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The course of the neural correlates of reversal learning in obsessive–compulsive disorder and major depression: A naturalistic follow-up fMRI study

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ABSTRACT

Objectives: Reversal learning (RL) is impaired in obsessive–compulsive disorder (OCD) as well as in major depressive disorder (MDD). It is yet unknown to what extent pathophysiological mechanisms are state-dependent.
Methods: Neural activation patterns during RL were measured using event-related functional magnetic resonance imaging (fMRI) reversal learning in patients with OCD ($N=18$) and MDD ($N=15$). A naturalistic follow-up design enabled investigation of the relationship between changes in clinical state, task performance and task-related neural activation over time.
Results: During follow-up, disease severity decreased significantly in both groups. Whereas task speed improved trend-significantly, task accuracy was unchanged. Task-related dorsal frontal-striatal activation decreased at follow-up in MDD, but increased in OCD. In both groups, symptom improvement was associated with reward-related changes in neural activation in the putamen and the orbitofrontal cortex.
Conclusions: In both OCD and MDD, symptom reduction over time was associated with partial normalization of task-related activation patterns in brain regions. Whereas in OCD this normalization was characterized by increased recruitment of previously hypoactive frontal-striatal brain regions (i.e. dorsal frontal-striatal failure), in MDD previously hyperactive brain regions (frontal-striatal inefficiency), were recruited less after recovery. These results show that in both disorders frontal-striatal dysfunction is at least partly state-dependent.

1. Introduction

Major depressive disorder (MDD) and obsessive–compulsive disorder (OCD) are the first and fourth most common psychiatric disorders, respectively, and both may have severe repercussions on daily functioning (El-Sayegh, Bea, & Agelopoulos, 2003; Fava & Kendler, 2000). Both disorders are frequently co-morbid and show overlap in symptoms, including cognitive rigidity (Ninan & Berger, 2001; Overbeek, Schruers, Vermetten, & Griez, 2002). Depressed patients experience negative emotions, motivational impairments, cognitive slowing and excessive rumination (Lyness, Conwell, King, Cox, & Caine, 1997), whereas OCD is characterized by recurrent, intrusive and persistent thoughts (obsessions) and/or repetitive behaviors (compulsions) (APA, 2005). The inability to halt obsessions and compulsions in OCD and rumination in MDD is thought to reflect deficits in cognitive and behavioral flexibility (Gotlib & Joormann, 2010; Kim, Yu, Lee, & Kim, 2011; Levens, Muhtadie, & Gotlib, 2009; Remijnse, 2011). OCD and MDD patients are not only prone to cognitive rigidity (Bradbury, Cassin, & Rector, 2011; Remijnse et al., 2013; Vriend et al., 2013) but also show other cognitive deficits, such as impairments in decision making, planning and behavioral inhibition (Cavedini, Gorini, & Bellodi, 2006; de Wit et al., 2012; Godard, Grondin, Baruch, & Lafleur, 2011; Gotlib & Joormann, 2010; Huyser, Veltman, Wolters, de Haan, & Boer, 2010; Kathmann, Rupertseder, Hauke, & Zaudig, 2005; Linden, Jackson, Subramanian, Healy, & Linden, 2011; Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Segalas et al., 2010; Tukel et al., 2011; van den Heuvel et al., 2005; Zucco & Bollini, 2011).

Reversal learning (RL) is defined as the ability to alter a response upon changing stimulus-reinforcement contingencies by

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means of motivational feedback (i.e. punishment and reward) (Cools, Clark, Owen, & Robbins, 2002; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). RL thus is an executive function calling upon both cognitive and affective flexibility which is vital for normal socio-emotional learning and behavior (Dias, Robbins, & Roberts, 1996). It has been hypothesized that anxiety relief and compulsive urge in OCD patients resemble reward and punishment, respectively (Huey et al., 2008). MDD patients tend to be oversensitive to negative feedback (i.e. punishment) (Chamberlain & Sahakian, 2006; Elliott et al., 1996; Taylor Tavares et al., 2008) and show blunted reward responses (Henriques, Glowacki, & Davidson, 1994; Must et al., 2006).

Lesions in the orbitofrontal cortex (OFC) in humans (Rolls, 2004) and ventral striatum and dorsolateral prefrontal cortex (DLPFC) in non-human primates lead to RL deficits (Clarke, Robbins, & Roberts, 2008). RL relies on proper functioning of the frontal-striatal circuits which have been implicated in various psychiatric disorders (Phillips, Drevets, Rauch, & Lane, 2003a, 2003b; van den Heuvel et al., 2010), and include a dorsal 'executive' circuit (involving the DLPFC, dorsal ACC, caudate nucleus and anterior prefrontal cortex (aPFC)), and a ventral 'affective' circuit (involving the OFC and ventral striatum) (Alexander, Crutcher, & DeLong, 1990). During RL activation of the OFC is related to the magnitude and value of the feedback (O'Doherty et al., 2001). RL-related activation of the OFC and ventral striatum is mostly associated with reward processing, whereas insular cortex activation is mainly associated with punishment (O'Doherty et al., 2001; Remijnse, Nielen, Uylings, & Veltman, 2005). Relearning stimulus-reward associations (i.e. affective switching) is related to activation of both the ventral and the dorsal frontal-striatal circuit (Cools et al., 2002; Remijnse et al., 2005). OCD (Britton et al., 2010; Chamberlain et al., 2008; Dickstein et al., 2010; Figee et al., 2011; Remijnse et al., 2006; Saxena, Brody, Schwartz, & Baxter, 1998; Valerius, Lumpp, Kuelz, Freyer, & Voderholzer, 2008) and MDD (Remijnse et al., 2009) are both associated with abnormal RL performance and alterations in task-related brain activation.

In our previous published study, regarding the baseline results of the same samples, we found in MDD patients compared with controls specific hyperactivity of the putamen during reward, and precuneus and insular cortex during punishment processing (Remijnse et al., 2009), whereas OCD patients showed decreased responsiveness of the OFC and caudate nucleus in response to reward (Remijnse et al., 2006). At baseline MDD and OCD patients, compared with controls, both showed decreased activation of the insula, aPFC and DLPFC during affective switching, and OFC during reward processing (Remijnse et al., 2006, 2009).

Until now, some studies on OCD, but none in MDD, have evaluated the effects of treatment on specific aspects of RL, e.g. pharmacotherapy on task switching (Han et al., 2011) and cognitive behavioral therapy (CBT) on strategy change (Freyer et al., 2011). At follow-up, OCD patients showed increased activation in ventral frontal-striatal regions during switching events, and were correlated with symptom improvement (Freyer et al., 2011; Han et al., 2011). However, neither study employed motivational feedback (punishment/reward) in their task-switching paradigms. Sensitivity to motivational feedback and relearning rewarding associations in relation to recovery-related changes have not been studied across MDD and OCD. Such comparisons are important because it allows one to differentiate between general treatment- or recovery-induced changes and disorder-specific changes in cognitive functioning. It has been suggested that with symptom improvement, some neuropsychological deficits may recover (Maalouf et al., 2011) (*state-dependent changes*), while other impairments persist (*trait characteristics*) (Douglas, Porter, Knight, & Maruff, 2011; Fava, 2003; Kerestes et al., 2011; Li et al., 2009; Milne, Macqueen, & Hall, 2011; Paelecke-Habermann, Pohl, & Leplow, 2005).

Using a naturalistic follow-up design, our aim was to investigate general and disorder-specific changes in RL-related frontal-striatal activation during fMRI scanning and relate these to clinical improvement in OCD and MDD over time. Specifically, in OCD, we hypothesized that clinical improvement would be associated with normalization of reduced activation at baseline of the ventral frontal-striatal regions during reward, and dorsal and ventral frontal-striatal regions during affective switching. In MDD, we expected to find that the initially enhanced activation of putamen and insular cortex on reward and punishment would normalize. In addition, we expected dorsal frontal-striatal normalization during affective switching in MDD.

2. Materials and methods

2.1. Subjects

Baseline data of all patients (OCD $n=28$, MDD $n=21$) have been reported previously (Remijnse et al., 2006, 2009). From these, ten OCD and six MDD patients were lost for follow-up, leaving data from 18 OCD and 15 MDD patients. See Table 1 for demographic and clinical details. Main diagnosis and co-morbid diagnoses were established using the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID) (Spitzer, Williams, Gibbon, & First, 1992).

Eligible patients were not receiving any psychotropic medication at least one month prior to baseline measurements (Remijnse et al., 2009). Main exclusion criteria were the presence of alcohol or substance abuse at the time of study, and currently present and/or a history of major internal or neurological disorders. During follow-up there were no restrictions related to treatment. All participants gave written informed consent and the study was approved by the ethical review board of the VU university medical center.

2.2. Clinical measures

Clinical rating scales were administered one week before scanning at both time points. The Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1967), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) were used to measure depression severity. OCD symptoms (both groups) and severity (OCD group only) were assessed with the Padua Inventory-revised (Padua-IR) (Beck et al., 1961; Sanavio, 1988) and the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) (Goodman et al., 1989), respectively. We used the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) as a measure of general anxiety.

2.3. Reversal learning task and experimental procedure

We used a self-paced, probabilistic reversal learning task (RLT) (Cools et al., 2002; O'Doherty et al., 2001), which allowed investigation of three components: reward, punishment and affective switching. This paradigm has been extensively described previously (Remijnse et al., 2005, 2006, 2009). Briefly, subjects were instructed to select one of two presented stimuli on each trial in order to gain points. Stimulus-response contingencies were reversed in a probabilistic fashion. Positive or negative feedback was given in the form of addition or subtraction of points. Behavioral outcome measures were the reaction time per trial type and the total number of acquired points (see data-analysis paragraph). The task ended after 400 trials (approximately 25 min).

2.4. Data acquisition

Imaging data were collected on a Sonata 1.5-T MRI system (Siemens, Erlangen, Germany) with a standard circularly-polarized head coil. Functional T2*-weighted images were acquired using an echo-planar imaging (EPI) sequence (TR, 2.18 s, TE=45 ms), consisting of 35 slices ($3 \times 3 \times 2.5$ mm; matrix size 64×64). To compensate for susceptibility-induced BOLD sensitivity losses, a customized EPI sequence was used (Deichmann, Gottfried, Hutton, & Turner, 2003) and the acquisition plane was tilted parallel to the air/tissue interface of the OFC for each subject (between 0° and 15° from the anterior–posterior commissure line). The scanner automatically discarded the first two EPI-volumes (dummy scans) to avoid non-equilibrium effects. We also acquired a T1-weighted coronal 3D gradient-echo (voxel size, $1 \times 1 \times 1.5$ mm: 160 slices) structural image. Task stimuli were generated by a personal computer and projected onto a screen behind the subject's head, which was visible through a mirror mounted on the head coil. We used a MRI-compatible two-key response box to record button-presses.