Moving the brain: Neuroimaging motivational changes of deep brain stimulation in obsessive-compulsive disorder
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Introduction
Over the past 20 years, deep brain stimulation (DBS) of various targets has been successfully applied for the treatment of neuropsychiatric conditions in more than 100,000 patients (Lozano and Lipsman, 2013). The DBS target for a particular disorder is still predominantly based on previous effective stereotactic lesions, and little is known about the underlying brain changes of DBS. Neuroimaging techniques are crucial for understanding the mechanism of action of current targets and to explore future targets. Combining DBS with neuroimaging techniques may offer a unique opportunity to reveal how brain circuits are related to motor and cognitive-emotional processes.

Neuroimaging studies in implanted patients have predominantly used positron emission tomography (PET) or single photon emission computed tomography (SPECT) to track metabolic or blood flow changes related to effective DBS (Dormont et al, 2010). Unlike PET and SPECT imaging, fMRI is able to detect rapid task-related and functional connectivity changes that may better probe the neural effects of DBS. At our institution, we apply DBS targeted at the nucleus accumbens (NAc) for treatment of refractory obsessive-compulsive
disorder (OCD). We have observed that DBS induces fast and remarkable improvement of mood, anxiety and obsessive-compulsive symptoms (Denys et al, 2010), suggesting that local stimulation modulates neural function of broader networks. Hence, we set out to explore if we could safely and reliably apply fMRI in these patients to probe therapeutic local and network brain changes.

Potential problems of fMRI with DBS

First, we evaluated documentation of safety and quality of fMRI with DBS. At the time of our investigation (2010), fMRI in fully implanted DBS patients had never been performed before due to safety issues. In-vitro testing and clinical case-reports indicates that the MRI static and gradient magnetic field and radiofrequency pulses may induce heating or movement of the DBS system, or interfere with neurostimulator function (Medtronics, 2006; Zrinzo et al, 2011). In addition, the metallic implants may cause significant artifacts and/or distortion of the MRI image. Finally, if MRI would increase brain tissue temperature around the electrode, this may cause local cerebral blood flow changes interfering with potential therapeutic signals (Carmichael et al, 2007). Therefore, the manufacturer MRI guidelines recommend to only perform MRI scans in DBS patients if absolutely necessary using strict parameters that are assumed to be safe: scan at 1.5 T with a transmit/receive head coil, limit the displayed average head SAR to 0.1 W/kg or less, limit the gradient dB/dT to 20 T/s or less and program the neurostimulator to off, 0V and bipolar (Medtronic, 2006). Seven case-studies reported on intraoperative fMRI in a total of 20 subjects (18 Parkinson’s disease, 1 essential tremor, 1 OCD) with externalized leads, before implantation of the neurostimulator (Rezai et al, 1999; Jech et al, 2001; Nuttin et al, 2003; Stefurak et al, 2003; Hesselmann et al, 2004; Arantes et al, 2006; Phillips et al, 2006). FMRI scans were obtained at 1.5 T according to manufacturer guidelines, expect for one study that scanned 5 patients on a 3 T machine (Phillips et al, 2006). No adverse events were reported in any of these studies and despite significant image artifacts, brain activation signals related to stimulation or to sensorimotor task performance were demonstrated around the electrode and across the brain. However, these studies were all performed during the intraoperative phase, and it has been argued that at this time residual
anesthesia effects and local edema or microlesions due to lead placement may limit or alter fMRI results (Phillips et al, 2006; Jech et al, poster presentation HBM 2011). Moreover, at this time no lasting clinical effects have occurred yet because the neurostimulator has not been implanted. Safety testing of fMRI with fully implanted devices was only performed in phantoms (Carmichael et al, 2007). A gel-filled phantom with an implanted Medtronic Kineta DBS system (unipolar stimulation, pulse width 60 μs, 130 Hz, 3 V) was scanned for 5 minutes with 1.5 T and 3 T MRI scanners. No significant RF-induced heating was detected in the 1.5 T scanner, and only moderate temperature elevations at 3 T. No damage or alteration of neurostimulator settings was observed after scanning. FMRI induced in the DBS system low-frequency voltages of which it can be assumed that they were below the thresholds for neuronal stimulation. Together, available documentation suggests that fMRI could be safely applied at 1.5 T using strict scanning parameters in patients with the electrodes implanted, whereas DBS did not seem to interfere with the function of the implanted neurostimulator in phantom models.

**Methods of fMRI with fully implanted DBS**

We first acquired pilot data of healthy individuals to optimize image quality within the strict limits of the MRI guidelines for DBS. Next, we tested fMRI image quality and safety in two DBS implanted patients that performed a simple finger-tapping task for 5 minutes in the scanner. Finally, we performed full fMRI sessions in 16 OCD patients that had been treated with DBS targeted at the NAc for at least one year. All patients had bilateral electrodes implanted (model 3389 Medtronic, platinum/iridium conductor wires, with four 0.5 mm platinum/iridium stimulating electrodes), which were connected to infraclavicular neurostimulators (bilateral Soletra or unilateral Activa PC, Medtronic, titanium cover) via subcutaneous extensions (model 7482 Medtronic, platinum/iridium wires with stainless steel connection blocks).

Effective stimulation for OCD requires voltages that are often two times higher than those needed for movement disorders, and higher voltages were never tested properly with fMRI. Therefore, we decided to follow the manufacturer guidelines and program the stimulator to 0 V, off, bipolar just before scanning, allowing measurement of neuronal activity related to clini-
cally effective DBS for OCD, as symptom recurrence usually takes several days after the modulator has been switched off. Note that these settings may be less optimal for Parkinson’s disease where symptoms often reoccur immediately. Prior to scanning, we tested whether batteries were sufficiently charged, we tested for possible open circuits by measuring electrode impedance and battery current, and reviewed the programmed parameters for reference. Finally, we instructed patients to minimize head movements because this may amplify interaction of the DBS device with magnetic fields.

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. Specific absorption rate (SAR) levels were limited to 0.1 W/kg. We performed two scanning sessions of 43.3 minutes each, separated by 8 days: one structural MRI scan, one resting-state fMRI scan and two task-related fMRI scans. 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; 80, 370 and 505 volumes respectively), and the first 10 volumes were discarded. A T1-weighted structural image was acquired for anatomical registration purposes. All subjects 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.

**Safety results**

We observed no serious adverse events during or after the 2 pilot scans or the 32 scanning sessions. One patient reported slight hyperventilation related to claustrophobia during scanning, which she had experienced previously without DBS as well. Two patients experienced a mild headache that they had also reported before scanning and was probably related to caffeine withdrawal. However, significant changes in the neurostimulator settings were observed after the majority of scanning sessions. The stimulator switched on during scanning 2 times bilaterally and 12 times unilaterally, with voltage remaining at 0V so no effective stimulation could have induced. Notably, one patient reported tingling sensations in the head during scanning at the side were the electrode had been switched on, but was found to be in good health after careful
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medical examination. On nine occasions, scanning modulated the neurostimulator pulse-width from 60 to 210 microseconds and the frequency from 2 to 30 Hertz, and on 12 occasions the active contact point was altered from the two most dorsal contacts (2 and 3) bipolar, to the upper and lower contacts (0 and 3). We were able to reprogram each neurostimulator back to its original settings immediately after scanning and all stimulators continued to function normally.

**Reliability results**

Functional 2D-EPI images from the pilot data revealed significant drop out artifacts located bilaterally around the electrodes and parietal cortex, probably corresponding to the place where the steel connection blocks of the extensions are connected to the leads (**figure 1**). Despite these artifacts, we were able to measure significant activation signals related to 30-second blocks of finger tapping in sensorimotor brain regions.

**Figure 1**: single subject’s EPI series viewed from axial sections of patient with bilateral NAc electrodes. Image distortion and signal drop out can be observed around the electrodes and lead extension connections. Significant activation (finger tapping > rest; thresholded at $p < 0.005$, uncorrected) can be observed in the motor cortex, supplementary motor area and cerebellum.
Next, we confirmed in a second implanted patient that we were also able to measure activation around the NAc target area (Figure 2), using a monetary incentive delay paradigm (see also chapters 2 and 6).

**Figure 2**: sagittal, coronal and axial views of functional MRI scan from one patient with bilateral NAc electrodes, depicting BOLD signals (T>3) related to monetary rewards (reward anticipation > neutral) in the NAc. Cross-hair position = 15, 13, -5 (MNI).

We repeated this reward paradigm along with two other fMRI paradigms in 16 DBS implanted patients when they were stably treated with DBS for at least one year, and after 8 days of DBS discontinuation. Detailed methods and results are described in chapters 6 and 7. Figure 3 shows that we were able to reliably estimate group activation differences around the NAc target area between patients and healthy controls (Figee et al., 2013). Moreover, we calculated acceptable temporal signal-to-noise ratios in the NAc region that did not change significantly between the two scanning sessions.

**Figure 3**: group x session interaction during reward anticipation in the NAc target region at p < 0.005 uncorrected, in 9 implanted patients (DBS on and off) and 13 healthy controls.
Finally, we could measure resting-state connectivity patterns between the prefrontal cortex and the NAc seed region, by excluding voxels with signal dropout around the DBS lead (chapter 6).

**Conclusion**

We demonstrated that fMRI could be reliably used in OCD patients with fully implanted DBS systems to study local and network neural changes underlying effective NAc stimulation. However, despite the application of strict safety guidelines, fMRI scanning significantly modulated neurostimulator settings in most patients, probably due to interaction with radiofrequency pulses. Given our own clinical observations that minimal modulation of the stimulation parameters is able to produce substantial symptomatic changes or serious adverse events, we suggest to perform fMRI with OCD patients only with the stimulator switched off at 0V, bipolar. Using these settings in our experiments, fMRI caused no adverse events and we were still able to measure clinical relevant brain changes, as OCD symptoms did not relapse within the first hours after DBS discontinuation. Moreover, fMRI during active stimulation has only been performed in movement disorders, with significantly lower voltages than those that would be needed for treatment of obsessive-compulsive symptoms (Kahan *et al*, 2012).