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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - SHORT COMMUNICATION

Effects of dopaminergic and subthalamic stimulation on musical performance

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Abstract Although subthalamic-deep brain stimulation (STN-DBS) is an efficient treatment for Parkinson's disease (PD), its effects on fine motor functions are not clear. We present the case of a professional violinist with PD treated with STN-DBS. DBS improved musical articulation, intonation and emotional expression and worsened timing relative to a timekeeper (metronome). The same effects were found for dopaminergic treatment. These results suggest that STN-DBS, mimicking the effects of dopaminergic stimulation, improves fine-tuned motor behaviour whilst impairing timing precision.

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Introduction

Subthalamic-deep brain stimulation (STN-DBS) is an efficient symptomatic treatment for motor symptoms in Parkinson's disease (PD) with beneficial effects on rigidity, tremor and bradykinesia (Deuschl et al. 2006). Its effects on more subtle motor functions are less clear. There is evidence that STN-DBS is more effective on proximal motor functions than on finger movements (Wenzelburger

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et al. 2003). However, STN-DBS may improve manipulative finger force control in PD (Nowak et al. 2005), while negatively affecting performance on behavioural motor tasks that are embedded in more complex mental processes or requiring bimanual coordination (Saint-Cyr et al. 2000).

Here, we present the case of a professional musician treated with STN-DBS due to motor fluctuations and dyskinesias. We prospectively documented the effects of both dopaminergic medication (DA) and STN-DBS on musical performance employing a novel standardized musical evaluation paradigm.

Methods

Subject

The 42-year-old, right-handed male professional violinist had a 4-year history of PD before being treated with DBS. The initial PD motor symptom consisted in bradykinesia of his left upper extremity. Treatment with levodopa and the dopamine agonist ropinirole allowed for satisfying symptom control during the first years of the disease. Three years after clinical PD onset, the patient developed dyskinesias, and during the 5th year of disease progression, functionally relevant motor fluctuations were noted. His Unified Parkinson's Disease Rating Scale (UPDRS; Fahn and Elton 1987) dyskinesia-score was 6/13. An acute levodopa challenge revealed a good levodopa response as indicated by an improvement of motor functioning by 58 % on the UPDRS motor-score. The patient was neither demented nor depressed and there were no medical or psychiatric findings on comprehensive pre-operative neuropsychological and psychiatric evaluation (data not reported).

The bilateral, two-staged stereotactic implantation of DBS-electrodes and -stimulator (Kinetra) was performed as previously described (Bejjani et al. 2000) and remained without any complication. The evaluations of musical performance and motor functions were realized 5 months after DBS surgery. PD symptoms at that time were markedly asymmetric with only minimal right-sided motor symptoms. Therefore, only the right STN was stimulated. The stimulation parameters were (right STN): contact 2 (−), case (+), 130 Hz, 60 μs, 2.8 V. The anatomical localization of each of the four contacts of each electrode had been determined postoperatively by MRI, as previously described (Yelnik et al. 2003, 2007; see Online Resource). Contact 2 of the right STN (and contact 7 of the left STN) was found to be localized in the sensorimotor territory of the STN (Fig. 1).

Assessments

After an overnight withdrawal (>12 h) of DA (levodopa 300 mg/day; ropinirole 20 mg/day), the patient was tested in the following treatment conditions: MED-off/DBS-on, MED-off/DBS-off, MED-on/DBS-off, and MED-on/DBS-on. For the MED-on condition, 200/50 mg of levodopa/benserazide was administered. The stimulation parameters were set as reported above. To evaluate global motor functioning, during each of the four treatment conditions, the patient was assessed using the motor part of the UPDRS and by speeded repetitive hand movement tests (see Online Resource).

Musical performance evaluations

The patient was recorded playing on the violin (1) a G major scale across two octaves with metronome (60 beats per minute, 4 notes per beat), (2) three G major scales without metronome, (3) a theme from the E minor violin concerto by Felix Mendelssohn-Bartholdy and (4) the "Méditation" from Jules Massenet's opera Thaïs. Recordings made across the four treatment conditions thus yielded a total of 16 sequences (see Online Resource).

Using Java-based software, 11 violin or viola conservatory students rated the recordings for timing, intonation, articulation and emotionality. In a first block, the four recordings of the metronome-paced G major scale made during the four treatment conditions were presented twice in random order. The participants rated the sequences'

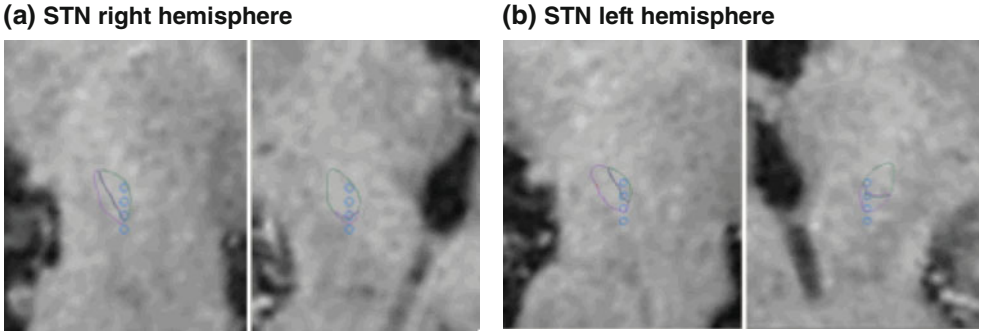

Fig. 1 2D views of electrode contacts within right (**a**) and left (**b**) STN projected on preoperative T1-MRI scans. *Left* side of image: sagittal view, *right* side of image: frontal view. Color coding: *green* sensorimotor territory, *purple* associative territory. Contact coding: *right STN* 0, 1, 2, 3 from *bottom to top*; *left STN* 4, 5, 6, 7 from *bottom to top*

timing precision and intonation on separate continuous scales ranging from −4 to +4. In a second block, the four recordings of the three G major scales played without metronome were presented and rated for timing and intonation as described above. In a third block, the sequence from the Mendelssohn concerto was rated for emotionality (of the melody) and articulation (of the fast triplet figures). In the final block, the Massenet theme was judged for emotionality. Thus, all recordings within each block were presented twice and in random order. The raters were blinded to the medical history and treatment conditions related to the recordings.

Data analysis

For the statistical analysis of therapy effects on musical performance, Bonferroni-corrected Wilcoxon signed-rank tests were used. To test the medication effects, the ratings obtained during MED-on/DBS-off and MED-off/DBS-off conditions were compared, and to probe for DBS effects, ratings for MED-off/DBS-off versus MED-off/DBS-on conditions were compared.

Results

As expected, both therapies improved motor functions as assessed by the UPDRS and alternate hand tapping (Table 1).

The intra-rater correlation for ratings for each of the two presentations of each sequence was good (mean Spearman $\rho = 0.54 \pm 0.20$), providing evidence for the validity of the musical rating paradigm. Both ratings of each sequence were therefore averaged for further analysis. The inter-rater agreement was moderate to high on each of the seven rating dimensions (average Kendall's coefficient of concordance: $w = 0.50 \pm 0.18$; see also Online Resource).

Table 1 Effects of treatment on UPDRS motor-score and hand tapping

	UPDRS (III)	Alternate tapping	
		Right hand (1 min)	Left hand (1 min)
MED-off/DBS-on[a]	21	173	202
MED-off/DBS-off	27	153	116
MED-on/DBS-off	11	229	201
MED-on/DBS-on[a]	5	265	244

[a] Note that only the right STN was stimulated. DBS therefore affects primarily left-sided motor functions

Analysis revealed less accurate timing precision when playing with metronome during the MED-on compared to the MED-off condition. In contrast, intonation in the absence of a metronome, emotionality of the Massenet piece and articulation of the Mendelssohn sequences were perceived as being better during the MED-on condition (Fig. 2, left; Online Resource eTable 1).

In a similar way, metronome-paced timing was found to be worse during the DBS-on condition, whereas intonation without metronome, articulation, and emotional expression proved to be better on-DBS (Fig. 2, right; Online Resource eTable 2).

Discussion

Here, we show that STN-DBS—fully mimicking the effects of dopaminergic stimulation—improves artistic musical expression requiring sophisticated motor control while impairing paced timing accuracy.

Musical performance relies on a complex neuro-biological interplay of motor processes and different perceptual, cognitive, and limbic-emotional functions (Altenmüller 2008). STN-DBS for the treatment of motor symptoms

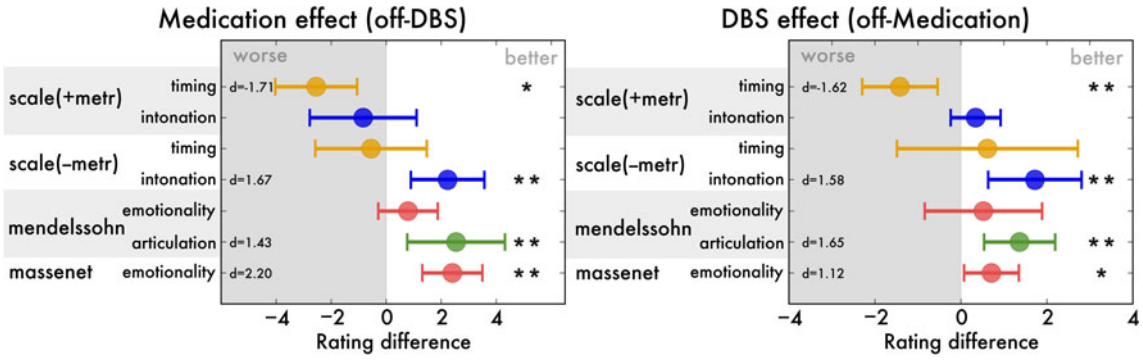

Fig. 2 Effects of DA (*left*) and DBS (*right*). *Scale*(+*metr*), *scale*(−*metr*): recordings with and without metronome. *Bullets* (±SD): mean difference between "on"-relative to ("baseline") "off"-performance; positive differences indicate better "on"-performance. *Asterisks*: $*p < 0.007$, $**p < 0.0014$, $***p < 0.00014$. Effect sizes: Cohen's *d*

targets the so-called motor part of the STN. However, although on postoperative localization of the lead location, the active electrode contact was found to be localized in the sensorimotor territory of the STN, DBS in our patient may also have affected non-motor, cognitive-associative parts of the STN via current spread (Mallet et al. 2007). Further, there is evidence that the three functional modalities, emotional, cognitive, and motor, are not processed in a strictly segregated manner within the STN (Mallet et al. 2007). In keeping with our results, there is evidence for STN-DBS-induced changes of emotional processes and of artistic expression (Witt et al. 2006). It therefore is tempting to speculate that STN-DBS not only improved musical performance via enhanced thalamo-cortical motor outflow but also via modulation of non-motor processes.

On the other hand, both DA and STN-DBS impaired externally paced timing precision. The basal ganglia have long been implicated in timing mechanisms and the dopaminergic modulation of temporal processing is well known (Meck et al. 2008). However, the effect of STN-DBS on timing presented here suggests an implication of the STN in temporal processing. Further support for this claim stems from a recent study demonstrating that STN-DBS specifically affects interval timing (Wojtecki et al. 2011). Yet, as the present study was not designed to delineate potentially underlying mechanisms for treatment effects, we cannot rule out the possibility that the observed impairment of timing precision results from DBS-induced effects on cognitive-associative processes (Witt et al. 2008) or sensory-motor integration (Shivitz et al. 2006) rather than from interference of STN-DBS with timing mechanisms.

STN-DBS and DA induced the same pattern of both improvements and impairment. This is in line with the fact that beneficial STN-DBS motor effects on rigidity, tremor, and bradykinesia resemble those mediated by DA (Deuschl et al. 2006). Although DA and STN-DBS modulate basal ganglia functioning via different mechanisms, both appear to suppress, up to a certain extent, beta (13–35 Hz) oscillatory activity in the loops connecting the cortex and the basal ganglia, which is considered to be one major electrophysiological correlate of parkinsonian motor symptoms (Giannicola et al. 2010). The result of the similar effects of DA and STN-DBS on musical performance is also compatible with previous research indicating that STN-DBS mimics emotional processing enhancement and psychotropic effects of DA (Funkiewiez et al. 2003).

In summary, the findings from this case study, which need to be corroborated by future research, indicate that STN-DBS, as well as DA, may improve fine-tuned, complex expressive motor behaviour as involved in musical performance whilst impairing timing relative to an external pacing stimulus. The study finally suggests musical rating as a novel tool for the evaluation of treatment effects in movement disorders.

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Conflict of interest The authors declare that they have no conflict of interest.

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