Subthalamic nucleus stimulation and somatosensory temporal discrimination in Parkinson’s disease

Antonella Conte, Nicola Modugno, Francesco Lena, Sabrina Dispenza, Barbara Gandolfi, Ennio Iezzi, Giovanni Fabbrini and Alfredo Berardelli

1 Department of Neurological Sciences, ‘Sapienza’, University of Rome, 00185 Rome, Italy
2 Neuromed, Institute, (IRCCS), Pozzilli (IS), Italy

Correspondence to: Prof. Alfredo Berardelli,
Department of Neurological Sciences,
‘Sapienza’, University of Rome,
Viale dell’Università,
30, 00185 Rome, Italy
E-mail: alfredo.berardelli@uniroma1.it

Whereas numerous studies document the effects of dopamine medication and deep brain stimulation on motor function in patients with Parkinson’s disease, few have investigated deep brain stimulation-induced changes in sensory functions. In this study of 13 patients with Parkinson’s disease, we tested the effects of deep brain stimulation on the somatosensory temporal discrimination threshold. To investigate whether deep brain stimulation and dopaminergic medication induce similar changes in somatosensory discrimination, somatosensory temporal discrimination threshold values were acquired under four experimental conditions: (i) medication ON/deep brain stimulation on; (ii) medication ON/deep brain stimulation off; (iii) medication OFF/deep brain stimulation on; and (iv) medication OFF/deep brain stimulation off. Patients also underwent clinical and neuropsychological evaluations during each experimental session. Somatosensory temporal discrimination threshold values obtained in patients were compared with 13 age-matched healthy subjects. Somatosensory temporal discrimination threshold values were significantly higher in patients than in healthy subjects. In patients, somatosensory temporal discrimination threshold values were significantly lower when patients were studied in medication ON than in medication OFF conditions. Somatosensory temporal discrimination threshold values differed significantly between deep brain stimulation on and deep brain stimulation off conditions only when the patients were studied in the medication ON condition and were higher in the deep brain stimulation on/medication ON than in the deep brain stimulation off/medication ON condition. Dopamine but not subthalamic nucleus deep brain stimulation restores the altered somatosensory temporal discrimination in patients with Parkinson’s disease. Deep brain stimulation degrades somatosensory temporal discrimination by modifying central somatosensory processing whereas dopamine restores the interplay between cortical and subcortical structures.

Keywords: subthalamic deep brain stimulation; somatosensory temporal discrimination; Parkinson’s disease

Abbreviations: DBS = deep brain stimulation; MMSE = mini-mental state examination; SEP = somatosensory evoked potential; STD = somatosensory temporal discrimination; UPDRS = Unified Parkinson’s Disease Rating Scale
Introduction

Research over the past decade has extended its interest from the characteristic motor signs to the role of sensory alterations in the pathophysiology of Parkinson’s disease (Demirci et al., 1997; Abbruzese and Berardelli, 2003). Several studies provide objective clinical evidence that patients with Parkinson’s disease have numerous somatosensory deficits, including tracking and targeting movements on the basis of sensory feedback (Klockgether et al., 1995), two-point discrimination (Sathian, 1997), and tactile stimuli location (Schneider et al., 1986). Neurophysiological testing in patients with Parkinson’s disease has also found altered central somatosensory processing and show that somatosensory evoked potential (SEP) abnormalities are partially restored by apomorphine and levodopa intake (Rossini et al., 1993; De Mari et al., 1995). Recent evidence describing altered somatosensory processing in asymptomatic PINK1 mutation carriers (Giertzmühl et al., 2009), suggests that somatosensory deficits could be an endophenotype feature of Parkinson’s disease.

In a neurophysiological study investigating temporal discrimination of tactile, auditory and visual stimuli in patients with Parkinson’s disease, Artieda et al. (1992) found defects in all three tasks and showed that levodopa partially normalized abnormal somatosensory temporal discrimination (STD). STD is a purely sensory process that allows the brain to select relevant sensory inputs for processing information coming from external sources (Burke et al., 1982; Costa et al., 2008). According to Graham’s theory (Graham, 1992), afferent sensory input gating is needed to protect sensory input processing against potential interference from any other subsequent and repetitive stimuli (Braff et al., 1992). Selection of relevant sensory information from concurrent sources involves a time-locked interplay between cortical (pre-supplementary motor area, parietal primary somatosensory cortex, anterior cingulate cortex) and subcortical structures (basal ganglia and cerebellum). Among the several cortical areas activated during STD, the pre-supplementary motor area is thought to play an integrative role providing a link between perception and motor action by receiving inputs from and directing them to basal ganglia (Inase et al., 1999; Hernandez et al., 2002; Pastor et al., 2004).

The most frequently applied surgical procedure for advanced Parkinson’s disease is deep brain stimulation (DBS) of the subthalamic nucleus (Gross and Lozano, 2000; Obeso et al., 2000; Olanow et al., 2000; Deuschl et al., 2006, 2009; Hamani et al., 2008). Despite the numerous clinical and neurophysiological studies investigating the effects of DBS on motor function (Agostino et al., 2008a, b; Lozano and Snyder, 2008; Timmermann et al., 2008), few studies have investigated its effects on sensory functions in Parkinson’s disease. A previous study investigating DBS-induced changes in SEPs in Parkinson’s disease found that DBS reduces the size of the cortical SEP components (Pierantozzi et al., 1999; Priori et al., 2001).

Nothing is known about whether DBS modulates the STD in Parkinson’s disease and whether possible DBS-induced effects on STD resemble changes induced by levodopa.

Material and methods

Subjects

We studied 13 patients with advanced Parkinson’s disease with predominantly akinetic-rigid syndrome and 13 age-matched healthy volunteers. Patients were recruited from the movement disorders outpatients clinic at the Neuromed Institute, ‘Sapienza’ University of Rome. Written informed consent was obtained from all subjects. The experimental procedures were approved by the local institutional review board and were carried out in accordance with the Declaration of Helsinki. The diagnosis of Parkinson’s disease was based on the United Kingdom Parkinson’s Disease Society Brain Bank criteria (Hughes et al., 1992). All patients had DBS electrodes implanted for the treatment of severe motor fluctuations, dyskineties and motor deficits. Table 1 lists patients’ demographic and clinical features. Severity of disease was assessed with the Unified Parkinson’s Disease Rating Scale (UPDRS) and neurocognitive functions were assessed with the mini-mental state examination (MMSE), attentive matrices, Raven’s Progressive Matrices, Corsi’s test, Rey’s test and verbal fluency test. Inclusion criteria were treatment with subthalamic nucleus-DBS for at least 12 months; MMSE > 24; absence of clinical sensory deficits with DBS switched on; and no changes in stimulation or medications within the past 3 months. Patients with Parkinson’s disease were clinically evaluated before each experimental session.

Experimental procedures and assessments

Clinical assessment (UPDRS scores III) and STD threshold procedures took place in four experimental sessions on 2 separate days, at least 2 weeks apart. Patients were tested under four experimental conditions: medication OFF/DBS off, medication OFF/DBS on, medication ON/DBS off, and medication ON/DBS on. Neurocognitive tests took place in three experimental sessions (medication OFF/DBS off, mediation ON/DBS off and medication ON/DBS on) on two separate days.
Somatosensory evoked potential recording

To evaluate the effects of DBS on central somatosensory pathways, in 6 of the 13 patients (three bilateral DBS, three unilateral DBS with right subthalamic nucleus implants) upper-limb SEPs were recorded under the conditions: medication ON/DBS on and medication ON/DBS off. SEPs were recorded bilaterally from scalp Ag–AgCl surface electrodes placed 2 cm posterior from C3 or C4 (parietal component) referred to Fz according to the 10–20 electrode system for EEG placement. Electrical stimulation was delivered to the median nerve at the wrist at 3 Hz with a pulse width of 0.2 ms. The intensity of stimulation was fixed at the motor threshold and was checked throughout the experiment by monitoring the evoked EMG response in the abductor pollicis brevis muscle. SEPs were recorded in the medication ON/DBS off condition using a Synergy recorder (band-pass of 3 Hz–1 kHz). All data were collected at a sampling rate of 5 kHz for a 200 ms epoch beginning 20 ms before each stimulus. To reduce DBS artefacts on SEP recordings, a further SEP recording was then acquired using a band-pass of 3–100 Hz and this bandwidth was maintained in DBS on and DBS off conditions. A total of 500 responses were averaged in each session. SEP variables (N20-P25 and P25-N33) amplitude were measured peak-to-peak and expressed in microvolts.

Statistical analysis

In the two Parkinson’s disease groups, STD threshold values were analysed using a between-group repeated-measures ANOVA with factors ‘body region’ (hand, neck and eye), ‘body side’ (left and right), ‘medication’ (medication ON versus medication OFF) and ‘DBS’ (neurostimulators on and neurostimulators off) as main factors. A between-group repeated-measures ANOVA was also used to compare STD threshold values in the three body regions in patients (medication OFF/DBS off and medication ON/DBS on conditions) with those obtained in the 13 age-matched healthy subjects. A further repeated-measures ANOVA with factors ‘body region’ (hand, neck and eye), ‘body side’ (left and right), ‘medication’ (medication ON versus medication OFF) and ‘DBS’ (neurostimulators on versus neurostimulators off) as main factors was also used to test the STD threshold values separately in the group of nine patients implanted bilaterally. Parietal SEP component amplitudes (N20-P25 and P25-N33) were also
analysed using a between-group repeated measures ANOVA with factors ‘body side’ (left and right) and ‘DBS’ (neurostimulators on and neurostimulators off) as main factors. Tukey’s Honest Significant Difference test was used for post hoc analysis. Friedman’s repeated-measures ANOVA was used to test changes in the UPDRS scores and neurocognitive scores. Wilcoxon’s test was used for post hoc analysis. Spearman’s correlation coefficient was calculated to correlate individual scores in hand, neck and face with their respective STD threshold values. Pearson’s correlation coefficient was also calculated to assess the correlation between changes in SEP amplitudes and changes in STD threshold values in medication ON/DBS on and medication ON/DBS off conditions. P < 0.05 were considered to indicate statistical significance. For statistical analysis we used Statistical Package for the Social Sciences (SPSS) software.

Results

DBS and dopaminergic therapy-induced changes in UPDRS scores and neurocognitive tests

Friedman’s repeated-measures ANOVA for UPDRS scores showed that UPDRS scores changed significantly across the four experimental sessions (χ² = 35.67; P = 0.0008). Wilcoxon’s test used for post hoc analysis showed that UPDRS scores decreased significantly when patients were tested with medication ON (P < 0.05) and DBS on (P < 0.05) (Table 1).

Repeated-measures ANOVA for MMSE, attentive matrices, Raven’s Progressive Matrices, Corsi’s test, Rey’s test and verbal fluency test showed no significant changes across the experimental sessions. Nor were significant changes found for the attentional battery: attentive matrices (medication ON/DBS on: 46.22 ± 2.90; medication ON/DBS off: 44.32 ± 2.60; medication OFF/DBS off: 43.05 ± 2.40; P = 0.1) and Raven’s Progressive Matrices (medication ON/DBS on: 29.36 ± 0.70; medication ON/DBS off: 27.50 ± 1.30; medication OFF/DBS off: 28.80 ± 1.0, P = 0.14).

Among the various cognitive tests, MMSE only tended to change, even though not significantly across the experimental conditions (P = 0.058). Post hoc analysis showed that MMSE scores were lower though not significantly lower when the patients were tested with medication OFF than with medication ON (P = 0.06) whereas no changes were found between DBS on and DBS off conditions (P > 0.05). The lower MMSE scores in the medication OFF condition depended on lower scores in the sub-items verbal fluency and delayed recall.

Comparison of STD threshold values between patients with Parkinson’s disease and age-matched healthy subjects

Between-group repeated-measures ANOVA between patients and healthy subjects showed a significant effect of factor ‘group’ [F(2, 26) = 5.44, P = 0.00005] and factor ‘body region’ [F(2, 4) = 5.44, P = 0.006] with a non-significant interaction [F(4, 72) = 1.43, P = 0.23]. Post hoc analysis showed significantly higher STD threshold values in patients than in healthy subjects with the highest STD threshold values in the ‘hand’ (medication ON/DBS off versus healthy subjects: P = 0.006; medication OFF/DBS off versus healthy subjects: P = 0.00004) (Fig. 1).

DBS and dopaminergic therapy-induced changes in the STD threshold values

Between-group repeated-measures ANOVA for STD threshold values in parkinsonian patients receiving unilateral- and bilateral-DBS showed a significant effect of factor ‘body region’ [F(1, 11) = 4.04, P = 0.03], a significant effect of factor ‘medication’ [F(1, 11) = 8.91, P = 0.01], a significant effect of factor ‘DBS’ [F(1, 11) = 8.73, P = 0.01] but a non-significant effect of factors ‘body side’ [F(1, 11) = 0.15, P = 0.70], factor ‘group’ [F(1, 11) = 1.90, P = 0.19] and a non-significant interaction of the main factors (P > 0.05). Post hoc analysis for STD threshold values showed that the significant effect of factor ‘body region’ depended on the higher STD threshold value in the ‘hand’ than in the ‘eye’ (P = 0.05) and ‘neck’ (P = 0.04). Post hoc analysis showed significantly lower STD threshold values when patients were studied in medication on than in medication off conditions (medication ON/DBS on versus medication OFF/DBS on: P = 0.04; medication ON/DBS off versus medication OFF/DBS off: P = 0.01) (Fig. 2). Post hoc analysis showed that STD threshold values differed significantly between DBS on and DBS off conditions only when the patients were studied in the medication ON condition, STD threshold values were higher in the DBS on/medication-ON than in the DBS off/medication ON condition (P = 0.006), whereas in both medication OFF conditions STD threshold values remained unchanged (P = 0.11). Repeated-measures ANOVA testing the STD threshold values separately in the group of nine patients with subthalamic nucleus-DBS implanted bilaterally confirmed the
significant effect of factor ‘body region’ [$F_{(2-16)} = 6.66, P = 0.007$], a significant effect of factor ‘medication’ [$F_{(1-8)} = 11.53, P = 0.009$], a significant effect of factor ‘DBS’ [$F_{(1-8)} = 25.33, P = 0.001$] but a non-significant effect of factors ‘body side’ [$F_{(1-8)} = 0.05, P = 0.81$], and a non-significant interaction of the main factors ($P > 0.05$).

DBS-induced effects on parietal SEP component amplitudes (N20-P25 and P25-N33)

Between-group repeated-measures ANOVA for upper-limb SEP parietal component amplitudes in patients receiving unilateral and bilateral DBS tested in the medication ON condition showed a significant effect of factor ‘DBS’ (DBS on and off) [N20-P25: $F_{(1-4)} = 7.72, P = 0.04$; right DBS off versus right DBS on: $3.61 \pm 0.5 \mu V$ versus $1.73 \pm 0.4 \mu V$; left DBS off versus left DBS on: $3.00 \pm 0.5 \mu V$ versus $1.62 \pm 0.5 \mu V$; P25-N33: $F_{(1-4)} = 9.79$, $P = 0.03$; right DBS off versus right DBS on: $2.68 \pm 0.2 \mu V$ versus $0.9 \pm 0.2 \mu V$; left DBS off versus left DBS on: $1.9 \pm 0.3 \mu V$ versus $0.60 \pm 0.1 \mu V$] but a non-significant effect of factors ‘body side’ [N20-P25: $F_{(1-4)} = 2.10, P = 0.22$; P25-N33: $F_{(1-4)} = 5.10, P = 0.09$] and factor ‘group’ [N20-P25: $F_{(1-4)} = 0.30, P = 0.60$; P25-N33: $F_{(1-4)} = 1.15, P = 0.34$] and non-significant interaction of the main factors ($P > 0.05$).

Correlations between UPDRS scores and STD threshold values

Spearman’s correlation coefficient showed no significant correlations between the individual UPDRS scores for the ‘hand’, ‘neck’ and ‘face’ with their respective STD threshold values in all the experimental conditions ($P > 0.05$).

Correlations between changes in SEP component amplitudes and changes in STD threshold values

Pearson’s correlation coefficient showed no significant correlations between the changes in SEP component amplitudes and changes in STD threshold values in medication ON/DBS on and medication ON/DBS off conditions ($P > 0.05$).

Discussion

In this study we first confirm, by measuring STD threshold values in patients with Parkinson’s disease receiving subthalamic nucleus-DBS and healthy subjects, abnormal STD in Parkinson’s disease (Artieda et al., 1992). The STD threshold deficits differed in the three body regions tested on both body sides, values being highest on the ‘hand’ region. The new finding in this study is that when we switched DBS on while patients were ON dopaminergic therapy, STD threshold values worsened but when we switched DBS on while patients were OFF dopaminergic therapy, STD threshold values remained unchanged. STD threshold values were significantly better in patients ON than OFF medication. The distinctive finding in our study is therefore that in patients with Parkinson’s disease, DBS worsens (medication ON) or leaves the STD threshold unchanged (medication OFF) whereas levodopa improves it.

Owing to our complex experimental design, to ensure reliable data on levodopa and DBS-induced changes in STD threshold in patients with Parkinson’s disease, we took into account several potential confounding factors. To exclude a learning effect in improving STD threshold values and neurocognitive tests due to the ‘multi-session’ study design we randomized all the patients for the medication/DBS conditions and also for body regions and body sides. We also excluded the possibility that altered STD thresholds depended on possible cognitive and attentional deficits. All eligible patients underwent a complete neurocognitive evaluation and we included only those without significant deficits. To ensure that patients’ overall neurocognitive condition had no influence on the altered STD thresholds all patients underwent a neurocognitive evaluation in medication ON/DBS on, medication ON/DBS off and medication OFF conditions. To disclose a potential response bias related to attention, we checked attentional levels throughout and our STD threshold testing procedure explicitly included trials consisting of a single stimulus every 10 pairs (Scontrini et al., 2009). By testing patients at least 1 h after DBS was switched off or on and at least 1 h after oral intake of their usual dopaminergic therapy, we ensured that our findings were unaffected by possible transient unstable changes in dopaminergic neurotransmission (Priori et al., 2001). Finally, the significant improvement in UPDRS scores confirmed that dopaminergic therapy and DBS effectively improved our patients’ clinical conditions.
In contrast to the clinical motor improvement described by others (Deuschl et al., 2006; Agostino et al., 2008a, b; Lozano and Snyder, 2008; Timmermann et al., 2008)—and also confirmed by the clinical motor improvement our patients had after DBS—our experiments showed that DBS failed to improve STD. The finding that STD threshold values tested in patients ON medication increase when DBS is turned on suggests that DBS degrades STD processing. Because DBS can induce cognitive changes (Herzog et al., 2003; Morrison et al., 2004; Videnovic and Metman, 2008) cognitive dysfunction might in theory explain why subthalamic nucleus-DBS degraded STD thresholds. In our study, however, when we studied patients under dopaminergic therapy their neurocognitive assessments remained unchanged regardless of whether we switched DBS on or off. Because our patients’ performance at the Raven’s progressive matrices, attentive matrices and verbal fluency tests—tests specifically investigating frontal circuits involved in attention demanding tasks—were unchanged in patients ON medication when DBS was turned on, we consider it unlikely that the DBS-induced worsening in STD threshold reflects subthalamic nucleus-DBS-induced altered attention-demanding functions in frontal circuitry. A possible alternative reason why DBS degraded STD thresholds is that local electrical fields generated by subthalamic nucleus-DBS interfered with the nearby somatosensory pathways reducing the signal-to-noise ratio. Concordantly, confirming a previous observation (Piori et al., 2001), in a subgroup of patients when we recorded SEPs in both experimental conditions (DBS on and DBS off), we found that parietal SEP components recorded with DBS on had reduced amplitudes. Because we used similar variables for recording SEPs before and after DBS we conjecture that DBS decreased SEP amplitudes by interfering with subcortical somatosensory pathways. Our finding that STD thresholds changed to a similar extent on both body sides in patients with unilateral as well as those with bilateral implants makes it unlikely that subthalamic nucleus-DBS electrodes interfere with the nearby somatosensory pathways. The hypothesis we favour is that the DBS-induced chronic subthalamic nucleus inactivation actively elicits changes in central somatosensory processing, as the SEP amplitude decrease reported in previous studies (Pinter, 1999; Piori et al., 2001) and confirmed here, show. How it does so remains open to question, possibly by altering the interplay between cortical (pre-supplementary motor area and somatosensory primary areas) and subcortical (thalamus, striatum, subthalamic nucleus and cerebellum) neural circuits underlying SDT. When we tested patients OFF dopaminergic medication and STD threshold values were severely altered, DBS induced negligible effects.

Our finding that STD threshold improved significantly when patients were receiving medication confirms and extends findings reported by Artieda et al. (1992), who tested STD thresholds in a single body region (‘hand’), thus suggesting that dopaminergic therapy is important in modulating STD. That dopaminergic therapy improves STD thresholds is in line with experimental evidence in animals and in humans, showing that dopamine plays a role in attentional processes (Nieoullon, 2002; Nieoullon and Coquerel, 2003; Remy and Samson, 2003) and that dopamine improves performance in attention-demanding tasks and cognitive executive alterations in patients with Parkinson’s disease (Pagonabarraga et al., 2007; Moustafa et al., 2008; Rowe et al., 2008; Suppa et al., 2010). Dopaminergic therapy could therefore improve STD by restoring cognitive executive alterations and attentional dysfunctions. Because neurocognitive test findings, (including frontal battery assessment) remained practically unchanged during the various experimental conditions, we consider it unlikely that the improved STD threshold performance during medication ON conditions reflected a global dopaminergic-induced improvement in cognitive performance. Hence dopamine might directly modulate the neural circuits for STD processes, thus restoring the interplay between the interconnected areas of the cortico-subcortico-cortical loop underlying STD. A direct dopamine action on cortical neural circuits receives support from functional imaging studies in healthy subjects as well as from studies in patients with ischaemic lesions or chronic neurological diseases, suggesting that STD is controlled by cortical areas including primary sensory areas, pre-supplementary motor area, anterior cingulate cortex and cerebellum (Lacruz et al., 1991, Harrington et al., 1998; Pastor et al., 2004). A functional magnetic resonance imaging (fMRI) study comparing STD with spatial discrimination tasks in healthy subjects has shown that a STD task preferentially activates the pre-supplementary motor area (Pastor et al., 2004). The pre-supplementary motor area, because of its extensive connections with most prefrontal areas, not only receives basal ganglia inputs via the parvocellular ventral anterior nucleus and nucleus Ventralis Lateralis pars caudalis, rostral division but also cerebellar input via the nucleus Ventralis Lateralis pars caudalis, rostral division and medialis dorsalis pars paralamellars in the thalamus, and sends direct inputs to the striatum and subthalamic nucleus (Inase et al., 1996, 1999).

Supporting a basal ganglia role in STD is the observation that the STD threshold is altered in other neurological disorders that affect basal ganglia such as dystonia (Tinazzi et al., 2004; Fiorio et al., 2008) and multiple system atrophy (Lyoo et al., 2007). A recent study conducted in our laboratory, in patients with various focal dystonias (Scontrini et al., 2009) found STD threshold deficits in affected and unaffected body parts. Similarly to previous findings in patients with dystonia, we also found, in our patients with Parkinson’s disease, STD threshold alterations in the affected and unaffected body side. STD threshold alterations could therefore be a non-specific feature typical of basal ganglia disorders. The observation that STD threshold is altered in patients with Parkinson’s disease as well as in various focal dystonias focuses on the basal ganglia as the neural structure playing a role, even though non-specific, in STD. Accordingly, in a recent study using voxel-based morphometry in patients with primary torsion dystonia and unaffected relatives (Bradley et al., 2009), in subjects with altered STD threshold, MRI scans disclosed a putaminal enlargement. Whether the basal ganglia are per se the main neural structure responsible for this alteration or whether basal ganglia dysfunction could modify the interplay with the cortical areas responsible for encoding temporal processing is unclear. Whatever the explanation, our observation that when patients were ON medication, STD thresholds improved when DBS was turned off and worsened when DBS was turned on argues strongly for a prominent role of basal ganglia in STD.
In conclusion, in patients with Parkinson’s disease implanted with unilateral and bilateral electrodes for subthalamic nucleus-stimulation, DBS degrades, whereas dopaminergic therapy improves the STD threshold. DBS degrades STD by interfering with central somatosensory processing whereas dopamine mainly modulates neural activity in the complex cortico-subcortico-cortical circuit involved in STD processing, probably restoring the interplay between cortical and subcortical neural structures. The DBS-induced STD deficit suggests that although subthalamic nucleus-DBS significantly improves parkinsonian patients’ motor function it interferes with their sensory functions. The interference with central sensory processing should be included among the adverse events reported after subthalamic nucleus-DBS (Videnovic and Metman, 2008).

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References


