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LETTER TO THE EDITORS

Resolution of apathy after dorsal instead of ventral subthalamic deep brain stimulation for Parkinson's disease

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Dear Sirs,

Subthalamic deep brain stimulation (STN DBS) is an effective treatment for advanced Parkinson's disease (PD). The prevalence of apathy, i.e., loss of motivation and energy, after STN DBS in the previous studies is high, ranging between 21 and 71%, and is associated with a decreased quality of life [1–6]. Neuro-imaging studies suggest a possible explanation for these symptoms because of an association between STN DBS-related apathy and stimulation of non-motor limbic circuits in the ventral region of the STN [7–9]. In this study, we describe three PD patients with STN DBS-related apathy who experienced a fast resolution of symptoms after switching stimulation from ventral to dorsal STN stimulation.

Bilateral electrodes (model 3389, Medtronic) were implanted in the STN under local anesthesia, followed by the placement of a pulse generator (Activa PC model 37,601, Medtronic) into the chest wall and post-surgical optimization of the stimulation settings [10]. Dopaminergic medication was reduced post-surgery as part of standard care and will be reported as Levodopa equivalent daily dosage (LEDD).

The first patient was a 65-year-old male who had been suffering from PD for 14 years when he received STN DBS. He had no history of somatic or psychiatric disorders. A pre-operative MRI and neuropsychological screening revealed no cognitive impairment. STN DBS was performed without complications and the post-operative CT-scan showed no hemorrhages. After 8 weeks of DBS, the PD symptoms minimalized, leaving only a mild right-sided tremor, and the LEDD was reduced with 50%. However, in the subsequent months, he started reporting progressive fatigue. He lost interest in his previous passions like writing and reading, and spent his days lying awake, doing nothing in particular. There were no signs suggesting a depression, such as a depressed mood, anhedonia, or feelings of guilt, and the patient still enjoyed reading articles of the PD association's magazine. 8 month post-surgery, the patient was referred to a psychiatrist and he scored 30 out of 42 on the Starkstein's Apathy Scale (SAS, cut-off: 14), consistent with severe apathy. Since the right electrode was activated at the most ventral contact, we switched activation to a more dorsal contact on this side. Within 2 weeks, the patient's apathy symptoms dramatically improved. He showed more initiative and regained the motivation to resume writing online blogs and assisting in daily household chores. His apathy score was reduced to 11/42. T2-weighted pre-operative MR images fused with the post-operative CT-scan (fused MR images) confirmed that the apathy-related contact was located ventral of the STN (Fig. 1a). 2 years later, the patient's restored motivation was still present with minimal motor symptoms, and the LEDD had been further reduced with 90% in total.

The second patient was a 64-year-old female who had been suffering from PD for 14 years when she received STN DBS. Her psychiatric history showed a mild depressive disorder, effectively treated with citalopram 30 mg per day, which was maintained to prevent a relapse. She did not suffer from somatic illnesses except hypertension. The pre-operative MRI showed an old infarction of the right putamen and neuropsychological screening revealed no cognitive impairments. STN DBS was performed and post-surgical neurological examination revealed a temporary dysarthria, which was interpreted as a result of surgery-related intracerebral

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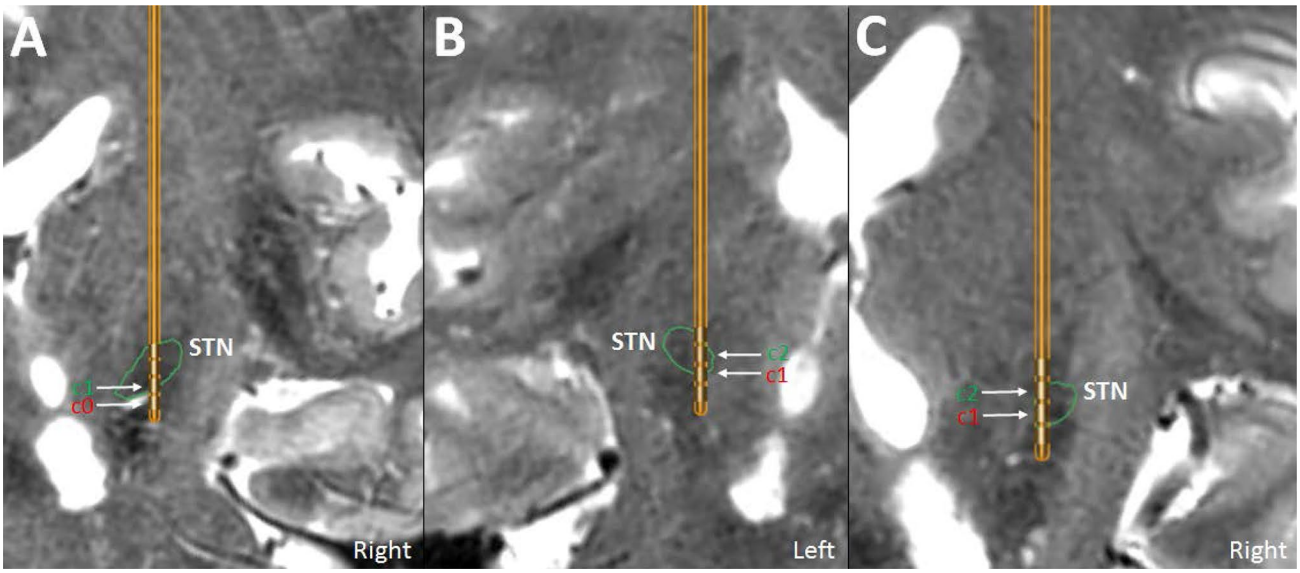

Fig. 1 Anatomical localizations of the electrode relative to STN of the ventral contact (red) associated with apathy, and the more dorsal contact (green) associated with resolution of apathy for the first patient (**a**, right electrode), second patient (**b**, left electrode), and third patient (**c**, right electrode). Note that, in all three patients, the apathy-related contact is situated ventrally in or just outside the STN, most likely in or near the substantia nigra

edema. The PD symptoms minimalized, leaving only a tremor of the right hand and dyskinesias of both legs after which the voltage of the left electrode was increased and the LEDD was reduced with 20%. After having increased the voltage, the patient started feeling more lethargic and losing her motivation for former hobbies, such as painting and cycling. She did not show a depressed mood or anhedonia and still enjoyed being with her family. Entacepone was started but quickly discontinued as it had no effect on apathy and caused visual hallucinations. 3 months after the surgery, the patient was hospitalized to our psychiatric inpatient unit for evaluating apathy. On admission, she scored 21 out of 42 on the SAS, consistent with moderate apathy. Since the apathy symptoms started after increasing the voltage of the left electrode, this electrode was temporarily switched off. The SAS score immediately reduced to 9 /42, but the patient experienced a relapse of disabling dyskinesias. The electrode was re-activated at a more dorsal contact and the dyskinesias improved, while the SAS score further dropped to 4/42. Fused MR images confirmed that the apathy-related contact was located ventral of the STN (Fig. 1b). The patient was delighted with the new DBS settings and reported experiencing a greatly increased quality of life.

The third patient was a 51-year-old male who suffered from PD for 11 years when he received STN DBS. His psychiatric history showed a mild depressive disorder, effectively treated with citalopram 30 mg per day, which was maintained to prevent a relapse. In addition, he suffered from hypersexuality, pathological gambling, and excessive spending of money related to dopaminergic medication. A pre-operative MRI and neuropsychological screening revealed no cognitive impairment, and he had no somatic illnesses. STN DBS was performed without complications and a post-operative CT-scan showed no hemorrhages. After 2 months of DBS, the patient did not experience any dyskinesias, but reported increased impulsive gambling, after which the LEDD was reduced with 54%. 2 months later, he started noticing that he had become less active and had lost the motivation for his daily activities. He showed no signs of depression and enjoyed spending time with his friends to play poker. He was referred to our psychiatry outpatient department with a score of 27 out of 42 on the SAS, indicating severe apathy. The activated contact on the right electrode was located more ventrally than the left, and was, therefore, adjusted to a more dorsal contact. During the car ride home, the patient noticed feeling more energetic, and that evening, he started doing household chores that he had neglected for several months. His SAS score dropped with 87%, without an increase of motor symptoms or impulsivity. Fused MR images confirmed that the apathy-related contact was located in the ventral–medial STN (Fig. 1c). During visits in the following 6 weeks, his restored motivation persisted without showing the signs of the previous impulse control disorders.

We present three patients with apathy after STN DBS for PD that completely resolved after switching the activated contact from a ventral contact, located ventrally in or just outside the STN, to a more dorsal location on the electrode. Based on these observations, we propose that DBS-related apathy may be caused by ventral stimulation of the STN and

connecting fibers, affecting motivational behaviors associated with the limbic circuit. This hypothesis is supported by the previous functional neuro-imaging studies that suggest an association between stimulation of the ventral STN with limbic changes and symptoms of apathy [7–9]. Our results may be of importance, as the reported intervention is easily applicable and could greatly increase the quality of life of many patients depending on STN DBS for PD.

Other explanations that have been considered for apathetic behavior in STN DBS patients are pre-existing apathy, dopaminergic medication withdrawal, or cognitive side-effects of the DBS surgery [11–13]. However, these factors cannot explain the resolution of apathy after DBS adjustment in our patients. Although the development of apathy after STN DBS coincided with reduction of LEDD in all three patients, resolution of apathy occurred after switching to dorsal stimulation without increasing medication dosage. Moreover, the second patient's LEDD was reduced with only 20% and she did not develop apathy until the voltage of the DBS was increased. The previous studies have not consistently demonstrated a correlation between apathy score and medication [14–16]. Of note, switching to more dorsal STN stimulation did not induce impulsive behaviors, and even resolved impulsivity in one patient. This could suggest that both apathetic and appetitive symptoms may be induced by ventral STN stimulation and can be reversed by switching to dorsal stimulation. Although no decrease of motor functioning was observed in the presented cases, a possible problem of this intervention is deviating from the optimal stimulation settings for motor symptoms. A limitation for the interpretation of our findings is the small number of patients, the non-blinded setting, and lack of functional or diffusion-weighted neuro-imaging data. For future studies, we suggest functional and diffusion-weighted neuro-imaging to visualize the network associated with apathy at various DBS settings in cases with stimulation-induced apathy, including its resolution by reprogramming.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards All studies in this case study have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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