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Switch the itch: A naturalistic follow-up study on the neural correlates of cognitive flexibility in obsessive-compulsive disorder

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ABSTRACT

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder characterized by intrusive thoughts and behaviors that dominate daily living, like an itch patients cannot ignore. Deficits in executive functioning are common in OCD and are thought to be related to dysfunctional frontal-striatal systems. One of those executive functions is cognitive flexibility, defined as the ability to rapidly switch response strategies following changes in task-relevant information. The temporal stability of cognitive flexibility impairments in OCD has been incompletely investigated since previous studies have suggested both state and trait dependency. In this study, 16 OCD patients performed a functional magnetic resonance imaging version of a task-switching paradigm twice, intervened by a follow-up period of on average 6 months. Results show that functional abnormalities in the dorsal frontal-striatal circuit and anterior cingulate cortex at baseline normalized at follow-up. This change in the recruitment of task-related brain circuits correlated with change in disease severity. These results support the view that the imbalance between the dorsal and ventral frontal-striatal circuits is at least partly state-dependent, and is associated with a reduction in symptom severity.

1. Introduction

Obsessive-compulsive disorder (OCD) is, with a lifetime prevalence of around 2–3% (Ruscio et al., 2010), the fourth ranked psychiatric disorder (Fava and Kendler, 2000; El-Sayegh et al., 2003). OCD is characterized by recurrent, intrusive and persistent thoughts (obsessions) and/or repetitive behaviors (compulsions) which patients need to perform in order to reduce the concomitant anxiety or distress (American Psychiatric Association, 1994). These patients therefore suffer from a metaphorical itch that is not alleviated until it is scratched, while in the long run scratching enhances the itch. The disorder has a detrimental impact on daily life functioning and frequently runs a chronic, relapsing/remitting course (Fenske and Schwenk, 2009).

Apart from the time-consuming obsessions and/or compulsions, OCD patients also show cognitive symptoms. Neuropsychological tests have revealed deficits in spatial working memory, spatial recognition, and motor initiation and execution in OCD (Purcell et al., 1998). In recent years, these tests have been combined with functional magnetic resonance imaging (fMRI) to elucidate the neural correlates of aberrant task performance in OCD patients. It is thought that dysfunction of the dorsal frontal-striatal circuit underlies the executive deficits in OCD patients (Remijnse et al., 2005; Friedlander and Desrocher, 2006; de Wit et al., 2012). Frontal-striatal circuits interconnect prefrontal areas with the basal ganglia and limbic areas and are, among others, involved in executive functioning, motor initiation and control, and emotion processing (Cummings, 1993; Remijnse et al., 2005; Menzies et al., 2008; van den Heuvel et al., 2010). These circuits have been implicated in the pathophysiology of many psychiatric disorders (Phillips, 2003; Phillips et al., 2003a,b; van den Heuvel et al., 2010), including OCD (Remijnse et al., 2005; Mataix-Cols and van den Heuvel, 2006; van den Heuvel et al., 2009). The dorsal 'executive' frontal-striatal circuit encompasses the dorsal areas of the prefrontal cortex (dorsolateral prefrontal cortex, DLPFC), the dorsal anterior cingulate cortex (ACC), and the dorsal part of the caudate nucleus (Mataix-Cols and van den Heuvel, 2006). The ventral 'affective' circuit consists of the orbitofrontal cortex and ventral subcortical areas, such as the ventral striatum (Friedlander and Desrocher, 2006; Mataix-Cols and van den Heuvel, 2006). A current model of OCD pathophysiology postulates that key aspects of OCD, i.e. compulsive behavior and persistent focus on certain aspects of the environment (e.g. danger or hygiene) (Friedlander and Desrocher, 2006; Fibbe et al., 2012), may result

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from an imbalance between a hyperactive ventral and a hypoactive dorsal circuit. Additional support for an imbalance between dorsal and ventral circuits in OCD comes from two recent resting-state studies that showed increased and reduced functional coupling in, respectively, the ventral (Harrison et al., 2009; Sakai et al., 2011) and dorsal circuit (Harrison et al., 2009) in patients with OCD compared with healthy controls. Although this model is overly simplistic, for instance due to the clinical heterogeneity of OCD and lack of specificity among disorders (Mataix-Cols and van den Heuvel, 2006), it provides a useful framework for investigating the complex interactions between emotional and cognitive processes underlying OCD symptoms.

The dorsal frontal-striatal circuit is involved in cognitive flexibility, i.e. the ability to rapidly change response strategies with alterations in task-relevant information in the environment (Fineberg et al., 2010). Cognitive flexibility is impaired in OCD and related disorders (Friedlander and Desrocher, 2006; Chamberlain and Menzies, 2009), which has frequently been associated with dysfunction of the dorsal frontal-striatal circuit (Remijnse et al., 2006; Gu et al., 2008; Woolley et al., 2008; Page et al., 2009). Abnormal cognitive flexibility in OCD patients probably relates to their tendency to perseverate and their inability to engage in new behaviors. Cognitive flexibility can be investigated with different paradigms, e.g. the reversal learning task and the switch task paradigm. In the reversal learning task, subjects have to alter their responses with changing stimulus-reinforcement contingencies, i.e. punishment and reward (Remijnse et al., 2006). The switch task has two separate task instructions which are introduced by a certain cue. After several trials the cue changes and subjects have to switch their behavior accordingly. An advantage of the task-switching paradigm over the reversal learning task is that it is not biased by contingency learning (Robbins, 2007); i.e. subjects do not receive feedback on their responses and successful switches are therefore generated internally rather than triggered by external cues. A previous study by our group (Remijnse et al., 2012) showed that OCD patients had more accurate but slower performance than the control group, although switch cost (i.e. RT switch events minus RT repeat events) did not significantly differ between OCD patients ($n=19$) and controls ($n=29$). This latter finding is in line with other studies (Gu et al., 2008; Woolley et al., 2008; Page et al., 2009). Interestingly, in the OCD group accuracy increased linearly with the severity of obsessive-compulsive symptoms. Imaging results of that study showed that OCD patients had lower task-related activity in the anterior prefrontal cortex during switching and increased recruitment of the dorsal ACC and putamen compared with healthy controls. Activation of the dorsal ACC and putamen correlated positively with disease severity (Remijnse et al., 2012). Furthermore, in contrast to controls, OCD subjects showed no switch-related activity in the DLPFC, an integral part of the dorsal frontal-striatal circuit. The correlation between performance accuracy and disease severity suggests that altered switching capability in OCD is state dependent. However, its stability over time has only rarely been investigated. A recent preliminary study of Han et al. (2011) on cognitive flexibility in 10 OCD patients showed overall normalization of ventral frontal-striatal activity at 16-week follow-up with changes in task-related thalamic activity positively correlating with symptom improvement. Dorsal frontal-striatal dysfunction was found to persist. In contrast, in a comparison of the neural correlates of a planning task in pediatric OCD patients before and after 16 sessions of cognitive behavioral therapy, (Huyser et al., 2010) showed normalized activity in the DLPFC after successful treatment, suggesting state-dependency.

In the present study, we aimed to further investigate these above-mentioned questions regarding the state-dependency of dorsal and ventral frontal-striatal dysfunction in OCD. To this end, we obtained fMRI data from 18 OCD patients using a naturalistic longitudinal approach. Based on the above-reviewed literature and theoretical models, we hypothesized that a decrease in disease severity would result in normalization of task performance and task-related recruitment of the dorsal frontal-striatal circuit and the ACC.

2. Methods

2.1. Subjects

Eighteen medication-free subjects diagnosed with OCD were included in this study, in follow-up of a previous study (Remijnse et al., 2012). We adopted a naturalistic follow-up design since subjects were recruited from various sources (psychiatric outpatient clinics in Amsterdam and Nijmegen, the Netherlands, and by online advertisements), hampering controlled treatment conditions. At follow-up, diagnoses of OCD and any comorbid disorders (see Table 1) were established by an experienced clinician (PR, co-author), with the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I) (First et al., 2002). Exclusion criteria were the presence of alcohol or substance abuse, or major medical or neurological disorders.

Participants were free from psychotropic medication for at least 2 weeks before the first scanning session, while medication was allowed during the second session. All participants provided written informed consent and the study was approved by the ethical review board of the VU University Medical Center in Amsterdam, the Netherlands.

2.2. Questionnaires

To assess obsessive-compulsive symptom characteristics and severity, we administered the Padua Inventory-Revised (Padua-IR) (Sanavio, 1988) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989), respectively. To rate the presence and severity of depressive symptoms the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) was used. All questionnaires were administered at T_0 (baseline session) and T_1 (follow-up).

2.3. Task-switching paradigm

Subjects performed a self-paced task-switching (letter/digit) paradigm during fMRI scanning. Subjects were presented with a letter (a, e, i, u, b, c, d, f) and a digit (2, 4, 6, 8, 3, 5, 7, 9) displayed on a colored background for a maximum of 4 s. A blue background indicated that subjects had to respond to the *letter* (discriminate vowel or consonant), while a red background cued a *digit* discrimination (i.e. odd or even). Responses were given with the right index finger on an MRI-compatible button box. Two consecutive trials never contained the same letter or digit. Task switching occurred randomly after four to six trials to avoid predictability. The first trial immediately after task switching was defined as a 'switch event' (SE); all other trials were 'repeat events' (RE) (see Fig. 1). The task ended after 32 discrimination stages, i.e. after 31 task switches. E-prime (Psychology Software Tools, Inc., Sharpsburg, PA, US) was used for the task presentation and recording of behavioral data (reaction times and accuracy).

Table 1
Sample characteristics OCD patients ($n=16$).

Demographics	
Age, years (mean, (S.D.))	30 (8.6)
Education level, range: 1–10 (mean, (S.D.))	8.3 (1.9)
Gender, M/F (n)	4/12
Handedness, R/L (n)	13/3
T_0–T_1 interval, days (mean, S.D.)	180 (44,6)
Co-morbidity	**No. subjects**
Major depressive disorder (mild to moderate)	5
Dysthymia	2
Agoraphobia	2
General anxiety disorder	4
Panic disorder	2
Social phobia	1
Therapy during follow-up*	**No. subjects**
Cognitive behavioral therapy	8
Medication	2
None	4
Insufficient data	2

* All patients were medication-free at baseline.