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Medial prefrontal brain activation to anticipated reward and loss in obsessive–compulsive disorder

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ABSTRACT

Obsessive–compulsive disorder (OCD) is associated with dysfunctional brain activity in several regions which are also involved in the processing of motivational stimuli. Processing of reward and punishment appears to be of special importance to understand clinical symptoms. There is evidence for higher sensitivity to punishment in patients with OCD which raises the question how avoidance of punishment relates to activity within the brain's reward circuitry. We employed the monetary incentive delay task paradigm optimized for modeling the anticipation phase of immediate reward and punishment, in the context of a cross-sectional event-related FMRI study comparing OCD patients and healthy control participants ($n = 19$ in each group). While overall behavioral performance was similar in both groups, patients showed increased activation upon anticipated losses in a medial and superior frontal cortex region extending into the cingulate cortex, and decreased activation upon anticipated rewards. No evidence was found for altered activation of dorsal or ventral striatal regions. Patients also showed more delayed responses for anticipated rewards than for anticipated losses whereas the reverse was true in healthy participants. The medial prefrontal cortex has been shown to implement a domain-general process comprising negative affect, pain and cognitive control. This process uses information about punishment to control aversively motivated actions by integrating signals arriving from subcortical regions. Our results support the notion that OCD is associated with altered sensitivity to anticipated rewards and losses in a medial prefrontal region whereas there is no significant aberrant activation in ventral or dorsal striatal brain regions during processing of reinforcement anticipation.

1. Introduction

Patients with obsessive–compulsive disorder (OCD) get stuck on a particular aversive thought or urge and just cannot let go compensatory behaviors like hand washing or controlling. Qualitatively similar thoughts or actions are common in everyday life but are usually terminated in time in non-OCD subjects. Empirically, there is strong evidence from resting state, symptom provocation as well as treatment studies that the disease is associated with dysfunctional brain structures including the basal ganglia, the thalamus, as well as frontal and parietal cortex structures (Menzies et al., 2008). Activation of these regions is provoked by cues associated with symptoms and appears to reflect processing of negative mood states (Heinz, 1999; Rotge et al., 2008). Brain regions implicated in OCD are also involved in tasks related to monetary reward and punishment. From a clinical perspective, responses to anticipated reward and punishment may be crucial for obsessive–compulsive behaviors. Compulsive behaviors are purported to reduce distress and anxiety (Salkovskis, 1999), that is they are experienced as immediate avoidance of punishment. There is also evidence for higher sensitivity to punishment in patients with OCD on the behavioral level (Fullana et al., 2004a). It is therefore a central question of OCD pathopsychology how avoidance of punishment relates to activity within the brain's reward circuitry.

So far, two studies challenged the reward circuitry in obsessive–compulsive disorder (Figee et al., 2011; Jung et al., 2011). While Jung et al. (2011) found no group differences, Figee et al. (2011) reported attenuated activity within the dorsal striatum of OCD patients during reward anticipation. Additionally, Jung et al. found decreased activity within the dorsal striatum in OCD upon loss receipt while Figee et al. did not analyze loss receipt (because they restricted their experimental design to stimuli indicating reward). Therefore, heterogeneity of these

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results may be due to distinct differences in experimental task design. Nevertheless, both studies showed for the first time evidence for altered brain activity in OCD in the context of monetary incentive delay tasks.

During the last decade the monetary incentive delay task paradigm (Knutson et al., 2001) was employed in numerous FMRI studies in health and disease (Juckel et al., 2006; Knutson et al., 2008; Schlagenhauf et al., 2008; Strohle et al., 2008; Wrase et al., 2007). The experimental paradigm in its original form is optimized for modeling the anticipation phase of immediate reward and punishment. In healthy participants anticipation of rewards and losses was repeatedly found to be associated with BOLD responses in thalamic, striatal and frontal brain structures in healthy subjects (Breiter et al., 2001; Kirsch et al., 2003; Knutson et al., 2000, 2001; Zink et al., 2004). More specifically, mesial prefrontal cortex (MPFC) activity preferentially tracks rewarding outcomes (Knutson et al., 2003). Activity of a caudate region during anticipation of both reward and punishment was shown to code for expected outcome magnitude whereas ventral striatal activity was associated with expected positive incentive valence (Knutson et al., 2001). Dopamine release from ventral tegmental area (VTA) neurons projecting to cortical and subcortical regions is increased during reward expectancy (Ikemoto and Panksepp, 1999), and hence drives activity in the ventral striatum and the MPFC. Further, serotonergic transmission in the forebrain regulates decision making and motivated choices about obtaining reinforcers (Crean et al., 2002; Dalley et al., 2004).

Following this line of research the aim of the present study was to elucidate neural correlates for the proposed hypersensitivity to punishment in OCD within the brain's reward circuitry using the monetary incentive delay task focusing on the anticipation phase of incentive processing. According to the literature we hypothesized that hemodynamic activity of the ventral and dorsal striatum, thalamus, cingulate and medial prefrontal cortex would be altered during anticipation of reward and punishment in OCD. Because of indecisive evidence with respect to increased or decreased brain activity in OCD patients relative to healthy controls we refrained from postulating directions of effects. We were additionally interested whether clinically assessed symptom severity and hemodynamic activity would be correlated.

2. Materials and methods

2.1. Participants

Patients (n = 19) were consecutively recruited from the OCD outpatient clinic at the Humboldt-Universität zu Berlin. They fulfilled DSM-IV criteria for obsessive–compulsive-disorder (300.3), and were currently or had recently been under treatment with cognitive-behavioral psychotherapy. The Structured Clinical Interview for DSM-IV (SCID; German version: Wittchen et al., 1997) was used by a trained clinical psychologist not involved in the study to confirm clinical axis I diagnoses. Severity of OCD symptoms was evaluated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS: Goodman et al., 1989). Patients with past or present psychotic symptoms, or with past or present substance dependence, and with known or self-reported head trauma or neurologic disease were excluded. Ten patients had comorbid diagnoses (affective disorder, $n = 7$; phobic disorders, $n = 3$; impulse control disorder, $n = 1$; personality disorder, $n = 3$). Three out of the 19 patients were taking antiobsessional drugs (one clomipramine 10 mg/d, one venlafaxine 75 mg/d, and one a combination of clomipramine 75 mg/d and paroxetine 30 mg/d). No patient took benzodiazepines within 4 weeks before the scanning session.

Additional information with respect to symptom profiles according to the Y-BOCS symptom-checklist for all available OCD patients ($n = 17$), which were summarized using a recently described method (Katerberg et al., 2010) is provided as *supplementary material* (Table S1a and b).

Participants of the control group ($n = 19$) were matched to the patients regarding gender, age, handedness, and verbal intelligence (Table 1). None of them had present signs or a history of psychiatric or neurologic disorder according to a SCID-I-based screening interview. They also reported to not having used psychoactive drugs during the past 3 months.

All participants had normal or corrected-to-normal vision. They completed a German vocabulary test (Wortschatztest, WST: Schmidt and Metzler, 1992), the Edinburgh Handedness Inventory (EHI: Oldfield, 1971), and the State-Trait Anxiety Inventory (STAI: Laux et al., 1981). OCD patients were additionally assessed using the Obsessive–Compulsive Inventory-Revised (OCI-R: Foa et al., 2002), and the Beck Depression Inventory (BDI: Beck et al., 1995). All participants gave written informed consent according to the institutional guidelines before enrollment. The study was approved by the local ethics committee.

2.2. Task

The task (Fig. 1) was adapted from the monetary incentive delay task (MID) as described by Knutson et al. (2001). There were seven different types of trials: three trial-types with the possibility of winning money on a correct (i.e. timely) button press (reward trials), three trial-types with the possibility to avoid losing money on a correct button press (loss-avoidance trials), and in the remaining trial-type there were no monetary consequences at all (neutral trials). At the beginning of each trial, one of seven different cues was shown to indicate trial type. Participants were asked to press a button as soon as the target stimulus (gray colored square) appeared. Depending on the performance (i.e. timely motor response) participants received feedback about winning or losing money. Each run consisted of 72 trials, i.e. 27 gain, 27 loss, and 18 neutral trials with each trial lasting for 11.6 s on average (see Fig. 1 for details). Subjects performed the task three times in succession. The first run was a training session while structural MR-sequences were obtained, and the remaining two runs were conducted subsequently. Task difficulty was continuously adapted to come up with a 66% success level in each subject across a task run. This was achieved by using individually tailored reaction times of the training session, and by adapting the response deadline as a result of the averaged reaction times in previous trials and the correctness of the immediately preceding trial during the test runs. Participants effectively received the money they had earned in the game. After the end of the session, they reported whether they had in fact believed in this announcement. From the two task sessions during which FMRI was done, one was selected for final analysis. This selection was made with the aim to match patient and control groups for global performance according to their success level, i.e. total earnings. Selection was carried out blind to FMRI results. The number of sessions selected from first and second runs was comparable in patients and controls (OCD 8/11; controls 9/10). Subsequently, both runs were included in an additional analysis in order to ensure whether FMRI findings remain constant.

Table 1
Demographic and psychometric data and total earnings in the MID task of OCD patients and matched healthy controls; comparisons are based on two-sample *t* tests.

$N = 19$ vs. 19	OCD (M ± SD)	Control	*t* (*p* value)
Sex [female (male)]	11 (8)	11 (8)	
Age	34.8 (11.0)	34.9 (11.8)	0.03 (.98)
Intelligence (verbal)	104 (10)	107 (12)	−1.07 (.29)
Handedness	77 (55)	67 (47)	0.65 (.52)
STAI-X1 (state)	54 (13)	49 (6)	1.61 (.12)
STAI-X2 (trait)	61 (13)	50 (6)	3.32 (.002)
Earnings in €	21.80 (7.80)	22.00 (6.40)	−0.07 (.95)
Y-BOCS (*range* 9–39)	20.7 (7.9)		
OCI-R (*range* 9–61)	24 (14)		
BDI (*range* 0–38)	17 (11)		
Medication (*N*)	3		
Comorbidity (*N*)	10		