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Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder

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Little is known about the underlying neural mechanism of deep brain stimulation (DBS). We found that DBS targeted at the nucleus accumbens (NAc) normalized NAc activity, reduced excessive connectivity between the NAc and prefrontal cortex, and decreased frontal low-frequency oscillations during symptom provocation in patients with obsessive-compulsive disorder. Our findings suggest that DBS is able to reduce maladaptive activity and connectivity of the stimulated region.

DBS of a specific target can cause fast and marked improvement in a variety of motor and cognitive-emotional processes[1], suggesting that local stimulation modulates neural function of broader networks. DBS has recently become an effective treatment strategy for obsessive-compulsive disorder (OCD). Compulsions and obsessions that impair goal-directed motivational behavior are core features of OCD. These core features are associated with dysfunction of the NAc and its connectivity with the frontal cortex[3–5]. We hypothesized that NAc DBS would decrease obsessive-compulsive symptoms 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 Online Methods), and patients showed stable clinical improvements on active DBS treatment (DBS ON) for at least 1 year. Turning the stimulators off (DBS OFF) for 1 week resulted in a 50% increase in obsessive-compulsive symptoms, an 80% increase in anxiety symptoms and an 83% increase in depressive symptoms (**Supplementary Table 1**). We used three methods that have been used to show clinically relevant abnormalities in OCD patients and probe aspects of brain function that we expected to change after NAc DBS.

We probed NAc activity during fMRI scanning (**Fig. 1a**) using a reward anticipation task (**Supplementary Fig. 1** and Online Methods) that requires goal-directed behavior, measures NAc responsiveness and has previously revealed blunted NAc activity in OCD patients, particularly those who were candidates for DBS[3]. Nine OCD patients and 13 matched healthy controls underwent two scanning sessions, separated by 1 week. NAc activity changed significantly between DBS OFF and ON in patients compared with repeated measures in controls (P = 0.031; **Fig. 1b**, **Supplementary Table 2** and **Supplementary Fig. 2**). During DBS OFF, the NAc activity in patients was lower than in controls, whereas the patients with DBS ON had similar NAc activity to the controls. These results suggest that DBS normalizes NAc activity.

We then investigated whether NAc DBS also affects 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 found excessive NAc-frontal coupling in OCD[4]. 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 3** and **Supplementary Fig. 4**). Follow-up testing showed that connectivity was stronger in OCD patients (N = 11) than in controls (N = 11) during DBS OFF, but not during DBS ON (**Supplementary Table 4** and **Supplementary Fig. 5**). Notably, we found a strong correlation (r = 0.72) between DBS-induced changes

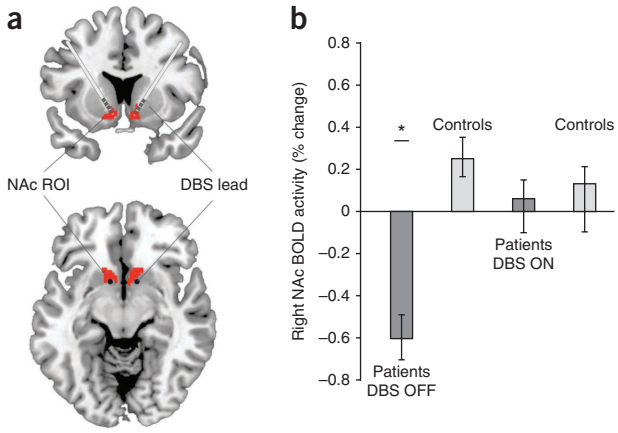

Figure 1 DBS normalizes brain activity in the NAc. (**a**) Region of interest (ROI; red) for blood oxygenation level–dependent (BOLD) responses. (**b**) DBS-induced changes in the right NAc (reward anticipation – no-reward anticipation (mean ± s.e.m.); group × scan session interaction, F = 4.47, P = 0.031). NAc activity increased from DBS OFF to DBS ON (t = 2.79, $P_{corrected}$ = 0.050) and was lower in patients than in controls during DBS OFF (t = –3.165, $^*P_{corrected}$ = 0.010).

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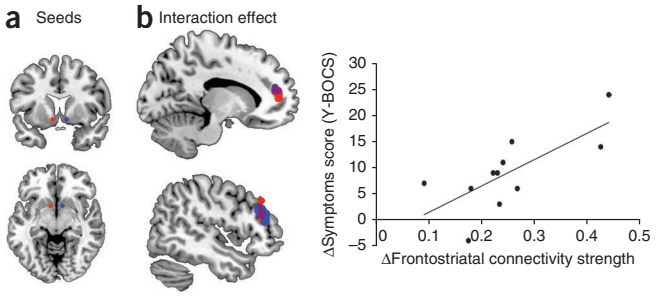

Figure 2 DBS normalizes excessive frontostriatal connectivity. (**a**) Left, the left NAc (red) and right NAc (blue) seed regions. Right, the group × session interaction revealed DBS-related connectivity changes between the left NAc and mPFC ($Z = 4.29$, $P_{FWE} = 0.002$; FWE, family wise error) and lPFC ($Z = 3.85$, $P_{FWE} = 0.017$) in red and between the right NAc and mPFC ($Z = 4.47$, $P_{FWE} = 0.050$) and lPFC ($Z = 4.53$, $P_{FWE} = 0.001$) in blue. Purple indicates overlap. (**b**) Graph illustrating the correlation ($r = 0.72$, $P = 0.013$) between changes in OCD symptoms (Y-BOCS, Yale-Brown Obsessive-Compulsive Scale) and changes in functional connectivity between the left NAc and lPFC.

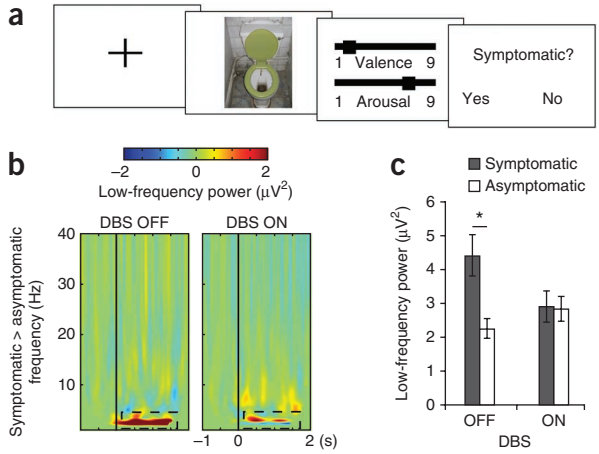

Figure 3 DBS modulates frontal low-frequency EEG oscillations in response to disease-related symptom-provoking stimuli. (**a**) Patients rated the valence and arousal and whether the stimulus induced any symptoms (Online Methods). (**b**) Time-frequency representation showing the differences in frequency power over time elicited by the symptom-provoking and non–symptom-provoking stimuli (at $t = 0$). The black dashed rectangles show the time-frequency analysis window selected for statistical testing on the basis of the grand average. (**c**) Average power values in the analysis window (mean ± s.e.m.). 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 that for non–symptom-provoking stimuli when DBS was OFF ($T_{1,12} = 3.84$, $P_{corrected} = 0.004$), but not when DBS was ON.

in connectivity and changes in obsessions and compulsions (**Fig. 2b**), suggesting that DBS reduces OCD symptoms by decreasing excessive frontostriatal connectivity.

Low-frequency EEG oscillations (2–5 Hz) over the frontal cortex are associated with goal-directed behavior and the severity of obsessions and compulsions[6,7]. Thus, we examined whether NAc stimulation modulates low-frequency oscillations over the frontal cortex. We recorded EEG (Online Methods) while patients ($N = 13$) rated pictures with OCD-related and OCD-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. 2**). These results suggest that DBS tapered the frontal brain response evoked by symptom-provoking events.

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[8–10] have led to the hypothesis that DBS resets the neural output of the stimulated nucleus by overriding disruptive oscillations between brain network nodes[2,10]. Our findings fit with this hypothesis and go further, demonstrating 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 indirectly by stimulation of corticothalamic pathways[11,12].

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[5] along with blunted NAc processing[3]. 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 toward 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

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

D.D. and M.F. conceived the study. M.F., R.S., C.-E.V.-A., A.N. and M.V. designed experiments. M.F., J.L. and B.d.K. conducted functional neuroimaging. M.F., J.L., M.V. and L.D. carried out neuroimaging data processing and analysis. R.S., N.L. and C.-E.V.-A. conducted EEG recording, data processing and analysis. N.V., P.d.K., M.M. and P.O. acquired behavioral data. P.v.d.M. and P.R.S. performed neurosurgery and edited the manuscript. M.F., J.L. and R.S. prepared the manuscript. D.D., W.v.d.B., G.v.W., A.N., P.v.d.M., P.R.S. and A.M. edited the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

Participants. We asked 16 OCD patients (27–59 years) and 13 healthy controls (25–56 years) to participate 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 Y-BOCS[13], the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A)[14]. Healthy control subjects were only included if they were free of psychoactive drugs and mental disorders according to the Mini International Neuropsychiatric Inventory (MINI)[15]. 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 when no second scan was available (three patients and one control for reward experiment two patients for resting state), when movement during scanning was >4 mm (one patient for reward experiment two patients and two controls for resting state), and when participants executed less than 50% of the task trials of the reward experiment (three patients). One patient was excluded from both fMRI experiments because of deviating electrode placement disturbing the signal in the NAc region of interest. Two patients were excluded from the EEG experiment because they had incomplete data sets, and one because of a lack of pictures rated as symptom provoking.

DBS settings. All patients had electrode implantation in the same target area (see ref. 2). We included only patients that had completed the optimization phase of 1–2 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 2 min before patients entered the scanner, and programmed it at 0 V in bipolar mode. Specific absorption rate levels were limited to 0.1 W kg^{-1}. For functional scans, two-dimensional echo-planar imaging was used (repetition time = 2,000 ms, echo time = 30 ms, field angle = 90°, matrix = 64 × 64, 25 slices, field of view = 230 × 230 mm, slice thickness = 4 mm, slice gap = 0.4 mm, reward experiment = 370 volumes, resting-state experiment = 180 volumes), and the first ten volumes were discarded. A T1-weighted structural image was acquired for anatomical registration purposes.

Reward task. The task that we used was based on the monetary incentive delay task[3] (**Supplementary Fig. 1**) and involved responding to a target to earn or to prevent the loss of money. We presented 108 trials, each lasting 3–7 s, 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 three 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 on the basis of individual reaction times during training immediately before the experiment. This assured that all subjects performed almost equally (**Supplementary Table 5**), were rewarded in 67% of the reward trials and could avoid loss in 67% of the loss trials.

fMRI data analysis. Because the NAc has mainly been implicated in reward anticipation[3], 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 ref. 3. 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 0.006 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. An ROI analysis was performed to test for effects of DBS (DBS ON versus DBS OFF) on NAc responses using the contrasts reward anticipation versus no-reward (neutral) anticipation. We chose this ROI because it was closest to the stimulated region. Furthermore, we 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 yet received DBS treatment[3]. We defined the NAc ROI on the basis of the AAL atlas and as part of the caudate nucleus below $Z = 0$ mm (MNI coordinates = [±10, 14, −8]; **Fig. 1a**)[16]. NAc ROI data were used for correlation analysis between DBS effects and clinical measures (severity scores on Y-BOCS, HAM-A and 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. 5**). 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 versus loss anticipation and monetary feedback, which yielded no significant DBS related changes during anticipation of losses (group × scan interaction $P = 0.118$ (right NAc) and $P = 0.106$ (left NAc)), 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 $4 \times 4 \times 4$ mm^3, spatially smoothed (8 mm at full-width at half maximum), linearly detrended and band-pass filtered ($0.01 \text{ Hz} < f < 0.08 \text{ Hz}$). As done previously[17], we defined spherical seed ROIs (radius = 4 mm) for the NAc centered at [±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.mccauslandcenter.sc.edu/mricro/mricron/install.html). We correlated the seed reference with the whole brain, correcting for white matter, cerebrospinal fluid, 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 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 × 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 lPFC with the difference in clinical scores (HAM-D, HAM-A and Y-BOCS). To avoid dependency between the definition of the lPFC ROI and symptom differences, the peak voxel was defined for each subject separately using a leave-one-out procedure.

EEG symptom-provocation procedure. We recorded EEG and electro-oculogram at 512 Hz using 64 shielded Ag/AgCl electrodes (Advanced Neuro Technology B.V.) following the international '10/10' system. We used a task designed to investigate symptom-like brain activity. Patients were exposed for 2 s 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[18] and the OCD pictures were obtained from the Internet. Patients ($n = 13$) rated arousal, valence, the presence of symptoms, and whether the picture was symptom provoking or non–symptom provoking. We matched the valence and arousal ratings between self-rated symptomatic and nonsymptomatic pictures to isolate the symptomatic component.

EEG data analysis. Data were analyzed using EEGlab 9.4.6 (ref. 19) and Fieldtrip[20]. 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-s windows around the stimulus ([−1, 2]) and the epochs were checked for large artifacts. We then used independent component analysis to remove eye blinks and other residual noise sources from the data. The epochs were again checked and were considered to be 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 (TFRs) of power by convolving a hanning window with an adaptive time window of three cycles over the data. The TFRs were relative-change baseline corrected from −0.75 to −0.25 before stimulus onset. The average TFRs were computed by subtracting the average TFR of non–symptom provoking stimuli from the average TFR of symptom provoking stimuli. To compute statistics, we used repeated-measures ANOVAs in PASW statistics 18.0.

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