Moving the brain: Neuroimaging motivational changes of deep brain stimulation in obsessive-compulsive disorder

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Chapter 2

Dysfunctional reward circuitry in obsessive-compulsive disorder

Martijn Figee, Matthejs Vink, Femke de Geus, Nienke Vulink, Dick Veltman, Herman Westenberg and Damiaan Denys


Obsessive-compulsive disorder (OCD) is primarily conceived as an anxiety disorder, but has features resembling addictive behavior. Patients with OCD may develop dependency upon compulsive behaviors because of the rewarding effects following reduction of obsession-induced anxiety. Reward processing is critically dependent on ventral striatal-orbitofrontal circuitry and brain imaging studies in OCD have consistently shown abnormal activation within this circuitry. This is the first functional imaging study to investigate explicitly reward circuitry in OCD.

Brain activity during reward anticipation and receipt was compared between eighteen OCD patients and nineteen healthy controls, using a monetary incentive delay task and functional magnetic resonance imaging (fMRI). Reward processing was compared between OCD patients with predominantly contamination fear and patients with predominantly high-risk assessment. OCD patients showed attenuated reward anticipation activity in the nucleus accumbens compared to healthy control subjects. Reduced activity of the nucleus accumbens was more pronounced in OCD patients with contamination fear.
than in patients with high-risk assessment. Brain activity during reward receipt was similar between patients and controls. A hint towards more dysfunctional reward processing was found in treatment-resistant OCD patients who subsequently were successfully treated with deep brain stimulation of the nucleus accumbens. OCD patients may be less able to make beneficial choices due to altered nucleus accumbens activation when anticipating rewards. This finding supports the conceptualization of OCD as a disorder of reward processing and behavioral addiction.

Introduction

Obsessive Compulsive Disorder (OCD) is a chronic and disabling disease with an estimated prevalence between 1 and 3% (Ruscio et al., 2010; Fullana et al., 2009). OCD is characterized by the presence of recurrent and anxiety provoking thoughts, images or impulses (obsessions), typically followed by repetitive ritualistic behaviors (compulsions) to relieve anxiety.

The anxiety symptoms and inadequate fear responses pathognomonic for OCD may result from inadequate dorsal prefrontal-striatal control of the amygdala (van den Heuvel et al., 2004). However, obsessive-compulsive symptoms are not always anxiety-driven, and may also be related to cognitive and behavioral inflexibility, reflected by impairments in response inhibition and attentional set-shifting (Chamberlain et al., 2005) due to dysfunctional frontal-striatal circuitry (Chamberlain et al., 2008; Page et al., 2009). Alternatively, OCD has been conceptualized as a disorder of behavioral addiction, with obsessions and compulsions being related to loss of voluntary control and a dependency on repetitious, self-defeating behavior (Holden, 2001; Denys, 2004). Compulsions could be viewed as addictive because of their rewarding effects following reduction of obsession-induced anxiety. Addictive behavior is associated with defective processing of natural rewards. Likewise, OCD patients were found to be impaired in adjusting their behavior following monetary incentives (Nielen et al., 2009). Reward processing is critically dependent on ventral striatal-orbitofrontal circuitry (Töbler et al., 2009), and resting-state imaging studies have consistently shown abnormal metabolism in striatum and orbitofrontal
cortex in OCD (Whiteside et al., 2004). Moreover, recent studies have shown that the nucleus accumbens (NAc), as part of the ventral striatum, is a successful target for deep brain stimulation in OCD treatment (Sturm et al., 2003; Denys et al., 2010; Huff et al., 2010). Studying reward processing and its neuroanatomical correlates in OCD might therefore be a fruitful approach to unravel its pathophysiology. However, there is surprisingly little research capitalizing on this idea.

In the present study, we sought to investigate the neural basis of reward system function in OCD by comparing brain activation between OCD patients and healthy controls during reward processing using a robust monetary incentive delay paradigm, which allowed modeling of both reward anticipation and outcome relative to neutral events. We employed a very rapid 3D-sequence for acquiring whole-brain functional magnetic resonance images (fMRI), thereby increasing sensitivity of our design. Prior research in healthy humans showed distinct activation patterns within the frontal-striatal network during reward anticipation versus outcome: ventral striatum activation for reward anticipation and the orbitofrontal cortex (OFC) or VMFC activation for reward outcome (Schultz et al., 2000; Knutson et al., 2001). In OCD patients, obsessive-compulsive behaviors are likely to be associated with reward circuitry hyperactivity, reflected by findings of increased OFC-striatal activity at rest and in symptom provocation studies (Menzies et al., 2008; Mataix-Cols et al., 2004), at the expense of its responsiveness to natural rewards. Therefore, we expect to find decreased OFC-striatal activity during reward processing, more specifically, decreased reward anticipatory activation in the nucleus accumbens and decreased activation of the OFC related to reward feedback. In addition, we aimed to explore brain activation patterns in two distinct OCD subdimensions. We recruited a group of OCD patients suffering from obsessive fear of contamination and washing compulsions, and a group of OCD patients with obsessive high-risk assessment and checking compulsions. Previous research suggests that OCD with predominant contamination fear symptoms may be more related to dysfunctional brain circuits for emotion processing (Mataix-Cols et al., 2004). Because of its association with limbic regions, the reward system might thus be more dysfunctional in OCD patients with contamination fear symptoms. In addition, symptom provocation studies have consistently
shown that disgust and OCD washing symptoms are related to hyperactivation of the insula (Phillips et al., 2000; Mataix-Cols et al., 2004), an area that is also involved in processing of personally rewarding stimuli (Enzi et al., 2009). Therefore, decreased reward responsiveness of the insula is expected in contamination fear OCD.

**Methods and materials**

**Subjects**
We included eighteen patients with a primary diagnosis of OCD (13 female; mean age 35) and nineteen healthy controls (13 female; mean age 34) (Table 1). All subjects were right-handed. Patients were recruited from the outpatient clinic for anxiety disorders at our university hospital. All patients consented to participate in this study and signed an informed consent form. The study was approved by the Medical Ethical Review committee of our hospital. Diagnosis of patients was confirmed by the Mini International Neuropsychiatric Interview (MINI-IV) (Sheenan et al., 1998; van Vliet et al., 2007) according to DSM-IV criteria. Symptom severity was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989 I and II). We only included patients predominantly suffering from contamination obsessions with washing and cleaning compulsions on the one hand, and patients suffering from high-risk assessment obsessions, such as fear for burglary, disasters, etc., with checking compulsions on the other hand. The Y-BOCS symptom checklist was used in addition to a psychiatric interview with an experienced psychiatrist to validate the presence of OCD subdimensions. To rate depression and anxiety severity we used Hamilton rating scales (Hamilton, 1959 and 1960): Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). Exclusion criteria were the presence of severe alcohol or substance abuse (including nicotine) and major neurological or other medical disorders. Nine patients were medication-free at the time of investigation. For the remaining patients use of various types and doses of psychotropic drugs were reported: selective serotonin reuptake inhibitors (n = 5, dose 20-60 mg), tricyclic antidepressants (n=3; dose 125-225 mg) and combined noradrenergic and serotonergic antidepressant (n=1; dose 45 mg).
Reward Task

The monetary reward task (Figure 1, see also: van Hell et al., 2010) was based on the monetary incentive delay (MID) task (Knutson et al., 2000). The task consisted of 72 trials, each lasting six seconds on average (range 3-10s). At the beginning of each trial a cue was presented for 500 ms signaling a potentially rewarding (a circle) or non-rewarding (a square) trial. Following this cue, a target was presented to which subjects had to respond. Feedback on performance was given (either a reward or no reward). Subjects were instructed to respond as fast as possible to the target (by pressing a button) irrespective of cue type. The target was displayed for a time period equal to the average response speed of the subject during training trials. Ten practice trials were presented prior to the experiment. From these practice data, the shortest reaction time to the target was used to determine the individual time limit allowed for responses to the target during the task. That is, in case of a reward cue subjects could win two euro when they responded within the time limit. Subjects were rewarded in only 50% of the reward trials, allowing for maximal reward uncertainty (Fiorillo et al., 2003). This was achieved by increasing the time limit by 200 ms in half of the rewarding trials to make sure subjects would be fast enough to win the trial. The time limit was decreased by 200 ms in the other half of the rewarding trials to make sure subjects would miss the reward. Hence, all subjects earned the same amount (36 euro).

The task was designed in such a way that the blood-oxygen-level-dependent (BOLD) signal in response to anticipation of reward (i.e. time between cue and target) could be modeled independently from that of actual reward (i.e. feedback). This enabled us to differentiate between anticipation and outcome, which reportedly induces BOLD responses in different parts of the reward network (Knutson et al., 2001). To reduce colinearity between anticipation of reward and actual reward, anticipation time and intertrial interval were varied (3-10 sec; mean 6 sec, and 0-30 sec; mean 4.2 sec, respectively). Only one level of reward was used, and no loss trials were included, to obtain maximum power within a relatively short time period.
Image Acquisition

Brain imaging data were collected on a 1.5T Philips ACS-NT scanner (Philips Medical Systems, Best, The Netherlands) with fast gradients (PT6000). The head was held in place with a strap and padding. Structural and functional images were acquired in transverse orientation from the same section of the brain. The area that was scanned ranged from roughly $Z=-20$ to $Z=+60$, tilted somewhat anterior. The primary motor cortex and primary visual cortex were not included. For functional scans a navigated 3D-PRESTO pulse sequence (van Gelderen et al., 1995) was used with the following parameters: echo time 29.23 ms; repetition time 19.23 ms, flip angle 9 degrees; matrix $40 \times 64$, 20 slices, field of view $160 \times 256 \times 80$ mm; voxel size 4 mm isotropic; scan duration 1 second per 20-slice volume. Immediately after the functional scans an additional PRESTO scan of the same volume of brain tissue was acquired with a high (30 degrees) flip angle (FA30) for the image co-registration routine. Finally, a T1-weighted structural image was acquired for anatomical registration purposes. A total of 1008 functional images were acquired for each subject.

Data preprocessing and analysis

Preprocessing and analysis of individual fMRI time series data were performed with SPM2 (Wellcome Department of Imaging Neuroscience, London, UK).
First, all functional images were realigned to the FA30 image. Next, the structural image was coregistered to the FA30 image. The structural image was then registered to the T1-weighted MNI standard brain. The normalization parameters were then applied to all functional scans. Finally, all functional scans were smoothed with an 8mm at FWHM Gaussian kernel. For each individual subject, regression-coefficients for each voxel were obtained from a general linear model regression analysis, using a factor matrix that contained factors representing event-related changes time-locked to the anticipation of neutral (36 events) and reward (36 events) trials. The duration for these events were on average six second (varying between 3 – 10 sec). The third factor modeled hemodynamic responses during responding to the target (72 events). Three additional factors described the brain response during neutral feedback (36 events), feedback of rewarded targets (18 events), and feedback of missed targets (18 events). To correct for drifts in the signal, a high-pass filter with a cut-off frequency of 0.006 Hz was applied to the data. The task was designed such that the overlap between factors of interest was minimized (variance inflation factor (VIF) of neutral anticipation = 1.24; VIF of reward anticipation = 1.21, VIF of feedback of rewarded targets: 1.60; VIF of feedback of missed targets: 1.70). Factors for all six conditions (anticipation of neutral trials, anticipation of rewarding trials, response to the target, neutral feedback, feedback of rewarded targets, and feedback of missed targets) were convolved with a canonical hemodynamic response function. Group activation maps were generated for each factor using MULTISTAT (Worseley et al., 2002). This constitutes a mixed-effects analysis. Group results were tested for significance ($p < 0.05$, corrected for multiple comparisons) resulting in a critical $t$-value of 4.5 for every voxel. We used Gaussian Random Field theory as proposed by Kiebel et al. (Klebel et al., 1999). In the patient group, additional correlation analyses were performed between BOLD responses on reward processing and severity scores on the Y-BOCS, HAM-A and HAM-D.

**Results**

**Demographic and Clinical Characteristics**

Table 1 summarizes demographic and clinical characteristics for patients and
healthy controls, and for OCD subgroups. No statistical significant differences were found between patients and controls for age and gender. The average years of education were slightly lower for patients compared to healthy controls. Mean total Y-BOCS score for the patient group was 29.6 (SD 7.3), indicating severe OCD. Two patients were diagnosed with comorbid major depressive disorder, four patients were diagnosed with additional disorders on axis 1 (social phobia, dysthymic disorder and hypochondria) and two patients were diagnosed with obsessive-compulsive personality disorder.

Seven patients had predominantly symptoms of contamination fear and eleven had high-risk assessment and checking symptoms. There was no statistically significant difference between symptom subtypes in gender, Y-BOCS, HAM-A or HAM-D scores. There were no differences between symptom subtypes in medication use ($x^2 = 0.059, p = 0.808$). The contamination fear group was significantly older than the group with high-risk assessment symptoms.
<table>
<thead>
<tr>
<th></th>
<th>OCD (N=18)</th>
<th>Controls (N=19)</th>
<th>Statistic</th>
<th>Contamination Fear</th>
<th>High-risk Assessment</th>
<th>Statistic</th>
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<td>Gender, Male/Female, No.</td>
<td>5/13</td>
<td>6/13</td>
<td>$\chi^2 = 0.064$</td>
<td>2/5</td>
<td>$\chi^2 = 0.004$</td>
<td>p = 0.800</td>
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<td>Age, mean (SD), y</td>
<td>34 (8.3)</td>
<td>32 (6.6)</td>
<td>t = 1.01</td>
<td>40.0 (7.5)</td>
<td>30.6 (7.1)</td>
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<td></td>
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<td></td>
<td>p = 0.371</td>
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<td>p = 0.016</td>
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<td>Education, mean (SD), y</td>
<td>13 (2.37)</td>
<td>14.6 (1.9)</td>
<td>t = -2.29</td>
<td>11.6 (2.4)</td>
<td>14 (1.8)</td>
<td>t = 2.35</td>
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<td></td>
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<td></td>
<td>p = 0.028</td>
<td></td>
<td>p = 0.45</td>
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<td>Illness Duration, mean (SD), y</td>
<td>19.7 (7.2)</td>
<td>18 (6.2)</td>
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<td>20.7 (7.9)</td>
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<td>p = 0.54</td>
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<td>Y-BOCS obsessions, mean (SD)</td>
<td>14.9 (3.6)</td>
<td>30.2 (11.7)</td>
<td>t = 0.37</td>
<td>28.5 (6.5)</td>
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<td>p = 0.72</td>
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<td>p = 0.72</td>
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<tr>
<td>Y-BOCS compulsions, mean (SD)</td>
<td>15.2 (3.7)</td>
<td>14.3 (7.4)</td>
<td>t = 0.48</td>
<td>14.2 (3.9)</td>
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<td>p = 0.96</td>
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<td>Y-BOCS total score, mean (SD)</td>
<td>29.1 (8.5)</td>
<td>15.8 (4.5)</td>
<td>t = 0.82</td>
<td>14.3 (3.1)</td>
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<td>HAM-A score, mean (SD)</td>
<td>17.4 (8.2)</td>
<td>17.0 (8.5)</td>
<td>t = 0.13</td>
<td>17.7 (8.7)</td>
<td></td>
<td>p = 0.90</td>
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<td>p = 0.90</td>
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<tr>
<td>HAM-D score, mean (SD)</td>
<td>16.8 (6.6)</td>
<td>17.1 (6.9)</td>
<td>t = 0.08</td>
<td>16.7 (7.6)</td>
<td></td>
<td>p = 0.94</td>
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<td></td>
<td></td>
<td></td>
<td>p = 0.94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication, Y/N, No.</td>
<td>9/18</td>
<td>4/7</td>
<td></td>
<td>5/11</td>
<td>$\chi^2 = 0.059$</td>
<td>p = 0.808</td>
</tr>
</tbody>
</table>

**Table 1**: Demographic and Clinical Characteristics of 18 OCD Patients, 19 Healthy Control Subjects and OCD subtypes.
Behavior

Reaction times in anticipation of reward trials were significantly faster than in neutral trials when no reward was expected in both patients and controls. Patients were generally slower than controls (408 versus 349 ms; $F(1,34) = 13.07, p = .001$). However, patients and controls both reacted faster in anticipation to reward compared to no reward (385 vs. 418 ms; $F(1,16) = 15.49, p < .001$) and this did not differ between the groups ($F<1$). Reaction times did not differ between OCD patients with contamination fear patients and patients with high-risk assessment symptoms (426 vs. 390 ms; $F(1,16) = 1.78, p = 0.200$). As was modeled, patients and controls all won the same amount of money (36 euro).

Neuroimaging

Neuroimaging results are presented in Table 2, Figure 1, Figure 2 and Figure 3. For each group, a whole-brain analysis was performed to identify activity during reward anticipation and receipt by contrasting activity during anticipation or receipt of reward versus no reward. Reward feedback was defined as the activation associated with successful versus neutral responses. Both healthy controls and OCD patients showed reward-related activity in the ventral striatum, putamen, thalamus, insula and several frontal areas (inferior, medial and superior frontal gyrus), indicating that the task activated reward-related frontostriatal areas. Compared with controls, OCD patients showed reduced activation of the NAc (bilateral) during anticipation of monetary gain (Figure 2). In addition, OCD patients showed less reward anticipation activation of the left insula. Reduced activation of the NAc and insula were more pronounced in OCD with contamination fears compared to high-risk assessment OCD patients. BOLD differences between patient groups remained significant after including age as a covariate. Upon receiving rewarding feedback patients and controls showed comparable activation of the NAc, OFC and other regions belonging to the reward network (Figure 3).
Table 2: Maximum t-value and Talairach coordinates of brain regions that show altered reward activity in healthy controls versus OCD patients, and in high-risk assessment OCD versus contamination fear OCD.
Figure 2: Brain activation during reward anticipation in healthy control subjects and patients with obsessive-compulsive disorder (OCD), and in patients with high-risk assessment OCD versus patients with contamination fear OCD. Whole brain group results thresholded at $p < 0.05$ corrected.

Figure 3: Brain activation during reward outcome in healthy control subjects and OCD patients, and in patients with high-risk assessment OCD versus patients with contamination fear OCD. Reward
outcome was defined as the activation associated with successful versus neutral responses. Whole brain group results thresholded at $p < 0.05$ corrected.

**Figure 4:**
Explorative overview of brain activation during Reward Anticipation > Neutral Anticipation in Healthy Control Subjects (black bars), OCD Patients with High-Risk Assessment (grey bars), and OCD Patients with Contamination Fear (white bars). The regions were defined using the contrast Healthy Control Subjects > OCD Patients and are therefore only intended to provide information concerning activation levels in the OCD subgroups on an explorative basis.

**Correlation Analyses:**
No statistically significant correlations were found between BOLD responses during reward anticipation and symptom severity ratings on the Y-BOCS, HAM-D and HAM-A in the patient group. However, post-hoc ROI analyses revealed that the largest reduction in NAc activity during reward anticipation was found in a subgroup of nine patients. These patients suffered from an extremely severe, treatment-resistant form of OCD and were subsequently treated with deep brain stimulation of the NAc. Differences between the DBS-prone patients and the normal treatment-responders did not reach statistical significance ($p = 0.122$), presumably because of the small sample-size.

**Discussion**
This functional imaging study is unique in examining both reward anticipation
and receipt in a sample of OCD patients. By adapting a monetary incentive delay task we were able to focus on these different aspects of reward processing separately. Behaviorally, all subjects reacted significantly faster when a reward was expected, but OCD patients reacted significantly slower than matched healthy controls in anticipation of rewards. Compared to healthy controls, OCD patients showed greatly attenuated reward anticipation activity in the bilateral NAc. Reduced brain activity of the NAc was more pronounced in OCD patients with contamination fear, compared to patients with high-risk assessment symptoms. The difference between both patient groups in the absence of differences in performance speed indicates that blunted NAc activity is primarily accounted for by defective reward anticipation and not by motor impairments. Reward outcome was related to activation in various regions of the brain reward network, including the NAc and the OFC, but this did not differ between patients and controls.

Reward processing in OCD has only been sparsely investigated previously. Nevertheless, Remijnse et al. (2006) found in a reversal-learning task reduced OFC activity during monetary reward outcome. Our study confirmed an association between monetary reward feedback and OFC activity, but failed to detect a difference between patients and controls. It could be speculated that OCD patients in our study had primarily difficulties in estimating the value of a potential rewarding situation due to reduced NAc responsiveness, whereas subsequent appreciation and evaluation of rewards in the OFC was intact. Several other prefrontal areas were activated especially during reward feedback. Studies by Tobler et al. (2009), among others, have indicated that prefrontal areas subserve the individual evaluation of rewards, more specifically the integration of expected value and risk. OCD patients who suffered predominantly from contamination fear showed reduced ventral striatal activation when compared to patients with predominantly high-risk assessment and checking symptoms. This is in agreement with Rauch et al. (2007), who reported an inverse relationship between striatal activation and washing but not checking symptoms during implicit learning. Also, a study by Mataix-Cols et al. (2004) suggests that OCD with contamination fear may be characterized by dysfunctional brain circuits involved in emotion processing, whereas OCD with checking symptoms might be associated with regions that are important
for motor and attentional functions. The reward network, which is linked to limbic regions for emotion processing, may thus be more compromised in OCD with predominant contamination fear symptoms. Furthermore, patients with contamination fear showed reduced reward anticipation activity of the left insula, a region that is implicated in emotion perception and processing of personally rewarding stimuli (Enzi et al., 2009), but also in the integration of gustatory and olfactory inputs. Previous fMRI studies found increased activation of the left insula in OCD patients when viewing aversive pictures (Schienle et al., 2005) and in OCD patients with contamination fear when viewing pictures depicting washing or contamination (Phillips et al., 2000). The insula may thus be excessively activated during obsessive-compulsive symptoms, particularly in association to disgust-related symptoms, compromising its recruitment for normal reward processing.

The NAc, as part of the ventral striatum, has been implicated as a brain region that is critically involved in reward processing. In healthy humans, the ventral striatum is activated particularly in anticipation of a reward, and in proportion with its expected value (Knutson et al., 2001). OCD has been associated with structural and functional abnormalities of the striatum (reviewed in: Menzies et al., 2008). Within this circuit the NAc has been successfully used as a target for deep brain stimulation in the treatment of severely ill therapy-refractory OCD patients (Denys et al., 2010; Huff et al., 2010). Interestingly, in the present study we found a hint towards more dysfunctional reward processing in a subgroup of severely ill, treatment-resistant OCD patients who subsequently were successfully treated with deep brain stimulation of the NAc. Together, our findings suggest an important role for the NAc in the pathophysiology of OCD. OCD patients may be less able to make beneficial choices due to defective NAc activation when anticipating rewards.

Our results match up remarkably with the findings of functional imaging studies in addiction disorders. Blunted reactivity of the ventral striatum during anticipation of monetary gain was found in detoxified alcoholics (Wrase et al., 2007), nicotine smokers (Martin-Soelch et al., 2007; Buhler et al., 2009; van Hell et al., 2010) and cannabis smokers (Van Hell et al., 2010). Drug-related stimuli, however, increase activity of the reward circuitry in drug addicts (Diekhof et al., 2008). Likewise, blunted responsiveness of the reward circuitry in our study
is paralleled by increased activity in response to OCD-provoking stimuli in previous studies (reviewed by Menzies et al., 2008). Of interest, a recent case study showed efficacy of deep brain stimulation in the NAc in a patient with OCD, severe nicotine addiction and eating problems (chapter 1; Mantione et al., 2010). The NAc is important for focusing on potential alerting and rewarding environmental stimuli that can be used for modulation of behavior by reinforcement learning (Fiorillo et al., 2003). Therefore, the NAc may be less responsive when recruited during conventional reward processing due to its bias toward drugs of abuse in addiction, as well as toward obsessions and compulsions in OCD, supporting the conceptualization of OCD as a disorder of behavioral addiction (Holden et al., 2001; Denys, 2004). Although population studies show relatively little co-morbidity between OCD and substance abuse, dysfunctional brain reward circuitry underlying both disorders may explain some shared phenomena, such as a dependency on repetitious, self-defeating behavior that becomes more difficult to control over time. Since OCD patients are already fully engaged in reinforcing compulsive behaviors, they may be less prone to develop substance abuse.

The present study has a number of potential limitations. Nine of our eighteen OCD subjects were using medication. Post hoc, we tested for the effects of medication in the OCD group by comparing the activation between medicated and medication-free patients using a whole-brain two-sample t-test, which did not show any significant differences in our regions of interest. Even upon lowering the threshold to p<0.001, not corrected for multiple comparisons, no activation related to medication was found. We take this result to indicate that medication use is not likely to explain the significant differences observed between healthy controls and OCD patients. Also, whereas the nine medicated subjects used different types of drugs in various, often subtherapeutic doses, medication use was similar in the high risk-assessment and contamination fear groups.

Attenuated reward anticipation has been demonstrated in depression (Pizzagalli et al., 2009). Although our mean HAM-D score of 16.8 ± 6.6 is suggestive for minor to moderate depressive symptoms, only two patients met DSM-IV criteria for a comorbid diagnosis of depressive disorder. HAM-D scores were nevertheless measured in all patients as part of our routine screen-
ing. We therefore believe these scores reflect depressive features overlapping with or secondary to OCD. Moreover, depression scores were not related to BOLD changes and group differences remained significant even when excluding the patients with a diagnosis of depressive disorder.

Further, we included more females than males in this study, whereas recent research has indicated stronger striatal activation in healthy men than in women if money was to be expected (Spreckelmeyer et al., 2009). However, gender ratios did not differ between patients and healthy controls. Patients were slightly less educated than healthy controls (mean difference 1.6 years of education), most likely due to the illness process. Finally, within the patient group, the contamination fear group was significantly older than the group with high-risk assessment symptoms, however, NAc activation remained significantly smaller in the contamination fear group when age was included as a covariate.

The study also has several notable strengths. The patient group was highly relevant for studying OCD pathophysiology since mean Y-BOCS scores was of high severity (29.1, SD 8.5). We employed a robust reward paradigm coupled with a very rapid image acquisition method, revealing activation differences that survived whole-brain correction for multiple comparisons, both between groups and within our OCD group. Also, our main difference in BOLD activation was found in a focus that is anatomically comparable to the activation focus that was found by Knutson et al. (2000) in healthy subjects anticipating monetary gain.

In conclusion, the present study suggests that OCD is associated with reduced NAc activity during reward anticipation, especially in contamination fear. This finding is consistent with a proposed role for the NAc, as part of the frontal-striatal network, in the pathogenesis of OCD, and supports its conceptualization as a disorder of reward processing and behavioral addiction. Reward processing and its neural underpinnings in compulsivity may be important avenues for future research. NAc activity during reward anticipation in OCD patients might be explored as a potential marker for treatment response. Also, studying changes in brain activity that are related to deep brain stimulation of the NAc in OCD patients might further elucidate its role in the disease.