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

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Deep brain stimulation (DBS) of a specific target may cause fast and remarkable improvement in a variety of motor and cognitive-emotional processes (Kringelbach et al, 2011), suggesting that local stimulation modulates neural function of broader networks. Obsessive-compulsive disorder (OCD) has become a
successful indication for DBS (chapter 10) (Denys et al., 2010). Core features of OCD are compulsions and obsessions that impair goal-directed motivational behavior. These core features are associated with dysfunction of the nucleus accumbens (NAc) (chapter 2, Fige et al., 2011) and its connectivity with the frontal cortex (Harrison et al., 2009; Menzies et al., 2008). We hypothesized that NAc DBS would improve OCD by normalizing NAc-frontal network function. We investigated NAc-frontal network modulation of DBS in 16 OCD patients using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). The stimulation was targeted at the NAc (NAc-DBS, see Methods) and patients showed stable clinical improvements on active DBS treatment (DBS ON) for at least one year. Turning the stimulators off (DBS OFF) for one week resulted in an increase of 50% in obsessive-compulsive symptoms, of 80% increase in anxiety and of 83% increase in depressive symptoms (Supplementary Table 1). We used three experimental paradigms that have previously demonstrated clinically relevant abnormalities in OCD patients and probe aspects of brain function that we expected to change following NAc DBS.

To examine brain activity in the immediate surroundings of the NAc target (Fig. 1a), we probed NAc activity during fMRI scanning using a reward anticipation task (Methods, Supplementary Fig. 1) that requires goal-directed behavior, measures NAc responsiveness and has previously revealed blunted NAc activity in OCD patients, especially patients that were candidates for DBS3. Nine OCD patients and 13 matched healthy controls underwent two scanning session with one week in between. NAc activity changed significantly ($P = 0.031$) between DBS OFF and ON in patients compared to repeated measures in controls (Fig. 1b, Supplementary Table 3 and Supplementary Fig. 5). During DBS OFF the NAc activity in patients was lower compared to controls. In contrast, the patients with DBS ON had similar NAc activity as the controls. These results suggest that DBS normalizes NAc activity.
Figure 1: DBS normalizes brain activity around the target area (NAc).
(a) In red: region-of-interest (ROI) for analyzing blood-oxygenation-level–dependent (BOLD) responses. (b) DBS-induced changes in the right NAc (reward anticipation–no-reward anticipation (mean ± s.e.m.); group × scan session interaction: $F = 4.47, P = 0.031$). NAc activity increased from DBS OFF to ON ($t = 2.79, P_{\text{cor}} = 0.050$), and was lower in patients compared to controls during DBS OFF (*; $t = -3.165, P_{\text{cor}} = 0.010$).

Next, we investigated whether NAc-DBS also affected frontostriatal network connectivity. We performed a resting-state experiment that enabled us to probe stimulatory effects on the NAc-frontal network (Supplementary Fig. 3), as previous studies have demonstrated excessive NAc-frontal coupling in OCD (Harrison et al., 2009). Resting-state fMRI scans revealed that DBS reduced the connectivity between the NAc and the lateral prefrontal cortex (lPFC) and medial prefrontal cortex (mPFC) (Fig. 2a, Supplementary Table 4, Supplementary Fig. 4). Follow-up testing showed that connectivity was stronger in patients ($N = 11$) than controls ($N = 11$) during DBS OFF but not during DBS ON (Supplementary Table 5 and Supplementary Fig. 5). Notably, we found a strong correlation ($r = 0.72$) between DBS-induced changes in connectivity and changes in obsessions and compulsions (Fig. 2b), suggesting that DBS reduces OCD symptoms by decreasing excessive frontostriatal connectivity.
**Fig 2. DBS normalizes excessive frontostriatal connectivity.**

(a) Left: the left NAc (red) and right NAc (blue) seed regions. Right: The group×session interaction reveals DBS-related connectivity changes between the left NAc and mPFC ($Z = 4.29$, $P_{FWE} = 0.002$) and between the right NAc and mPFC ($Z = 4.47$, $P_{FWE} = 0.050$) in red and between the left NAc and mPFC ($Z = 4.53$, $P_{FWE} = 0.001$) in blue; purple indicates overlap.

(b) Graph illustrating the correlation ($r = 0.72, P = 0.013$) between changes in OCD symptoms (YBOCS: Yale-Brown Obsessive-Compulsive Scale) and changes in functional connectivity between the left NAc and lPFC.

Previous studies have shown low-frequency EEG oscillations (2-5 Hz) over the frontal cortex to be associated with goal-directed behavior and severity of obsessions and compulsions (Pogarell *et al.*, 2006; Knyazev, 2012). Therefore, we examined whether NAc stimulation modulated low-frequency oscillations over the frontal cortex. We recorded EEG (see Methods) while patients (N = 13) rated pictures with OCD-related and unrelated content (**Fig. 3a**). We found that DBS attenuated the increase in low-frequency activity elicited by symptom-provoking stimuli (**Fig. 3b-c and Supplementary Fig. 5**).

These results suggest that DBS tapered the frontal brain response evoked by symptom-provoking events.
Fig. 3. DBS modulates frontal low-frequency EEG oscillations in response to disease-related symptom-provoking stimuli. (a) Patients rated the valence and arousal and whether the stimulus induced any symptoms (Supplementary Material). (b) Time/frequency representation showing the differences in frequency power over time elicited by the symptom-provoking and non-symptom-provoking stimuli (at t = 0). The black squares show the time/frequency analysis window selected for statistical testing based on the grand-average. (c) Average power values in the analysis window. DBS attenuated the increased low-frequency power elicited by symptom-provoking stimuli (session × condition, F(1,12) = 10.65, P = 0.007). The response to symptom-provoking stimuli was larger than for non-symptom-provoking stimuli when DBS was OFF (T(1,12) = 3.84, P(eco) = 0.004) but not when DBS was ON.

The modulation of NAc activity and frontostriatal connectivity by DBS suggests that it is able to restore disease related brain networks to a healthy state. Although no comparable study exists that examined network changes of DBS with fMRI and EEG in fully implanted patients, previous findings of local and distant DBS effects (chapter 4) (van Laere et al., 2006; Bewernick et al., 2010; McIntyre and Hahn, 2010) have led to the hypothesis that DBS resets the neural output of the stimulated nucleus by overriding disruptive oscillations between brain network nodes (McIntyre and Hahn, 2010). Our study fits with
this hypothesis, and goes further to demonstrate that DBS normalizes NAc activity and restores intrinsic frontostriatal network dynamics. This restoration in turn correlates with symptom improvement. Inferring from fiber-tracking studies, we speculate that DBS normalizes NAc-frontal synchronization through antidromic stimulation of the ventral internal capsule that connects the mPFC with the NAc or alternatively indirectly by stimulation of corticothalamic pathways (Lehman et al., 2011; Haber et al., 2006).

Patients with OCD are obsessed with specific pathogenic stimuli and feel compelled to act in a particular way at the cost of healthy goal-directed behavior. The neural correlates of this imbalance may be found in OCD-symptom related frontostriatal hyperactivity (Menzies et al., 2008) along with blunted NAc processing (chapter 2) (Figee et al, 2013). NAc targeted DBS induced an average symptomatic change of 50% that was strongly correlated to frontostriatal network changes. Our results suggest that DBS interrupts a pathological frontostriatal loop allowing a shift from excessive processing of disease-related towards behaviorally relevant stimuli and restoration of goal-directed behavior. This process may explain how stimulation of a relatively small target area can lead to rapid, broad and clinically relevant symptom improvements.

Methods

Participants.
Sixteen OCD patients (27 to 59 years) and 13 healthy controls (25 to 56 years) participated in the experiments after written informed consent was obtained. All experimental procedures were approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam. Symptom severity was assessed using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989 I and II), the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960), and the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959). Healthy control subjects were only included if they were free of psychoactive drugs and mental disorders according to the Mini International Neuropsychiatric Inventory (MINI; Sheenan et al., 1998; van Vliet et al., 2007). Patients and controls were matched for age, gender and years of education.
Demographics of the study group and clinical details of patients are summarized in Supplementary table 1.

Participants were excluded from the fMRI analyses: (1) when no second scan was available (3 patients and 1 control for reward experiment 2 patients for resting state); (2) when movement during scanning was > 4 mm (1 patient for reward experiment 2 patients and 2 controls for resting state); (3) one patient was excluded from both fMRI experiments because of deviating electrode placement disturbing the signal in the NAc region of interest (4) when participants executed less than 50% of the task trials of the reward experiment (3 patients). Two patients were excluded from the EEG experiment because they had incomplete datasets, and one due to a lack of pictures rated as symptom provoking.

DBS settings.
All patients had electrode implantation in the same target area (see Denys et al., 2010). We included only patients that had completed the optimization phase of one to two years during which they were evaluated every 2 weeks for severity of symptoms and optimal stimulation parameters. All 16 patients received monopolar stimulation on the two dorsal contact points, implying that the most effective stimulation area was located at the border of the NAc core and anterior limb of the internal capsule.

fMRI data acquisition.
fMRI data were collected on a 1.5T Siemens Avanto. To minimize exposure of the DBS device to the pulsed radio-frequency field, we scanned all subjects using a transmit/receive (Tx/Rx CP) Head Coil, turned off the DBS system two minutes before patients entered the scanner, and programmed it at 0V in bipolar mode. Specific absorption rate (SAR) levels were limited to 0.1 W/kg. For functional scans, 2D-EPI (echo planar imaging) was used (TR = 2000ms; TE = 30ms; FA = 90°; matrix 64×64; 25 slices; FOV = 256×256mm; slice thickness = 4mm; slice gap = 0.4mm; reward experiment = 370 volumes; resting-state experiment = 80 volumes), and the first 10 volumes were discarded. A T1-weighted structural image was acquired for anatomical registration purposes.
Reward task.
The task was based on the monetary incentive delay task (chapter 2) (Supplementary Fig. 1) and involved responding to a target to earn or prevent losing money. One hundred eight trials, each lasting 3–7s, were presented during fMRI. Each trial started with a cue predicting rewarding, neutral or loss outcomes, followed by presentation of a target to which subjects had to respond and ending with feedback on performance. Cues had 3 levels of reward or loss (Supplementary Fig. 1) to enhance reward uncertainty and motivation, but we analyzed responses to all levels together to optimize power. The time to respond was limited by adjusting target presentation, based on individual reaction times during training immediately prior to the experiment. This assured that all subjects performed almost equally (Supplementary Table. 2) and were rewarded in 67% of the reward trials, and could avoid loss in 67% of the loss trials.

fMRI data analysis.
Because the NAc is mainly implicated in reward anticipation (chapter 2) (Knutson et al., 2001; Figue et al, 2011), we focused on BOLD differences between the anticipation of rewarding and neutral outcomes. Preprocessing and analysis of individual BOLD time series were performed using SPM5 as in Fige et al, 2011 (chapter 2). Voxel-wise event-related statistics contained the following conditions: reward anticipation (time between reward cue and target, 36 events), no-reward anticipation (time between neutral cue and target, 36 events) and target presentation. Data were high-pass filtered at .006 Hz. Exploratory whole-brain analysis confirmed that reward anticipation specifically activated frontostriatal areas (NAc, caudate, putamen, thalamus, insula, and several frontal areas) across all subjects. A region of interest (ROI) analysis was performed to test for effects of DBS (DBS ON vs. DBS OFF) on NAc responses, using the contrasts reward anticipation vs. no-reward (neutral) anticipation. We chose this ROI because it was closest to the stimulated region. We furthermore expected to find the largest effects in this region because of its role in goal-directed motivational behavior and our previous findings of dysfunctional anticipatory reward activity of this region in OCD patients that had not received DBS treatment yet (chapter 2; Figue et al, 2011). We defined
the NAc ROI on the basis of the AAL atlas and as part of the caudate nucleus below $Z=0\text{mm}$ (MNI coordinates=$[\pm 10, 14, -8]$), **Fig. 1a** (Tzourio-Mazoyer et al., 2002). NAc ROI data were used for correlation analysis between DBS effects and clinical measures (severity scores on Y-BOCS, HAM-A, HAM-D). Additional explorative whole-brain group analyses were performed to test for potential effects of DBS in the NAc on brain regions outside the ROI ($t > 3$, **Supplementary Fig. 2**). Although our focus was on NAc BOLD differences between the reward and neutral anticipation contrasts, we performed exploratory analyses comparing NAc BOLD responses during neutral vs. loss anticipation and monetary feedback, which yielded no significant DBS related changes during anticipation of losses (group x scan interaction $P = 0.118$ (rNAc) and $P = 0.106$ (lNAc)), during reward feedback ($P = 0.150$ and 0.115) or during loss feedback ($P = 0.901$ and 0.321).

**Resting-state data analysis**

Data analysis was performed using SPM8 and REST toolbox (http://resting-fmri.sourceforge.net). Images were realigned, co-registered with the T1, normalized to the MNI template, resampled at $4\times4\times4\text{ mm}^3$, spatially smoothed (8mm at FWHM), linearly detrended and band-pass filtered $(0.01\text{Hz} < f < 0.08\text{Hz})$. In line with Di Martino et al. (2008), we defined spherical seed ROIs (radius = 4mm) for the NAc centered at $[\pm 9, 9, -8]$ (**Fig. 2a**). The ROIs were modified using the anatomical scan of each subject to exclude voxels in the ventricle or with signal dropout around DBS lead using MRIcron (http://www.cabiatl.com/mricro/). We correlated the seed reference with the whole brain, correcting for white matter, CSF, global signal fluctuations and motion. The correlation coefficients were transformed to Z-scores resulting in spatial maps. The individual Z-score maps were entered into a factorial ANOVA with the factors group (patient versus control) and scan session (1 versus 2). The ROI was the prefrontal cortex, which was anatomically defined using the WFU Pickatlas. Statistical tests were family wise error (FWE) rate corrected for multiple comparisons across the entire brain or the target ROI ($P < 0.05$) on the cluster level using a height threshold of $P < 0.001$. Significant group x scan interactions were followed by simple effects testing. We correlated the functional connectivity strength difference in the peak voxel from the within-patient analysis in the IPFC with the difference in...
clinical scores (HAM-D, HAM-A and Y-BOCS). To avoid dependency between the definition of the IPFC ROI and symptom differences, the peak voxel was defined for each subject separately using a leave-one-out procedure.

**EEG Symptom-provocation Paradigm**

We recorded EEG and EOG (electro-oculogram) at 512Hz using 64 shielded Ag/AgCl electrodes (Advanced Neuro Technology B.V., Enschede, the Netherlands) following the international ‘10/10’ system. We used a task designed to investigate symptom-like brain activity. Patients were exposed for 2 seconds to a set of 200 pictures, preselected to include 50 OCD, 50 neutral, 50 negative and 50 positive pictures. The neutral, positive and negative pictures were obtained from the IAPS picture set (Lang et al., 2008) and the OCD pictures were obtained from the Internet. Patients (N = 13) rated arousal, valence and the presence of symptoms and if the picture was symptom-provoking or non-symptom-provoking. We matched the valence and arousal ratings between self-rated symptomatic and non-symptomatic pictures in order to isolate the symptomatic component.

**EEG data analysis**

Data were analyzed using EEGLab 9.4.6 (Delorme et al., 2011) and Fieldtrip (Oostenveld et al., 2011). The data were band-pass filtered between 0.5 and 40 Hz to exclude line noise, muscle- and DBS artifacts from the data. The data were subsequently epoched into 3-second windows around the stimulus ([–1 2]) and the epochs were checked for large artifacts. We then used independent component analysis (ICA), to remove eye-blinks and other residual noise-sources from the data. The epochs were again checked and were considered artifact free.

Trials were matched using an iterative procedure on the subject level that matched the number of symptom-provoking and non-symptom provoking stimuli and using paired-samples t-test checked for differences in valence and arousal between categories. The procedure was repeated until the t-tests were not significant or 10.000 iterations were performed. We obtained Time Frequency Representations of power (TFR) by convolving a hanning-window with an adaptive time-window of three cycles over the data. The TFRs were
Supplementary Figure 1: the monetary incentive delay task. Above, three different cues are depicted, predicting monetary rewards (circle), no rewards (triangle) or monetary losses (square). The cues had 3 levels of reward or loss: € 0.50 (1 horizontal line), € 1.00 (2 horizontal lines), or € 2.00 (3 horizontal lines). In the example, a blue circle (cue) is presented with 1 horizontal line for 500 milliseconds signaling a rewarding outcome of € 0.50. After a variable delay of 1-3 sec, an orange acclamation sign (target) is presented for a variable time (depending on the individual reaction times on training trials) to which subjects have to respond in time. At the end of each trial, feedback of the amount won during the current trial and the total amount are presented.
## Supplementary Table 1: demographics of the study sample and clinical details

OCD: Obsessive-Compulsive Disorder; YBOCS: Yale-Brown Obsessive-Compulsive Scale; HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety.

1 independent sample t-test. 2 Chi-square test. 3 Paired t-test
Patients | DBS OFF | DBS ON | P-value¹ | P-value² | scan 2 | scan 1 | P-value¹ | P-value² | P-value³
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
R. NAc (SEM) | -0.60 (0.29) | 0.06 (0.27) | 0.025 (0.20) | 0.25 (0.23) | 0.616 | 1 | 0.031
L. NAc (SEM) | -0.36 (0.30) | 0.10 (0.31) | 0.195 (0.16) | 0.390 (0.19) | 0.13 | 0.901 | 1 | 0.372

Supplementary Table 2: NAc response over the two scanning sessions.
Mean percentage of right and left NAc BOLD signal change (± SEM) during reward anticipation in 9 patients and 13 controls for the two scanning sessions. P¹ value is for difference between the two scanning sessions (paired t-test). P² value is after Bonferroni correction. P³ value is for group x scanning session interaction. Abbreviations: R: right; L: left; NAc: Nucleus Accumbens; SEM: standard error of mean.

Supplementary Figure 2: Changes for each individual patient in DBS OFF and DBS ON. In red: mean of all patients with standard error bars. (a) Mean percentage of right NAc BOLD signal change (regression coefficients) during reward anticipation. (b) Functional connectivity change between left NAc and right lateral PFC. (c) Frontal low-frequency EEG power in response to symptom-provoking stimuli.

Supplementary Table 3: Frontal clusters that showed significant interaction effect (group x scan) in connectivity strength with NAc seed. Abbreviations: BA Brodmann area; IPFC lateral prefrontal cortex; mPFC medial prefrontal cortex; P is cluster level P value, family wise error (FWE) corrected. Z is for voxel level Z-score.
Supplementary Figure 3. Functional connectivity maps of NAc seed across all subjects. Functional connectivity map of left NAc seed is shown in red while map of right NAc seed is shown in blue, overlap in purple. The connectivity maps of each NAc seed ($P_{FWEcorrected} < 0.05$ cluster level) were combined between groups. The NAc seeds showed the strongest positive coupling around the seed region and the contralateral homologous region. Furthermore, positive coupling was found with the orbitofrontal cortex, the anterior cingulate cortex, amygdala and the parahippocampal gyrus. The functional connectivity of the left NAc seed extended somewhat further than the right NAc and included the posterior cingulate cortex and precuneus and the middle temporal lobe extending to the inferior temporal lobe.

Supplementary Table 4. Additional differences in frontostriatal connectivity strength
between patients and controls, and within patients between DBS OFF and ON. 
Abbreviations: BA Brodmann area; DBS deep brain stimulation; lPFC lateral prefrontal cortex; 
mPFC medial prefrontal cortex; sPFG superior prefrontal gyrus; P1 is cluster level P value, family 
wise error (FWE) corrected. P2 value is after additional Bonferroni correction. Z is for voxel level 
Z-score.

Supplementary Figure 4. Illustration that shows a strong overlap in the location (lateral PFC) of 
functional connectivity change with the left NAc in the three tests of experiment 2: Interaction 
effect (group x session) in green, within patient group effect in yellow, between group effect 
(patients DBS OFF vs controls) in violet.

<table>
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<th>Patients</th>
<th>Controls</th>
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<td>Scan 2</td>
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<td>Earning, mean, euro (SD)</td>
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<td>11.3 (3.9)</td>
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<td>Reaction time reward trials, mean, ms (SD)</td>
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<td>291 (70)</td>
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<td>Reaction time neutral trials, mean, ms (SD)</td>
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<td>345 (55)</td>
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Supplementary Table 5: Performance reward experiment. Both groups responded faster when
they expected to win money as compared to neutral outcomes (mean reaction time 279 sec. vs. 324 sec., $P < 0.001$), indicating enhanced motivation for rewards. Patients and controls responded significantly faster during the second scanning session on reward trials ($P = 0.001$), and to a lesser extent on neutral trials ($P = 0.098$), which likely reflects learning effects for both groups.

1. Between groups. 2. Between scanning sessions. 3. Group x scanning session.

Supplementary Figure 5: voxel-wise analysis in 9 patients and 13 controls. Group x session interaction during reward anticipation in the nucleus accumbens at $p < 0.005$ uncorrected.