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

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Deep brain stimulation (DBS) targeted at the nucleus accumbens (NAc) has become an effective treatment for therapy-refractory obsessive-compulsive disorder (OCD) (Denys et al., 2010). We have recently demonstrated that NAc DBS for OCD normalizes ventral striatal reward responses and its connectivity with the prefrontal cortex (chapter 6; Figee et al., 2013; Smolders et al., 2013), leading to the therapeutic modulation of the ventral motivational frontostriatal network. In the current study, we extend our previous findings and report that DBS also restores the sensorimotor frontostriatal pathways that are involved in inhibitory control.

Patients with OCD are unable to stop unwanted compulsive behaviors, which has been linked to dysfunctional brain networks of motivational (chapter 2; Figee et al., 2011) and inhibitory control (Woolley et al., 2008; Roth et al., 2007; Page et al., 2009). We measured brain activity related to inhibitory control with functional magnetic resonance imaging (fMRI; 1.5T Siemens Avanto, repetition time 2 s, echo time 30 ms, voxel size 3.6 mm isotropic) in 8 DBS implanted
OCD patients (mean age 44.6 yr, SD = 10.9, 4 women), first with DBS on (DBS ON) and then after one week DBS off (DBS OFF). These 8 patients were part of a larger sample of 16 DBS-implanted OCD patients (Figee et al., 2013) and were chosen based on the availability of appropriate behavioral data and scanning data. To minimize exposure of the DBS device to the pulsed radio-frequency field, we used a transmit/receive (Tx/Rx CP) Head Coil, limited specific absorption rate levels to 0.1 W kg−1, turned off the DBS system 2 min pre-scanning, and programmed it at 0 V bipolar (Chapter 5). We also performed repeated scanning in 13 gender-, age- and education-matched healthy controls (mean age 46.1 yr, SD = 9.3, 6 women). We probed frontostriatal inhibitory control using a stop-signal task that requires responding to a go-signal and inhibiting this response after an occasional stop-signal (see Zandbelt et al., 2010 and 2011). The probability that a stop-signal would occur and a response was to be withheld was indicated via cues. In this way, we could focus on reactive inhibition (i.e. outright stopping in response to a stop-signal), and proactive inhibition (i.e. the anticipation of a potential stop signal). We assessed brain activity related to reactive inhibition by calculating the difference in activation during successful inhibition versus unsuccessful inhibition. Proactive inhibition was calculated as the parametric effect of stop-signal probability on go-signal (response-inhibition) activation. We assessed activation differences over the two scans between patients (DBS ON and OFF) and controls in the right striatum and right inferior frontal cortex using a region-of-interest (ROI) approach, as these frontostrial regions were found to be involved in reactive and proactive inhibition in our previous experiments (Zandbelt et al., 2010 and 2011). These ROIs were defined in healthy individuals performing the same task, using a cluster-level threshold (p < 0.001; cluster probability, p < 0.05, family-wise error (FWE) corrected (Zandbelt et al., 2010 and 2011). We also performed voxel-wise whole-brain analyses to explore activation changes outside these regions of interest using FWE corrections for multiple comparisons.

Turning the stimulators off for one week resulted in a 37% increase in obsessive-compulsive symptoms as measured with the Yale Brown Obsessive Compulsive Scale (t7 = −2.74, p = 0.003). At baseline, compared to controls, OCD patients had intact reactive inhibition as measured by the latency (measured by stop-
signal reaction time: $F < 1$) and accuracy of inhibition ($F < 1$), and the level of activation in the striatum ($F < 1$). None of these measures changed due to DBS (group x scan interaction for all measures: $F < 1$). Behaviorally, DBS did not significantly change proactive inhibition (the effect of stop-signal probability on mean go-signal response time) compared to changes over time in controls (group x scan interaction $F_{1,19} = 1.85, p = 0.19$). However, DBS induced significant changes in proactive inhibitory activation in the right striatum (group x scan interaction $F_{1,19} = 5.74, p = 0.027$) and right inferior frontal cortex (group x scan interaction $F_{1,19} = 7.63, p = 0.012$). Patients with DBS OFF had lower activity in these regions than healthy controls ($t_{19} = -2.18, p = 0.042$ right striatum; $t_{19} = -2.68, p = 0.015$ right inferior frontal cortex), whereas activity in the patients with DBS ON did no longer differ significantly from controls ($t_{19} = 1.78, p = 0.91$ right striatum; $t_{19} = 1.56, p = 0.135$ right inferior frontal cortex). These results suggest that DBS normalizes frontostriatal activity during proactive inhibition. DBS-induced brain activity changes were not correlated with changes in obsessions and compulsions. Explorative whole-brain group analyses revealed that reactive and proactive response inhibition activated regions across all subjects very similar to that reported on previously (Zandbelt et al., 2010), but yielded no significant group or scan differences.

**Figure 1.** DBS normalizes brain activity in frontostriatal network (A) Regions of interest (ROIs) for blood oxygenation level–dependent (BOLD) responses: 1. right dorsal striatum/putamen (blue) 2. right inferior frontal cortex (pink). (B) DBS-induced changes during proactive inhibition in the two ROIs. Activity in both regions increased from DBS OFF to DBS ON and was lower in patients than in controls during DBS OFF. * Significant ($p < 0.05$) group differences in post hoc analyses. Error bars indicate 95% confidence intervals. a.u., arbitrary units; HC, control subject; OCD, obsessive-compulsive disorder patients; r., right.
The normalization of striatal and inferior frontal inhibitory control by DBS suggests that it is able to restore the frontostriatal network to a healthy state, in line with and extending our recent observations. In these experiments, we found DBS in OCD restores the ventral frontostriatal network involved in motivational control (chapter 6; Figue et al., 2013; Smolders et al., 2013). The current findings imply that DBS also restores the sensorimotor frontostriatal pathways that are involved in inhibitory control. As stimulation in this patient group was most effective at the border of the NAc core and the ventral internal capsule (see also Denys et al., 2010), dorsal striatal and inferior frontal modulation likely occurred via ventral-dorsal internal capsule connections, which have found to be excessive in OCD (Harrison et al., 2009). Alternatively, NAc DBS may have influenced dorsal pathways indirectly by stimulation of corticothalamic pathways (Lehman et al., 2011).

DBS specifically affected neural processes underlying proactive inhibition. Rather than reacting upon an external stimulus, proactive control must be setup in advance internally according to one’s expectation (Aron, 2011), and is probably at play when one has to control the urge to perform a compulsion. Moreover, proactive in contrast to reactive control depends more on frontostriatal dopaminergic neurotransmission (Zandbelt et al., 2011; Eagle et al., 2011). We have recently demonstrated striatal dopamine release during effective NAc DBS for OCD (chapter 9; Figue et al., 2013). DBS-induced dopamine release may thus be one of the underlying mechanisms of improved frontostriatal proactive control. Patients with OCD are unable to stop unwanted compulsive behaviors, which several studies have linked to impaired striatal and inferior frontal activation during response inhibition (Woolley et al., 2008; Roth et al., 2007; Page et al., 2009). We confirmed these frontostriatal impairments in OCD and showed that they can be reversed by DBS along with symptom improvement. These results suggest that DBS for OCD interrupts a pathological frontostriatal loop, allowing successful inhibition of unwanted behaviors and restoration of goal-directed actions.