen Sie sich gedrängt fühlen, obwohl Sie vielleicht ihre Sinnlosigkeit oder Übertriebenheit erkennen. Vielleicht versuchen Sie, sich dem Drang zur Ausführung dieser Handlungen zu widersetzen, was Ihnen jedoch meist schwerfällt. Vielleicht verspüren Sie eine innere Spannung oder Angst, die erst abklingt, wenn das bewußte Verhalten ausgeführt wird.

Anleitung

Denken Sie beim Beantworten der Fragen bitte an die **letzten sieben Tage** (einschließlich des heutigen), und markieren Sie **eine** Antwort pro Frage.

6. Wie viel Zeit verbringen Sie mit der Ausführung von Zwangshandlungen? Wie oft kommt es zu Zwangshandlungen? – Wenn Ihre Rituale normale Arbeitsverrichtungen mit einschließen, überlegen Sie bitte, wie viel ***mehr*** Zeit Sie wegen Ihrer Zwangshandlungen für diese Dinge brauchen.

- ☐ 0 Führe keine Zwangshandlungen aus
- ☐ 1 Ich verbringe weniger als eine Stunde am Tag mit Zwangshandlungen bzw. gelegentliche Ausführung zwanghaften Verhaltens (nicht öfter als 8x/Tag)
- ☐ 2 Eine bis drei Stunden am Tag verbringe ich mit Zwangshandlungen bzw. häufige Ausführung zwanghaften Verhaltens (öfter als 8x/Tag, aber in den meisten Stunden des Tages kommt es nicht zu Zwangshandlungen)
- ☐ 3 Mehr als drei und bis zu acht Stunden am Tag verbringe ich mit Zwangshandlungen bzw. sehr häufige Ausführungen zwanghaften Verhaltens (öfter als 8x/Tag und in den meisten Stunden des Tages kommt es zu Zwangshandlungen)
- ☐ 4 Mehr als acht Stunden am Tag verbringe ich mit Zwangshandlungen oder fast ständige Ausführung zwanghaften Verhaltens (zu oft, um die Zwangshandlungen zählen zu können und es vergeht kaum eine Stunde ohne mehrfaches Auftreten von zwanghaften Handlungen)

7. Wie stark beeinträchtigen Sie die Zwangshandlungen in Ihrem Privat- und Berufsleben? – Wenn Sie momentan nicht beschäftigt sind, überlegen Sie bitte, wie sehr die Zwangshandlungen Sie bei Ihren täglichen Aktivitäten einschränken.

- ☐ 0 keine Beeinträchtigung
- ☐ 1 Geringe Beeinträchtigung bei beruflichen oder privaten Aktivitäten, insgesamt aber keine Einschränkung der Lebensführung
- ☐ 2 Mäßige Beeinträchtigung in bestimmten Bereichen des beruflichen oder privaten Lebens, aber noch zu verkraften
- ☐ 3 Schwere Beeinträchtigung, führt zu starken Einschränkungen der beruflichen oder privaten Lebensführung
- ☐ 4 Extreme, lähmende Beeinträchtigung

8. Wie würden Sie sich fühlen, wenn Sie an der Ausführung Ihrer Zwangshandlung(en) gehindert würden? Wie unruhig würden Sie werden?

- ☐ 0 Gar nicht unruhig
- ☐ 1 Nur ein bisschen unruhig
- ☐ 2 Es würde eine spürbare, aber erträgliche Unruhe entstehen
- ☐ 3 Es würde zu einem starken und kaum erträglichen Anstieg an innerer Unruhe kommen
- ☐ 4 Extreme lähmende Unruhe oder Angst

9. Wie stark sind Ihre Bemühungen, gegen die Zwangsgedanken anzugehen? – Überlegen Sie nur, wie oft oder wie sehr Sie versuchen, gegen die Zwangshandlungen anzugehen, nicht, wie gut es Ihnen gelingt.

- ☐ 0 Ich versuche jedes Mal dagegen anzugehen (oder der Drang, die Zwangshandlungen auszuführen ist so schwach, dass es nicht nötig ist, aktiv dagegen anzugehen)
- ☐ 1 Ich versuche meistens dagegen anzugehen (d.h. in mehr als der Hälfte der Fälle)
- ☐ 2 Ich versuche manchmal dagegen anzugehen
- ☐ 3 Es widerstrebt mir zwar ein wenig, aber ich gebe jedem Drang zur Ausführung einer Zwangshandlung nach, ohne zu versuchen, dagegen anzugehen
- ☐ 4 Ich gebe jedem Drang zur Ausführung der Handlungen bereitwillig nach

10. Wieviel Kontrolle haben Sie über Ihre Zwangshandlungen? Wie gut gelingt es Ihnen, sie zu stoppen? – Wenn Sie nur selten versuchen, dem Drang zur Ausführung der Handlung zu widerstehen, denken Sie bitte an eine der wenigen Gelegenheiten zurück, bei denen Sie es versucht haben.

- ☐ 0 Völlige Kontrolle
- ☐ 1 Meist gelingt es mir, die Zwangshandlungen mit einiger Anstrengung und Willenskraft zu stoppen
- ☐ 2 Manchmal gelingt es mir, die Zwangshandlungen zu stoppen, aber es fällt mir schwer
- ☐ 3 Ich schaffe es nur das zwanghafte Verhalten eine Weile hinauszuzögern, aber schließlich muß ich es doch komplett ausführen
- ☐ 4 Ich bin selten in der Lage, das zwanghafte Verhalten auch nur für eine kurze Zeit hinauszuzögern

OCI-R

In den folgenden Aussagen werden Verhaltens- oder Erlebensweisen beschrieben, die viele Menschen in Ihrem Lebensalltag zeigen. Markieren Sie bitte jeweils die Zahl, die am besten beschreibt, **WIE STARK** Sie im VERGANGENEN MONAT durch eine Verhaltens- oder Erlebensweise **BEEINTRÄCHTIGT** waren oder unter ihr **GELITTEN** haben. Den Zahlen sind folgende Bedeutungen zugeordnet:
0 = gar nicht, 1 = wenig, 2 = mittel, 3 = stark, 4 = sehr stark

		gar nicht	**wenig**	**mittel**	**stark**	**sehr stark**
1.	Ich bewahre so viele Gegenstände auf, dass sie mich behindern.	0	1	2	3	4
2.	Ich kontrolliere Dinge öfter als notwendig.	0	1	2	3	4
3.	Ich werde unruhig, wenn Gegenstände nicht korrekt (an)geordnet sind.	0	1	2	3	4
4.	Bei vielen Aktivitäten fühle ich mich zum Zählen gezwungen.	0	1	2	3	4
5.	Es fällt mir schwer, einen Gegenstand anzufassen, wenn ich weiß, dass er schon von Fremden oder von bestimmten Personen berührt wurde.	0	1	2	3	4
6.	Es fällt mir schwer, meine eigenen Gedanken zu kontrollieren.	0	1	2	3	4
7.	Ich sammle Dinge, die ich nicht brauche.	0	1	2	3	4
8.	Ich kontrolliere wiederholt Türen, Fenster, Schubladen etc.	0	1	2	3	4
9.	Ich werde unruhig, wenn andere etwas daran ändern, wie ich die Dinge (an)geordnet habe.	0	1	2	3	4
10.	Ich fühle mich gezwungen, bestimmte Zahlen zu wiederholen.	0	1	2	3	4

Bitte wenden!

		gar nicht	wenig	mittel	stark	sehr stark
11.	Manchmal muss ich mich waschen oder reinigen, einfach weil ich glaube, verunreinigt oder verseucht zu sein.	0	1	2	3	4
12.	Ich fühle mich durch unangenehme Gedanken beunruhigt, die mir gegen meinen Willen in den Sinn kommen.	0	1	2	3	4
13.	Ich vermeide es, Sachen wegzuwerfen, da ich Angst habe, ich könnte sie vielleicht später noch brauchen.	0	1	2	3	4
14.	Ich kontrolliere wiederholt Gas-/ Wasserhähne und Lichtschalter, nachdem ich sie zu-/ausgemacht habe.	0	1	2	3	4
15.	Für mich müssen Dinge in einer bestimmten Weise geordnet sein.	0	1	2	3	4
16.	Ich glaube, dass es gute und schlechte Zahlen gibt.	0	1	2	3	4
17.	Ich wasche meine Hände öfter und länger als nötig.	0	1	2	3	4
18.	Ich bekomme häufig abscheuliche Gedanken und es fällt mir schwer, sie wieder loszuwerden.	0	1	2	3	4

HAM-D

Kompetenznetzwerk „Depression"

Patient / Code: K-____-S61-0 Datum: ____-____-20__ Termin A/W/E/K: __ Rater: ____

Hamilton Depression Scale (HAMD)

1. Depressive Stimmung (Gefühl der Traurigkeit, Hoffnungslosigkeit, Hilflosigkeit, Wertlosigkeit)

0: Keine
1: Nur auf Befragen geäußert
2: Vom Patienten spontan geäußert
3: Aus dem Verhalten zu erkennen (z.B. Gesichtsausdruck, Körperhaltung, Stimme, Neigung zum Weinen)
4: Patient drückt fast ausschließlich diese Gefühlszustände in seiner verbalen und nonverbalen Kommunikation aus

2. Schuldgefühle

0: Keine
1: Selbstvorwürfe, glaubt Mitmenschen enttäuscht zu haben
2: Schuldgefühle oder Grübeln über frühere Fehler und „Sünden".
3: Jetzige Krankheit wird als Strafe gewertet, Versündigungswahn
4: Anklagende oder bedrohende akustische / optische Halluzinationen

3. Suizid (jeder ernste Versuch = 4)

0: Keiner
1: Lebensüberdruß
2: Todeswunsch, denkt an den eigenen Tod
3: Suizidgedanken oder entsprechendes Verhalten.
4: Suizidversuche

4. Einschlafstörungen

0: Keine
1: Gelegentliche Einschlafstörungen (mehr als ½ Stunde)
2: Regelmäßige Einschlafstörungen

5. Durchschlafstörungen

0: Keine
1: Patient klagt über unruhigen oder gestörten Schlaf
2: Nächtliches Aufwachen bzw. Aufstehen (falls nicht nur zur Harn- oder Stuhlentleerung)

6. Schlafstörungen am Morgen

0: Keine
1: Vorzeitiges Erwachen, aber nochmaliges Einschlafen
2: Vorzeitiges Erwachen ohne nochmaliges Einschlafen

7. Arbeit und sonstige Tätigkeiten (Arbeit oder Hobbies)

0: Keine Beeinträchtigung
1: Hält sich für leistungsunfähig, erschöpft oder schlapp bei seinen Tätigkeiten oder fühlt sich entsprechend
2: Verlust des Interesses an seinen Tätigkeiten, muß sich dazu zwingen. Sagt das selbst oder läßt es durch Lustlosigkeit, Entscheidungslosigkeit oder sprunghafte Entschlußlosigkeit erkennen.
3: Wendet weniger Zeit für seine Tätigkeiten auf oder leistet weniger. Bei stationärer Behandlung „3" ankreuzen, wenn der Patient weniger als 3 Stunden an Tätigkeiten teilnimmt. Ausgenommen Hausarbeiten auf der Station
4: Hat wegen der Krankheit mit der Arbeit aufgehört. Bei stationärer Behandlung ist „4" anzukreuzen, falls der Patient an keinen Tatigkeiten teilnimmt, mit Ausnahme der Hausarbeit auf der Station, oder wenn der Patient die Hausarbeit nur unter Mithilfe leisten kann

8. Depressive Hemmung (Verlangsamung von Denken und Sprache, Konzentrationsschwäche, reduzierte Motorik)

0: Sprache und Denken normal
1: Geringfügige Verlangsamung bei der Exploration
2: Deutliche Verlangsamung bei der Exploration
3: Exploration schwierig.
4: Ausgeprägter Stupor

12. Körperliche -gastrointestinale

0: Keine
1: Appetitmangel, ißt aber ohne Zuspruch
2: Muß zum Essen angehalten werden. Verlangt oder benötigt Abführmittel oder andere Magen-Darm Präparate

13. Körperliche Symptome allgemeine

0. Keine
1: Schweregefühl in den Gliedern,Rücken oder Kopf. Rücken-, Kopf- oder Muskelschmerzen, Verlust der Tatkraft Erschöpfbarkeit
2: Bei jeder deutlichen Ausprägung eines Symptoms „2" ankreuzen !

14. Genitalstörungen (z.B. Libidoverlust)

0: Keine
1: Geringe
2: Starke

15. Hypochondrie

0: Keine
1: Verstärkte Selbstbeobachtung (auf den Körper bezogen)
2: Ganz in Anspruch genommen durch Sorgen um die eigene Gesundheit
3: Zahlreiche Klagen, verlangt Hilfe usw.
4: Hypochondrische Wahnvorstellungen

16. Gewichtsverlust (entweder A oder B ankreuzen)

A. Aus Anamnese

0: Kein Gewichtsverlust
1. Gewichtsverlut, wahrscheinlich im Zusammenhang mit jetziger Krankheit
2. Sicherer Gewichtsverlust laut Patient

B. nach wöchtentlichem Wiegen in derKlinik wenn Gewichtsverlust

0: weniger als 0,5 kg / Woche
1: mehr als 0,5 kg / Woche
2: mehr als 1 kg / Woche

17. Krankheitseinsicht

0: Patient erkennt, daß er depressiv und krank ist
1: Räumt Krankheit ein, führt sie aber auf schlechte Ernährung, Klima, Überarbeitung, Virus, Ruhebedürfnis usw. zurück
2. Leugnet Krankheit ab

18. Tagesschwankungen

A. Geben Sie an, ob die Symptome schlimmer am Morgen oder am Abend sind. Sofern keine Tages Schwankungen auftreten, ist „0" anzukreuzen

0. Keine Tagesschwankungen -
1. Symptome schlimmer am Morgen
2. Symptome schlimmer am Abend

9. Erregung

0: Keine
1: Zappeligkeit
2: Spielen mit den Fingern, Haaren, usw.
3: Hin- und Herlaufen, nicht still sitzen können
4: Händeringen, Nägelbeißen, Haareraufen, Lippenbeißen, usw.

10. Angst – psychisch

0: Keine Schwierigkeiten
1: Subjektive Spannung und Reizbarkeit
2: Sorgt sich um Nichtigkeiten
3: Besorgte Grundhaltung, die sich im Gesichtsausdruck und in der Sprechweise äußert
4: Ängste werden spontan vorgebracht

11. Angst – somatisch (körperliche Begleiterscheinungen der Angst, z.B. kardiovaskuläre, Herzklopfen, gastrointestinale, Mundtrockenheit, Verdauungsstörungen, Durchfall, Krämpfe, respiratorische, Hyperventilation, Schwitzen, usw.)

0: Keine
1: Geringe
2: Maßige
3: Starke
4: Extreme (Patient ist handlungsunfähig)

☐

B. Wenn es Schwankungen gibt, geben Sie hre Stärke an. Falls es keine gibt, keuzen Sie „0" an.

0. Keine
1. Gering
2. Stark

☐

19. Depersonalisation, Derealisation ☐

(z. B. Unwirklichkeitsgefühle, nihilistische Ideen)

0. Keine
1. Gering
2. Mäßig
3. Stark
4. Extrem

☐

20. Paranoide Symptome ☐

0. Keine
1. Mißtrauisch
2. Beziehungsideen
3. Beziehungs- und Verfolgungswahn

21. Zwangssymptome ☐

0. Keine
1. Gering
2. Stark

SUMMENSCORE ☐

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