Pharmacological treatment of deep brain stimulation-induced hypomania leads to clinical remission while preserving motor benefits

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Pharmacological treatment of deep brain stimulation-induced hypomania leads to clinical remission while preserving motor benefits

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for Parkinson’s disease, but can lead to adverse effects including psychiatric disturbance. Little is known about the risk factors and treatment options for such effects. Here, we describe a patient who reproducibly developed stimulation-induced hypomania when using ventrally located electrodes and responded well to pharmacological intervention while leaving the stimulation parameters unchanged to preserve motor benefits. In spite of clinical remission, [15O]-positron-emission-tomography (PET) demonstrated activation patterns similar to those reported during mania. This case, therefore, highlights an important treatment option of adverse effects of DBS, but also points toward the need for investigations of its risk factors and their underlying neurobiological mechanisms.

Keywords: Subthalamic nucleus; Deep brain stimulation; Parkinson’s disease; Stimulation-induced hypomania; Pharmacological treatment; Positron-emission-tomography (PET).

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment option for idiopathic Parkinson’s disease (IPD) and alleviates motor symptoms (Deuschl, Schade-Britttinger, Krack, Volkman, Schafer, Botzel, et al., 2006). Adverse effects of STN-DBS, however, are also known and include severe psychiatric disturbance (Appleby, Duggan, Regenberg, & Rabins, 2007; Soulas, Guruchaga, Palfi, Cesaro, Nguyen, & Fenelon, 2008; Voon, Krack, Lang, Lozano, Dujardin, Schupbach, et al., 2008). Relatively little is known about the risk factors for the occurrence of these effects, their underlying mechanisms and treatment options (e.g., Troster, 2009).

Here, we describe the case of a patient who reproducibly developed hypomanic episodes when switching STN-DBS from ‘dorsal’ to ‘ventral’ stimulation sites (Figure 1a & b; ‘dorsal’ stimulation shown in blue, ‘ventral’ stimulation shown in red). Due to significant motor impairment during the former, we opted for pharmacological treatment of the stimulation-induced hypomania. While the hypomanic syndrome could be well controlled pharmacologically, [15O]-positron-
Figure 1. (a) Quadripolar electrodes (Medtronic® model 3387) used for DBS in patient KS illustrating ‘ventral’ (red) vs. ‘dorsal’ (blue) stimulation. Numbers denote the different contacts of each electrode that can be used for stimulation. (b) Localization of electrodes in KS (right electrode shown in green, left electrode shown in red; electrode contacts shown in black) as assessed by postoperative stereotactic X-ray imaging illustrated by means of overlays onto ascending axial slices (i–vii) of the preoperative T2 weighted MRI. The level of the axial slices is shown schematically on the left hand side. RN: Red nucleus; STN: Subthalamic nucleus. (c) Neural correlates of ‘ventral’ as compared to ‘dorsal’ stimulation of STN in KS (thresholded at $p < .05$ FWE corrected for multiple comparisons). Differential increase of neural activity in (i) DLPFC (Right middle frontal gyrus∗; MNI: 30, 5, 6; $k=164$; $T=23.64$ & MNI: 46, 16, 40; $k=20$; $T=15.54$), (ii) left MTG∗ (MNI: −48, −20, −14; $k=117$; $T=21.48$) and (iii) dACC (Left anterior cingulate cortex∗; MNI: −6, 22, 30; $k=37$; $T=15.54$). Common activations for ‘dorsal’ as compared to ‘ventral’ stimulation were observed in left lingual gyrus ∗(not illustrated; MNI: −22, −72, −2; $k=42$; $T=19.63$). ∗Anatomy assigned by using the SPM Anatomy Toolbox (Eickhoff et al., 2005).
emission-tomography (PET) performed during clinical remission several weeks later demonstrated stimulation-dependent neural activation differences similar to those reported during clinically manifest mania.

**CASE REPORT**

Patient KS was a 48-year-old man referred for admission to our inpatient psychiatric unit for evaluation and management of a manic syndrome which had developed after the STN-DBS stimulation parameters had been changed from ‘dorsal’ to ‘ventral’ stimulation several weeks before (Figure 1a). Using a more symmetrical ventral stimulation (electrodes 1 & 5) had not been effective in alleviating motor impairment. After having been changed to the ‘ventral’ stimulation (Figure 1a), the patient reported elation and developed symptoms of grandiosity, insomnia, racing thoughts and increased speed of speech. Reports by family members indicated conflicts resulting from the patient’s aberrant behavior and lack of proper judgment with respect to financial activities. Due to these difficulties KS was seen by a neurologist, who re-set the DBS to the dorsally located electrodes (Figure 1) and had the patient transferred to the hospital.

Upon admission – a few hours after STN-DBS had been re-set from the ‘ventral’ to ‘dorsal’ stimulation the mental status of the patient had changed significantly: All symptoms characteristic of mania had subsided and the patient was found to be cooperative and calm during the evaluation. His speech was found to be of normal speed and fluency. He described his mood as ‘lower than in the past days’ and did not appear irritable. His affect was euthymic and congruent with his mood. His thought processes were somewhat circumstantial, but there was no loosening of associations. His self-attitude was normal, and he exhibited adequate judgment of the current situation. He scored 30 of 30 on the Mini-Mental State Examination. Abnormalities upon neurological examination included significant motor impairment manifest in a hypokinetic–rigid syndrome including a resting tremor of the left hand and predominantly left-sided rigidity making the patient wheelchair-bound. Routine blood work, a toxicology screening, EKG and EEG did not show any significant abnormalities. Medication upon admission consisted of levodopa & carbidopa (5 × 50 mg/day), levodopa & benserazide (50 mg/12.5 mg/day), ropinirole (8 mg/day), amantadine (2 × 50 mg/day), valproate (450 mg/day) and clozapine (150 mg/day).

The past medical history revealed a diagnosis of idiopathic Parkinson’s disease (IPD) at the age of 32 which had been made due to a typical clinical presentation and in spite of a history of paranoid psychosis. Psychosis had been diagnosed at the age of 23 and led to three other acute episodes at the age of 24, 28 and 41. First-generation antipsychotics were used briefly during the acute episodes that required hospitalization, while long-term treatment consisted of second-generation drugs. After the last episode requiring hospitalization clozapine was used continuously. After good response to L-DOPA medication and a stable course of treatment of IPD for almost 10 years, the patient developed on-off fluctuations and pronounced dyskinesia. Three years later, off-states comprised 30% of the day leaving the patient immobile during these periods. In light of the progressive worsening of Parkinsonian symptoms, a lack of benefit from medication and no further psychotic episodes since 2002, the recommendation for DBS was given by a neurologist outside our department in 2007. Thereupon implantation of bilateral quadripolar electrodes was performed. Upon preoperative neuropsychological assessment, executive function, attention and memory were normal. STN-DBS implantation resulted in an improvement of motor impairments. Several months after the implantation, the patient developed a right-sided subdural hematoma, which required surgical intervention. After the operation, the patient made a full recovery and lead location was controlled by means of neuroimaging. Subsequently, bilateral stimulation of STN resulted in significant improvement of motor impairment comparable to the benefit observed prior to the subdural hematoma. Over the next two years, however, the DBS had to be adjusted to rely more on the ventral contacts due to the progressive development of significant motor impairment (Figure 1a). Switching to these contacts, however, also lead to the development of two hypomanic episodes that required hospitalization. During each episode, voltage applied to the ventral contacts was reduced to limit the hypomanic syndrome, but eventually STN-DBS had to be re-set to the dorsal contacts. Concomitantly, however, a significant worsening of motor symptoms was observed.

Due to the motor impairment apparent upon admission and in agreement with the patient, STN-DBS was again switched to the ‘ventral’
stimulation (Figure 1a) as this configuration had been most successful in treating motor symptoms and in spite of the fact that this stimulation setting had previously led to stimulation-induced hypomania. Within minutes, a significant improvement of motor functions and change in mental status could be observed. KS was able to walk with the help of a cane, began to speak more quickly and appeared more animated and expressive in mimic and gesture. He also described a sense of invigoration and improvement in mood. Within days the changes in cognition and behavior became more pronounced, finally resulting in a hypomanic syndrome (as measured by the Young Mania Rating Scale; Figure 2a).

Figure 2. (a) Observed change in motor function (as assessed by the UPDRS-III; higher scores indicating more pronounced motor impairment) and mental status (as assessed by the YMRS; < 5: Clinical remission, > 12: Hypomania, > 20: Mania) during the first two weeks of treatment after the change of stimulation (flash) from dorsal to ventral electrodes on the day of admission. (b) Daily dosages of anti-manic medication (VPT: Valproate; CLZ: Clozapine) used to treat stimulation-induced change of mental status during the first two weeks of treatment. (c) Blood serum levels of anti-manic and antipsychotic drugs (VPT: Valproate; CLZ: Clozapine) measured at different time points. Therapeutic range of VPT: 50–100 mg/l. Therapeutic range of CLZ: 350–600 µg/l.
In order to preserve the motor benefits (as measured by the Unified Parkinson Disease Rating Scale-III; Figure 2a), we decided to leave the stimulation parameters unchanged this time and opted for pharmacological treatment. The dosage of valproate and clozapine were increased while leaving the anti-parkinsonian medication unchanged (Figure 2b & c). This adjustment resulted in a remission of the hypomanic syndrome within the next week while preserving most of the motor benefits (Figure 2a).

In spite of the clinical remission, psychopathological differences in KS continued to be observable depending upon the stimulation site: This was assessed eight weeks later and reproducibly demonstrated 'dorsal' stimulation to result in a decrease of psychomotor function and lowering of his mood, while switching back to ‘ventral’ stimulation would increase his rate of speech and his subjective sense of well-being immediately. Based upon this clinical insight and in light of studies, which have demonstrated wide-spread activation differences as a result of STN stimulation during clinically manifest mania (e.g., Mallet, Schupbach, N’Diaye, Remy, Bardinet, Czernecki, et al., 2007), we utilized PET to investigate regional cerebral blood flow (rCBF) during ventral vs. dorsal STN-DBS. This study demonstrated a differential increase of rCBF in right dorsolateral prefrontal cortex (DLPFC), right middle temporal gyrus (MTG) and dorsal anterior cingulate cortex (dACC) (Figure 1c).

**METHODS**

**Anatomical localization of electrodes and stimulation sites**

In order to assess the precise anatomical localization of the different stimulation sites, i.e., the location of the quadripolar electrodes within STN bilaterally, the stereotactic coordinates of the electrodes as assessed by post-operative imaging were used to generate an overlay onto the individual preoperative MRI scan that had been coregistered to the stereotactic cerebral computed tomography (CCT) (Figure 1b). Schaltenbrand–Wahren atlas (SWA) coordinates (x,y,z) were determined for all 4 contact sites of the left and right electrode (RIGHT Contact0: 11.0, −1.4, −2.9; RIGHT Contact1: 11.7, −0.2, −1.5; RIGHT Contact2: 12.3, 1.0, 0.0; RIGHT Contact3: 13.1, 2.2, 1.5; LEFT Contact4: −10.0, −3.2, −4.6; LEFT Contact5: −10.5, −1.9, −3.1; LEFT Contact6: −11.2, −0.5, −1.7; LEFT Contact7: −11.8, 0.9, −0.2).

**PET scanning**

The patient was accompanied to the scanning site by the first author (LS). Upon arrival at about 08.00 h the patient was familiarized with the details of the scanning procedure by the second author (PW), YMRS and UPDRS ratings were carried out (YMRS: 5 UPDRS-III: 14) and informed consent was obtained. Approval for the procedure had been obtained from the University ethics committee and the regulatory authorities (Bundesamt fuer Strahlenschutz) gave permission to administer the radioactive substances. The first six PET measurements were carried out starting at 09.00 h during which DBS continued making use of the ventral stimulation settings. At 12:30 h, the stimulation parameters were changed to the dorsal settings. At 14:30 h, YMRS and UPDRS ratings were again carried out (YMRS: 0 UPDRS-III: 25). The second six PET measurements were carried out starting at 15:00 h. rCBF was measured by recording the regional distribution of cerebral radioactivity after the intravenous injection of [15O]-water. The PET measurements were carried out using an ECAT EXACT HR+ scanner (CTI Siemens, Knoxville, TN), with a total axial field of view of 155 mm covering the whole brain. Data were acquired in three-dimensional mode with interdetector collimating septa removed and a Neuro-Insert installed to limit the acceptance of events originating from out-of-field-of-view activity (i.e., the whole body). For each measurement of rCBF, 555 MBq of [15O]-water were given intravenously as a bolus injection. The patient was subjected to a radiation dose of 7.7 mSv (effective dose) during the entire course of the PET measurement. Twelve PET scans were collected, each beginning when the brain activity exceeded a threshold of 5 kilo counts per second (kcps) above the background level. Emission data were thereafter collected sequentially over 40 s. This process was repeated for each emission scan, with 10 min between scans to allow for the adequate decay of radioactivity. All emission scan data were corrected for scattered events and for radiation attenuation by means of a transmission scan taken prior to the first emission measurement. The corrected data were FORE rebinned and reconstructed into 63 transverse images (separation 2.4 mm) of 128 × 128 pixels (size 2.0 × 2.0 mm2) by
two-dimensional filtered back projection (DIFT) using a Shepp filter with a width of 6 mm. The reconstructed PET images had a resolution of 7 mm and were regarded to represent rCBF qualitatively.

Image processing

All calculations and image manipulations were performed on a Transtec Linux cluster using MATLAB version 6.5 (The Mathworks Inc., Natick, MA). Statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm5) was used for image realignment, normalization, and smoothing (low-pass Gaussian filter of 12 mm) and to create statistical maps of significant relative rCBF changes. The resulting voxel size in stereotactic space was $2 \times 2 \times 2$ mm. The stereotactic coordinates of the voxels of local maximum significant changes in relative rCBF within areas of significant relative rCBF change associated with the different factors were determined. The anatomical localization of these local maxima was assessed by reference to MNI space as well as by making use of the SPM Anatomy toolbox. Additional validation of this method of localization was obtained by superimposition of the SPMs maps on the single subject MRI template (in MNI space) provided by SPM5.

DISCUSSION

This case report adds to the growing body of evidence suggesting that a considerable number of patients treated with STN-DBS experiences significant psychiatric disturbance (e.g., Appleby et al., 2007; Soulas et al., 2008; Voon et al., 2008). Furthermore, our case demonstrates that pharmacological intervention can be an important treatment option for stimulation-induced hypomania.

Even though the risk factors for ‘psychiatric’ adverse effects of STN-DBS are not well understood, it has been demonstrated that their occurrence may depend upon the exact location with anterior and ventrally located contacts being more likely to produce them (e.g., Mallet et al., 2007; Okun, Fernandez, Wu, Kirsch-Darrow, Bowers, Bova, et al., 2009). Accordingly, we found evidence that ‘ventral’ as compared to ‘dorsal’ stimulation of the STN reproducibly resulted in hypomanic episodes in our patient. Clinically, the psychopathological features of hypomania induced by STN-DBS did not differ from manic syndromes resulting from other etiologies. Likewise, the syndrome in KS did respond well to pharmacological intervention. We opted for pharmacological treatment to control the symptoms in order to preserve the motor benefit that resulted from ‘ventral’ stimulation. Even during clinical remission occurring as a result of pharmacological treatment, however, differential stimulation effects on psychopathology continued to be noticeable. In accordance with these observations, PET imaging performed months later demonstrated a differential increase of neural activity in DLPFC, MTG and dACC for ‘ventral’ as compared to ‘dorsal’ STN-DBS. This pattern of activation serves as evidence for widespread changes of brain metabolism as a result of targeting what has been described as the ‘limbic’ subregion of the STN and is highly consistent with findings observed during clinically manifest mania (Mallet et al., 2007; Ulla, Thobois, Lemaire, Schmitt, Derost, Broussolle, et al., 2006). Here, it has been described as an activation of a subcortical-cortical limbic network whose modulation can alter mood, attentional and emotional processes (Mayberg, Lozano, Voon, McNeely, Seminowicz, Hamani, et al., 2005), but could also reflect compensatory processing of abnormal behavior (Ulla et al., 2006). More specifically, our findings seem to be in line with evidence, which suggests that the STN forms part of a network, which includes medial and lateral frontal cortex and contributes to cognitive control (e.g., Aron, Behrens, Smith, Frank, & Poldrack, 2007). Alterations of this network could, therefore, possibly contribute to mania-related cognitive changes. Recent evidence, indeed, suggests that STN-DBS may significantly impact impulse control (Frank, Samanta, Moustafa, & Sherman, 2007; Halbig, Tse, Frisina, Baker, Hollander, Shapiro, et al., 2009), which could relate to neurofunctional alterations of the above described neurocircuits (Ballanger, van Eimeren, Moro, Lozano, Hamani, Boulinguez, et al., 2009). In light of the suggestion of a possible link between a higher risk of suicide attempts after STN-DBS and stimulation-induced changes in impulsivity (Rodrigues, Rosas, Gago, Sousa, Fonseca, Linhares, et al., 2010), systematic investigations thereof and the underlying neural mechanisms as well as interdisciplinary approaches to postoperative patient care seem to be warranted.

With respect to the exact localization of the electrodes in the case of our patient, intra-operative recordings and post-operative anatomical localization are consistent with placement of the contacts within the STN. In light of the behavioral
responses to the different stimulation settings and their neural correlates as assessed by PET imaging, it seems likely that the most ventral contacts target the anterior-medial or ‘limbic’ subregion of the STN (Mallet et al., 2007). It is noteworthy, however, that the ‘ventral’ stimulation included relatively high voltage on the left-sided contact, which is closest to the substantia nigra (SN). In light of recent reports by Ulla and colleagues (Ulla et al., 2006; Ulla, Thobois, Llorca, Derost, Lemaire, & Chereau-Boudet, 2010), the possibility must, therefore, be raised that the observed effects of ‘ventral’ stimulation could also be due to current spread to neighbouring regions such as the SN. In this respect, the resemblance of the activation pattern resulting from bilateral stimulation of the SN described by Ulla et al. (2006) and our activation results is informative. Additional neuroimaging data (e.g., high-resolution contrast-based and diffusion-based magnetic resonance images) could have been helpful to relate individual contact location to the differential stimulation effects observed in other brain regions (e.g., Gutman, Holtzheimer, Behrens, Johansen-Berg, & Mayberg, 2009). However, such data was not available in our patient.

In the case of KS, it is interesting to note that the PET activation differences were observed even though he was in clinical remission. In the case of KS, we speculate that this might be related to his previous psychiatric history (cf. Bejjani, Damier, Arnulf, Thivard, Bonnet, Dormont, et al., 1999; Lilleeng & Dietrichs, 2008). In light of this, it might seem plausible that KS has a neurobiological predisposition to show an activation pattern that is also observed in bipolar disorder (Blumberg, Stern, Martinez, Ricketts, de Asis, White, et al., 2000) and stimulation-induced, clinically manifest mania (Ulla et al., 2006), but longitudinal investigations would be necessary to investigate this. Furthermore it must be noted that relatively little evidence appears to exist about the neural correlates of differential STN stimulation and their impact on cognition (Kalbe, Voges, Weber, Haarer, Baudrexel, Klein, et al. 2009; Hirano, Eckert, Flanagan, & Eidelberg, 2009). Additionally, similar activation patterns as those observed in the case of our patient have been reported for effective STN-DBS without mania (Hilker, Voges, Weisenbach, Kalbe, Burghaus, Ghaemi, et al. 2004). This suggests that caution needs to be exercised with respect to interpretations of causality. Additional imaging comparisons between dorsal stimulation vs OFF and ventral stimulation vs OFF states would have been helpful to investigate this issue further.

With respect to the putative neural mechanisms that underlie mania-associated change in cognition, it is tempting to speculate that STN-DBS-induced differences in cognitive function could be related to changes in dopaminergic neurotransmission (Hershey, Revilla, Wernle, Gibson, Dowling, & Perlmutter, 2004). Recently, it has been demonstrated that DBS can lead to increased levels of dopamine in parts of the subcortico-cortical loops that are targeted. Furthermore, this increase of dopamine may be accompanied by an increase of impulsive behavior (Sesia, Bulthuis, Tan, Lim, Vlaming, Blokland, et al., 2010). Here again, the previous history of a paranoid psychosis – known to be associated with alterations of the mesolimbic dopamine system – appears to be of crucial importance. In light of this diagnosis, it makes sense to assume that KS may have been even more vulnerable than other Parkinsonian patients to the modulatory effects of STN-DBS on dopaminergic neurotransmission. Consistent with the view of DBS-induced alterations of dopaminergic transmission possibly contributing to mania-related cognitive changes, effective pharmacological treatment of our patient included the dopamine receptor-binding agent clozapine.

Taken together, this case report demonstrates that hypomanic episodes induced by STN-DBS can depend upon the exact stimulation site and that the resulting states can be controlled pharmacologically. The latter may be clinically relevant when motor improvement and hypomanic side effect result from stimulation of the same electrode contacts. Given that therapeutic adjustments to adverse effects of DBS conventionally involve changes of stimulation sites and parameters, our finding suggests a clear benefit of pharmacological intervention. Furthermore, the here-described case demonstrates that stimulation-dependent activation differences, previously reported as the neural correlate of mania-related behavioral alterations, can be observed after clinical remission. We suggest that this highlights the need for investigations into the risk factors of adverse effects of DBS and their underlying neurobiological mechanisms.

REFERENCES


