doi:10.1093/brain/awt151 Brain 2013: 136; 2109–2119 | 2109

BRAIN
A JOURNAL OF NEUROLOGY

Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial

Karsten Witt,[1] Oliver Granert,[1] Christine Daniels,[1] Jens Volkmann,[1,*] Daniela Falk,[2] Thilo van Eimeren[1] and Günther Deuschl[1]

1 Department of Neurology, Kiel University, Kiel, Germany
2 Department of Neurosurgery, Kiel University, Kiel, Germany

*Present address: Department of Neurology, Würzburg University, Würzburg, Germany

Correspondence to: Karsten Witt, MD,
Department of Neurology,
University Medical Centre,
Campus Kiel,
Christian-Albrechts University, Arnold-Heller-Strasse 3,
Haus 41,
24105 Kiel,
Germany
E-mail: k.witt@neurologie.uni-kiel.de

Deep brain stimulation of the subthalamic nucleus improves motor functions in patients suffering from advanced Parkinson's disease but in some patients, it is also associated with a mild decline in cognitive functioning about one standard deviation from the preoperative state. We assessed the impact of the cortical lead entry point, the subcortical electrode path and the position of the active electrode contacts on neuropsychological changes after subthalamic nucleus–deep brain stimulation compared to a control group of patients receiving best medical treatment. Sixty-eight patients with advanced Parkinson's disease were randomly assigned to have subthalamic nucleus–deep brain stimulation or best medical treatment for Parkinson's disease. All patients had a blinded standardized neuropsychological exam (Mattis Dementia Rating scale, backward digit span, verbal fluency and Stroop task performance) at baseline and after 6 months of treatment. Patients with subthalamic nucleus–deep brain stimulation were defined as impaired according to a mild decline of one or more standard deviations compared to patients in the best medical treatment group. The cortical entry point of the electrodes, the electrode trajectories and the position of the active electrode contact were transferred into a normalized brain volume by an automated, non-linear registration algorithm to allow accurate statistical group analysis using pre- and postoperative magnetic resonance imaging data. Data of 31 patients of the subthalamic nucleus–deep brain stimulation group and 31 patients of the best medical treatment group were analysed. The subthalamic nucleus–deep brain stimulation group showed impaired semantic fluency compared with the best medical treatment group 6 months after surgery ($P = 0.02$). Electrode trajectories intersecting with caudate nuclei increased the risk of a decline in global cognition and working memory performance. Statistically, for every 0.1 ml overlap with a caudate nucleus, the odds for a decline >1 standard deviation increased by a factor of 37.4 (odds ratio, confidence interval 2.1–371.8) for the Mattis Dementia Rating Scale and by a factor of 8.8 (odds ratio, confidence interval 1.0–70.9) for the backward digit span task. Patients with subthalamic nucleus–deep brain stimulation who declined in semantic verbal fluency, Stroop task and the backward digit span

Received February 25, 2013. Revised April 8, 2013. Accepted April 22, 2013

task performance showed a position of the active electrode outside the volume built by the active electrodes of stable performers. Passage of the chronic stimulation lead through the head of the caudate increases the risk of global cognitive decline and working memory performance after subthalamic nucleus–deep brain stimulation in Parkinson's disease. Therefore the electrode path should be planned outside the caudate nuclei, whenever possible. This study also stresses the importance of precise positioning of the active stimulating contact within the subthalamic volume to avoid adverse effects on semantic verbal fluency and response inhibition.

Keywords: deep brain stimulation; Parkinson's disease; cognition; lead trajectory; electrode placement; neuropsychological complications

Abbreviations: DBS = deep brain stimulation; MDRS = Mattis Dementia Rating Scale; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Deep brain stimulation (DBS) of the nucleus subthalamicus (STN) improves motor function and quality of life in patients with advanced Parkinson disease (Deuschl *et al*., 2006; Campbell *et al*., 2008). Even though surgical complications are rare, neuropsychological and neurobehavioural sequelae have been reported in as many as 15–21% of patients (Parsons *et al*., 2006; Volkmann *et al*., 2010). It is important to note that the true prevalence of cognitive and behavioural changes is difficult to estimate from open-label studies, due to a possible observer and reporting bias, the inability to distinguish treatment from disease-related changes and the variable definition of what is deemed clinically relevant. We have previously reported neuropsychological and psychiatric outcomes after STN-DBS compared with a medically managed control group in a prospective, randomized trial (Witt *et al*., 2008). Six months after STN-DBS, we found significant group changes in verbal fluency and also Stroop Test performance indicating declines in specific cognitive domains resembling a subcortical type mild cognitive impairment, but no change in global cognitive performance (Witt *et al*., 2008). The observed neuropsychological sequelae are likely caused by several independent factors. First, there is a patient inherent risk profile including older age, impaired attention, higher anti-parkinsonian medication, higher scores on axial motor symptoms and a lower L-DOPA response before surgery (Daniels *et al*., 2010; Smeding *et al*., 2011). This profile characterizes patients in a more advanced stage, in which cognitive decline is accelerated by the natural course of disease (Kempster *et al*., 2010) and the patient may be more vulnerable to cognitive adverse effects of the procedure. However, patient-related risk factors explain only 23% of variance in a multivariate regression analysis of postoperative cognitive decline (Daniels *et al*., 2010). Secondly, because STN-DBS is invariably linked to marked postoperative medication reductions, some of the neurobehavioural and cognitive sequelae may reflect drug withdrawal phenomena rather than surgical effects (Thobois *et al*., 2010). Third, studies investigating the cognitive and behavioural impact of subthalamic high-frequency stimulation by directly comparing the on–off effects demonstrate little change except for subtle measures of impulsivity (Frank *et al*., 2007; Ballanger *et al*., 2009; Halbig *et al*., 2009) and response inhibition (Witt *et al*., 2004; van den Wildenberg *et al*., 2006), which could contribute to some of the chronic effects observed after STN-DBS. But most studies comparing the on with an off stimulation state did not find significant changes in verbal fluency performance (Jahanshahi *et al*., 2000; Pillon *et al*., 2000; Morrison *et al*., 2004; Witt *et al*., 2004; Okun *et al*., 2009), which represents the most solid postoperative neuropsychological change. A recent randomized trial used a deferred stimulation design to compare stimulation-induced changes in 101 patients receiving effective neurostimulation after device implantation and a control group ($n = 35$) not being stimulated for 3 months (Okun *et al*., 2012). Both groups had a comparable decline in verbal fluency from the pre-surgical performance at 3 months (Okun *et al*., 2012) indicating an implant rather than a stimulation-related cause.

A typical DBS lead trajectory with a precoronal entry point passes through the prefrontal cortex, the subcortical white matter, the anterior limb of the internal capsule, and the basal ganglia. These structures are all involved in cognitive or emotional functions and the STN itself subdivides into a motor but also a limbic and an associative part (Frank *et al*., 2007; Parent and Hazrati, 1995). To date, the relationship between lead trajectories, electrode location and neuropsychological changes has received little attention (Volkmann, 2012). Therefore, in this study we analysed our patients within a randomized controlled study comparing STN-DBS with best medical treatment to assess the impact of the lead trajectory and placement of the active stimulation contacts on those neuropsychological changes only observed in the DBS group.

Patients and methods

We prospectively recruited patients from a randomized trail (ClinicalTrails.gov, number NCT00196911) (Deuschl *et al*., 2006; Witt *et al*., 2008) and analysed retrospectively the neuropsychological and MRI data of a single centre (Kiel, Germany). The screening and randomization procedure have been reported elsewhere (Deuschl *et al*., 2006). Inclusion criteria were the clinical diagnosis of idiopathic Parkinson's disease (Hughes *et al*., 1992) for at least 5 years, age <75 years, and parkinsonian motor symptoms or dyskinesias that limited the patient's daily activities despite optimum medical therapy. Exclusion criteria were dementia [Mattis Dementia Rating Scale (MDRS), sum score $\leqslant 130$] (Mattis, 1988), a major psychiatric illness or surgical contraindications. The study protocol was approved by the ethics

committee, and all patients gave written informed consent. The patients were enrolled in pairs; one patient was randomly assigned to receive DBS surgery within 6 weeks of enrolment, the other patient to receive best medical treatment. The patients assigned to DBS underwent bilateral stereotactic surgery under local anaesthesia. The STN was targeted by means of stereotactic MRI and microelectrode recording. The anatomical target coordinates were confirmed to be 0 to 3 mm behind the midcommisural point, 4 to 6 mm below the intercomisural line, and 11 to 13 mm lateral to the midplane of the third ventricle. One to five microelectrodes were inserted through guide tubes (FC1018, FHC Inc). These guide tubes with a diameter of 1 mm (volume of 7.9 mm^3 per cm tube) were placed 3 cm before the anatomical target and microelectrodes (REF 22670, FHC Inc.) were pushed forward. Electrophysiological recordings started 4 mm before the anatomical target. The final implantation point was the position at which the most pronounced effect on rigidity and other symptoms of Parkinson's disease was obtained at the lowest stimulation intensity and with the largest safety margin (as determined by the difference in the intensity of simulation between the clinical effect and the occurrence of unwanted effects during intraoperative testing) (Deuschl *et al*., 2006). The permanent electrode (model 3389 DBS, Medtronic) was implanted and connected to the pulse generator (Kinetra, Medtronic). Electrode position was controlled after the stereotactic surgery by MRI. The postoperative standard pulse setting was 60 µs at 130 Hz, with voltage and antiparkinsonian medication individually adjusted. L-DOPA equivalence dosage was calculated to compare the amount of medication between patients (Deuschl *et al*., 2006).

Neurological and neuropsychological assessments were performed ON medication at baseline and at 6 months on neurostimulation and ON medication in the STN-DBS group and ON medication in the best medical treatment group. Neurological examination included the Unified Parkinson's Disease Rating Scale (UPDRS). Neuropsychological evaluation included the MDRS (Mattis, 1988). The backward digit span task was used according to the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1981). Verbal fluency was administrated as a letter and a semantic fluency task (Spreen and Strauss, 1991). In the letter fluency task subjects produce as many words as possible beginning with a particular letter in a period of 60 s. The test was applied twice on each visit using different letters ('R' and 'K' or 'P' and 'F'). Subjects should avoid proper names and the same word with a different suffix. In the semantic fluency task subjects generate as many words as possible belonging to a particular category ('male first names' and 'plants' or 'female first names' and 'animals') in a period of 60 s, again the task was administrated twice a visit. The total number of correct words produced was recorded. Response inhibition was assessed with a shortened version of the Stroop test (Spreen and Strauss, 1991) that consisted of the interference trail containing 36 items including the naming of the ink colour of the written words printed in incongruent colours. The number of errors and the time needed to complete the test were scored separately for each trial. Parallel versions of each test were administered in a counterbalanced order at the baseline and follow-up visits.

Statistics

Clinical and neuropsychological baseline parameters were compared using parametric *t*-test statistics and non-parametric Mann-Whitney tests when appropriate (lack of normal distribution of data). The differences in scores between baseline and the 6-month follow-up were calculated and analysed for each neuropsychological test result comparing patients with DBS and best medical treatment. For each test we split the DBS patients into two groups. The first group included STN-DBS patients who declined in a specific cognitive test ($DEC_{<test>}$), where a decline was defined as a delta of more than the mean plus one standard deviation (SD) of the corresponding change observed in the best medical treatment group. Such a change was deemed to reflect a relevant DBS-related change over disease and test-related variability between the two testing time points, since previous studies have shown mild cognitive decline after STN-DBS (Parsons *et al*., 2006). All other patients were classified as stable performers or improvers in the specific test ($STA_{<test>}$). This classification scheme was applied to the imaging data and also served to segregate STN-DBS patients for a binary logistic regression analysis. Binary logistic regression analysis was used to evaluate the proportion of the variance of the change score of a specific cognitive task that could be explained by previously defined risk factors for a cognitive decline (age, L-DOPA equivalence dosage at baseline, UPDRS axial score) (Daniels *et al*., 2010) and also the volume of deep grey nuclei (caudate nucleus, pallidum and thalamus) affected by the electrode path. This 'penetration' volume of the caudate nucleus, thalamus and pallidum was correlated with the change score for each neuropsychological test. We choose a one sided *t*-test to compare the lesioned volume of the caudate nucleus between patients who declined and stable performers, because it is well known that lesions of the caudate nucleus are associated with cognitive impairments (Mendez *et al*., 1989; Looi *et al*., 2009). To analyse the impact of the cortical lead entry point on neuropsychological changes, we created a 3D map on the spatially normalized cortex bounded by the electrode trajectories of cognitively stable patients (STA group) on the cortical entry level of each hemisphere. A permutation test (permutation of group labels) was used to test if the proportion from inclusion and exclusion in the DEC (patients with decline) group was significantly different from a random assignment. The impact of the subcortical position of the active electrode on neuropsychological changes was analysed in a similar way; the active electrode position of all stable performers built a volume for the right and left stimulation area. Again a permutation test was performed to analyse if the active electrodes of the cognitively declining group significantly overlap with the stimulation volume of the group of stable performers. A permutation analysis was preferred because of its higher discriminability compared with Wilcoxon rank-sum test and Fisher's exact test (Mukherjee *et al*., 2003; Golland *et al*., 2005).

Magnetic resonance image acquisition and data analysis

Each patient was scanned twice (immediately before the electrode implantation and 1–2 days after surgery). T_1-weighted images were acquired with a 1.5 T Siemens CM VA0 CMS MRI scanner (repetition time = 11.4 ms; echo time = 4.4 ms; flip angle = 8°; field of view = 25 cm × 25 cm; 256 × 256 matrix × 160 slices of 1 mm thickness). Image data preprocessing (normalization) and analyses were done with the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) on Matlab 7.7.0 (MathWorks) and with some additional in-house software components developed to determine lead and contact positions and masks.

To determine lead trajectory and contact positions in standardized and subject independent coordinate space, images from the preoperative stage were co-registered to the postoperative image using an affine transformation (Suetens and Marchal, 1995) and then normalized to the Montreal Neurological Institute (MNI) coordinate space that was defined at the McConnell Brain Imaging Centre, McGill University. The normalization parameters were determined with the

SPM segmentation function from the preoperative images (without electrode artefacts). Normalization of the postoperative images were achieved by concatenation of the affine (co-registration) and non-linear normalization transformations. We used this normalization procedure, because the preoperative images have no electrode image artefacts and therefore provide a better non-linear normalization than the postoperative images.

To locate the lead trajectory in normalized MNI space, we manually placed spatial control points (between 5 and 8 points along the midline of the image artefact for each electrode) within the postoperative images. We then performed a 3D least square optimization procedure to find the centre of the electrode in the individual patient. The MRI-T_1 intensity profile was extracted along this optimized lead trajectory. The area of the contact electrodes is characterized by a steep dip in T_1 signal, which can be used to manually position the four contacts according to the known contact distances from the data sheet of the implanted electrodes.

Gaussian weighed masks with a standard deviation of 1 (~2.35 mm full-width at half-maximum) in the two dimensions orthogonal to the electrode trajectory were produced. The Gaussian weight function should compensate for uncertainties in position. The individual trajectory masks and contact positions were then normalized to MNI space using the transformation parameters determined in the co-registration and segmentation step described previously. To obtain volume measures for the lesions, we approximated the volume influenced by the electrode trajectory by a cylinder with a radius of 2 mm. This will possibly overestimate the lesioned volume, but considers the limited resolution of our magnetic resonance images and the electronic atlas.

Evaluation of cortical entry points

To determine the cortical entry points of the electrodes, we generated a 3D triangle mesh from the T_1-weighted single subject template delivered with the SPM8 software by processing this template with FSL bet2 program (http://www.fmrib.ox.ac.uk/fsl/bet2). This program produced a binary brain mask that was smoothed with a Gaussian filter (full-width at half-maximum = 5 mm) and finally processed by a 3D contouring algorithm (Lorensen and Harvey, 1987) to generate a 'flattened' triangle mesh for the surface of the cortex in MNI space. The intersection point of this cortical surface model and the non-linear normalized electrode trajectories were calculated and used as 3D positions of the cortical entry points. Finally, the spatial distribution of these positions were compared between the cognitively declining and cognitively stable groups by performing the permutation test as described above. In addition, we analysed if the electrode trajectories pass through the dorsolateral prefrontal cortex as defined by the region 'AAL Frontal_Mid' and Broadmann areas 9 and 46 based on the electronic brain atlases (Tzourio-Mazoyer *et al.*, 2002) and Brodmann maps based on works from the Van Essen lab and Krish Singh and delivered a template image with MRIcro Software from Chris Rorden (http://www.mccauslandcenter.sc.edu/mricro/mricro/lesion.html#brod).

Exploration of normalized masks

Given the interindividual variability of the electrode trajectories, a voxel-wise statistical analysis of the trajectory masks is not conducive. Therefore, we calculated separate mean trajectory mask volumes for the cognitively declining and cognitively stable groups in each neuropsychological test by adding up individual trajectory masks and dividing by corresponding group sizes. Finally, both mean masks were subtracted (declining – stable), to visualize group differences in electrode trajectories. Voxels with values >0 can be interpreted as critical for the performance in the neuropsychological test, whereas voxels with values <0 can be interpreted as 'safe'.

Evaluation of active contact positions

Similar to the cortical entry point analysis, the impact of the electrode position on neuropsychological changes were analysed by calculating the collective volume (convex hull) of the spatially normalized, active electrode contact positions over all stable patients. We then checked the contact positions of the decline group for inclusion in this possibly save volume determined from the group of improvers. These tests were performed separately for each hemisphere. Finally, we used a permutation test to statistically access the differences in active contact positions between the two groups (see above).

Results

From 68 patients included into this study, three patients of the STN-DBS group (and their pairwise-matched best medical treatment control patients) were excluded because of incomplete imaging data (motion artefacts, incomplete scans). Clinical baseline characteristics and neuropsychological and motor outcome measures were not significantly different between the drop-outs and the enrolled patients completing the study. The final study sample consisted of 62 patients with Parkinson's disease, 31 STN-DBS (30 bilateral STN, one right STN) and 31 patients with Parkinson's disease undergoing best medical treatment. Baseline characteristics (age, gender, neurological and neuropsychological data) did not significantly differ between both groups (Table 1). UPDRS III score significantly improved after STN-DBS as shown in Table 2. Change score of the semantic verbal fluency task showed a significant reduction in the STN-DBS group compared to the best medical treatment group (Table 2). The number of microelectrodes used in the different patients is shown in Table 1. We found no significant correlations between the number of microelectrodes implanted and the change in neuropsychological performance (baseline test minus follow-up test, Spearman correlation $P > 0.2$ for all comparisons).

Analysis of the electrode trajectory

The cortical lead entry point showed a high interindividual variability. However, permutation analysis revealed that patients who decline in Stroop test performance (time criterion) had a cortical entry point outside the area of stable performers on the right hemisphere (Fig. 1A). The analysis of the remaining cognitive tests showed no significant differences between the two groups (Table 3).

Patients who declined in MDRS and the backward digit span task shared a more medially located electrode trajectory passing through the caudate nucleus (Fig. 2A). Here, patients who declined showed a significant greater overlap of the electrode trajectories within the caudate nuclei compared to stable performers (Table 3). Consequently the trajectory of stable performers passed the basal ganglia more laterally and theses patients had a significantly greater lesion within the globus pallidus (Table 3). In a binary logistic regression between the cognitively declining and stable groups based to the changes in the MDRS, the variables age [odds ratio (OR) 1.3;

Table 1 Baseline characteristics of patients with Parkinson's disease enrolled in pairs (best medical treatment and DBS)

	DBS, mean (SD)	BMT, mean (SD)
Number of patients	31	31
Gender (males : females)	17 : 14	17:14
Age (years)	59.8 (7.5)	58.9 (9.6)
Duration of disease (years)	13.3 (5.5)	13.1 (5.3)
Levodopa-equivalent medication (mg/day)	1244 (527)	1204 (522)
Hoehn and Yahr Stage		
Medication ON	2.3 (0.87)	2.3 (0.72)
Medication OFF	3.8 (0.85)	3.8 (0.86)
UPDRS III total score		
Medication ON	19.4 (8.6)	15.9 (8.5)
Medication OFF	47.2 (12.3)	45.0 (12.6)
Axial subscore (Items 27–30)		
Medication ON	3.7 (2.6)	2.7 (2.4)
Medication OFF	8.6 (3.4)	8.6 (3.7)
Left hemisphere		
No. of microelectrodes		
1	3	
2	1	
3	1	
4	7	
5	18	
Right hemisphere		
No. of mictroelectrodes		
1	3	
2	0	
3	4	
4	3	
5	21	

There are no significant differences between STN-DBS and the best medical treatment (BMT) group.

confidence interval (CI) 1.0–1.5] and the maximal volume of lesioned caudate tissue (right and left) (OR 37.4, CI 2.1–371.8) were accepted as the explanatory variable in the model, whereas L-DOPA equivalence dosage at baseline and UPDRS axial subscore failed to be accepted in the analysis. According to this analysis, an increase of a lesion volume of 0.1 ml of the nucleus caudate increases the odds for a decline in MDRS by a factor of 37.4 and one additional year of a patient's life increases the risk for a decline in MDRS by a factor of 1.3. In combination, both factors explain 49% of variance of the MDRS change score. A further binary logistic regression analysis between the declining and stable groups based on the changes in the backward digit span task showed that a lesion volume of 0.1 ml of the caudate nucleus increased the risk of a decline in the backward digit span task by a factor of 8.8 (OR 8.8, CI 1.0–70.9) (Fig. 2B).

Analysis of the active contact position in the subthalamic nucleus area

The mean position of active electrodes on the left side of the brain was localized in the MNI space $x = -11.1$ (SD = 1.2), $y = -14.9$ (SD = 1.7), $z = -6.5$ (SD = 1.5) and $x = 13.3$ (SD = 1.2), $y = -14.9$ (SD = 1.8), $z = -6.2$ (SD = 2.1) for the right side, respectively, which means active contacts did—on average—project close to the midpoint of the STN in MNI space ($x = \pm 12$, $y = -17$, $z = -6$, for the left and $z = +6$ for the right STN) (Mai *et al.*, 1997). Furthermore all patients of the STN-DBS group showed a positive response on motor performance as shown in Table 2. Table 4 reports the results of the electrode placement in relation to the changes in cognitive functions. Four of five patients (80%) who showed a decline in the backward digit span task showed an active electrode outside the volume of those patients who showed a stable performance. Nine of 12 patients (75%) who declined in the semantic verbal fluency task exhibited an active electrode outside the volume of stable performers (Fig. 1D). For Stroop task performance, all patients (100%) who declined showed an electrode position outside the volume of stable performers. This was demonstrated for the left electrode for the time criterion (Fig. 1B) and the error rate (Fig. 1C). Furthermore the active electrodes were localized in a ventral position compared to stable performers (Supplementary Video 1). Motor performance at baseline, 6 months after STN-DBS and also the change score between baseline and 6 months were not significantly different between the stable performers and the patients exhibiting a decline in a specific cognitive task (Mann-Whitney-U test $P > 0.2$ for all comparisons).

Discussion

This study corroborates subtle detrimental effects of STN-DBS surgery on cognitive performance. The individual outcome depends on patient inherent risk factors such as older age and advanced axial motor symptoms but also on the lead trajectory and the subthalamic location of the stimulating contact. The inclusion of a best medical treatment group enabled us to find changes in cognitive functions due to the STN-DBS procedure itself, because we controlled for non-specific factors such as a disease-related cognitive decline or test retest effects. On a group level only semantic verbal fluency scores significantly worsened 6 months after surgery which is in line with most previous studies assessing the effects of STN-DBS on cognitive functions (Parsons *et al.*, 2006; Witt *et al.*, 2008). Because cognitive changes after STN-DBS are rather mild and significant decline is only detectable in larger studies (Parsons *et al.*, 2006; Woods *et al.*, 2006), we therefore defined a more permissive categorical criterion of individual cognitive decline by considering a change of more than one standard deviation outside the mean of the medically treated control group as clinically relevant. This criterion is closely matched to the expected decline of cognitive functions after STN-DBS (Woods *et al.*, 2006) and it statistically stresses discreet changes, whereas a criterion built of statistical significance would ignore mild deficits. At the cortical level, the electrodes of patients who declined in Stroop task performance (time criterion) entered outside the area of cortical entry points of stable performers. No other neuropsychological outcome was related to a specific pattern of cortical entry points. Hence, it seems unlikely that a particular pattern of cortical microlesion by the electrode passage contributes in a

Table 2 Changes in motor and cognitive status at 6 months

Test	DBS ($n = 31$)	Best medical treatment ($n = 31$)	*P*-values	Decline in $\geqslant 1$ SD from baseline No. of patients DBS	Decline in $\geqslant 1$ SD from baseline No. of patients BMT
UPDRS motor score					
Medication OFF	47.2 (12.3)	45.0 (12.6)			
Change score	20.0 (11.8)*	2.9 (9.9)	**<0.001**	0	2
MDRS					
Total score	139.6 (3.4)	140.1 (3.4)			
Change score	−2.5 (4.9)	−1.1 (4.2)	0.22	7	4
Backward digit span task	4.4 (1.6)	4,52 (1.7)			
Change score	−0.6 (1.6)	0.03 (1.9)	0.13	6	6
Verbal fluency, semantic	36.2 (11,5)	36.8 (9,3)			
Change score	−6.1 (11.6)	0.3 (10.3)	**0.02**	12	5
Verbal fluency, letter	21.3 (10.4)	22.0 (7,3)			
Change score	−1.9 (8.1)	−0.5 (6.0)	0.45	7	3
Stroop interference condition					
Time (s)	62.3 (18.9)	59.2 (17.8)			
Change score	−12.3 (51.1)	0.3 (18.3)	0.20	6	5
Stroop interference condition					
Error rate	1.8 (2.7)	1.4 (2.4)			
Change score	−0.5 (3.6)	−0.3 (2.3)	0.76	5	3

*Motor evaluation in an OFF medication/on stimulation condition.
Positive change score indicates an improvement; negative change score indicates a worsening.
Data were given as mean (SD in brackets) and number of patients.
BMT = best medical treatment.

relevant way to the neuropsychological changes after STN-DBS. This is worth mentioning because the lead entry point of almost all electrode trajectories (98%) pass the dorsolateral prefrontal cortex known to be involved in executive functioning (Smith and Jonides, 1999) and working memory performance (Petrides *et al*., 1993; Petrides, 2000). All seven patients who were impaired on the MDRS in the course of STN-DBS had lead trajectories passing the caudate nucleus of both hemispheres, so their electrode trajectory lesioned a significantly larger volume of the caudate nucleus compared to stable performers. Every 0.1 ml volume penetrated by the electrode within the caudate nucleus increased the risk of a decline in global cognitive performance by a factor of 37. Interestingly this decline in global cognition was not owing to an impairment of verbal fluency performance, which would be self-evident, because this task alone accounts for 14% of the MDRS sum score. In fact working memory performance was also affected by caudate lesions and a penetration volume of 0.1 ml increased the risk for a decline in a working memory task by the factor of 9. The caudate nucleus is part of a cortical-subcortical loop system (Alexander and Crutcher, 1990) involved in aspects of executive functioning and working memory performance (Ashby *et al*., 2005; Marklund *et al*., 2009). Vascular lesions of the caudate nucleus are associated with an increased risk of subcortical dementia (Mendez *et al*., 1989; Looi *et al*., 2009). The statistical finding of a 'protective' property of a lesion within the globus pallidus for cognitive changes can be interpreted in two ways: trajectories passing laterally or in a steeper angle sparing the caudate area but passing through the region of the globus pallidus are associated with a lower risk for cognitive decline. We did not find a significant effect of the number of microelectrodes and cognitive changes. However, the guide tubes of the microelectrodes go from the cortex into the striatum, which stresses the point that macro-electrodes that pass the caudate are preceded by one to five of the guide tubes of the microelectrodes. Our results emphasize the fact that the electrode trajectory is more important than the number of microelectrodes implanted.

In line with previous studies (Daniels *et al*., 2010; Smeding *et al*., 2011), we identified age as a risk factor for a global cognitive decline after STN-DBS. One year of life increased the risk of a global cognitive decline by a factor of 1.3. Other patient-related factors previously associated with a decline in executive functioning, such as L-DOPA equivalence dosage and UPDRS axial score were not accepted in a regression analysis. This might be explained by the lower number of patients enrolled into this study ($n = 31$ in the DBS group), compared to the number of patients in our previous study ($n = 61$) (Daniels *et al*., 2010). Especially, the low number of patients exhibiting an individual cognitive score decline after STN-DBS limited the power of the statistical analysis. Therefore we had to adopt a more liberal criterion of one standard deviation outside the range of the control group for a decline in a specific cognitive test. For the analysis of the electrode trajectories, both approaches—classification on the basis of statistical significance and the one standard deviation criterion—revealed comparable results. Both analyses point to the fact that a lesion of the caudate nuclei is an important risk factor for a cognitive decline.

A large proportion of patients who declined in the semantic verbal fluency task showed an electrode position outside the stimulation area of the left STN of stable performers. All patients who were classified as impaired in the Stroop task showed an

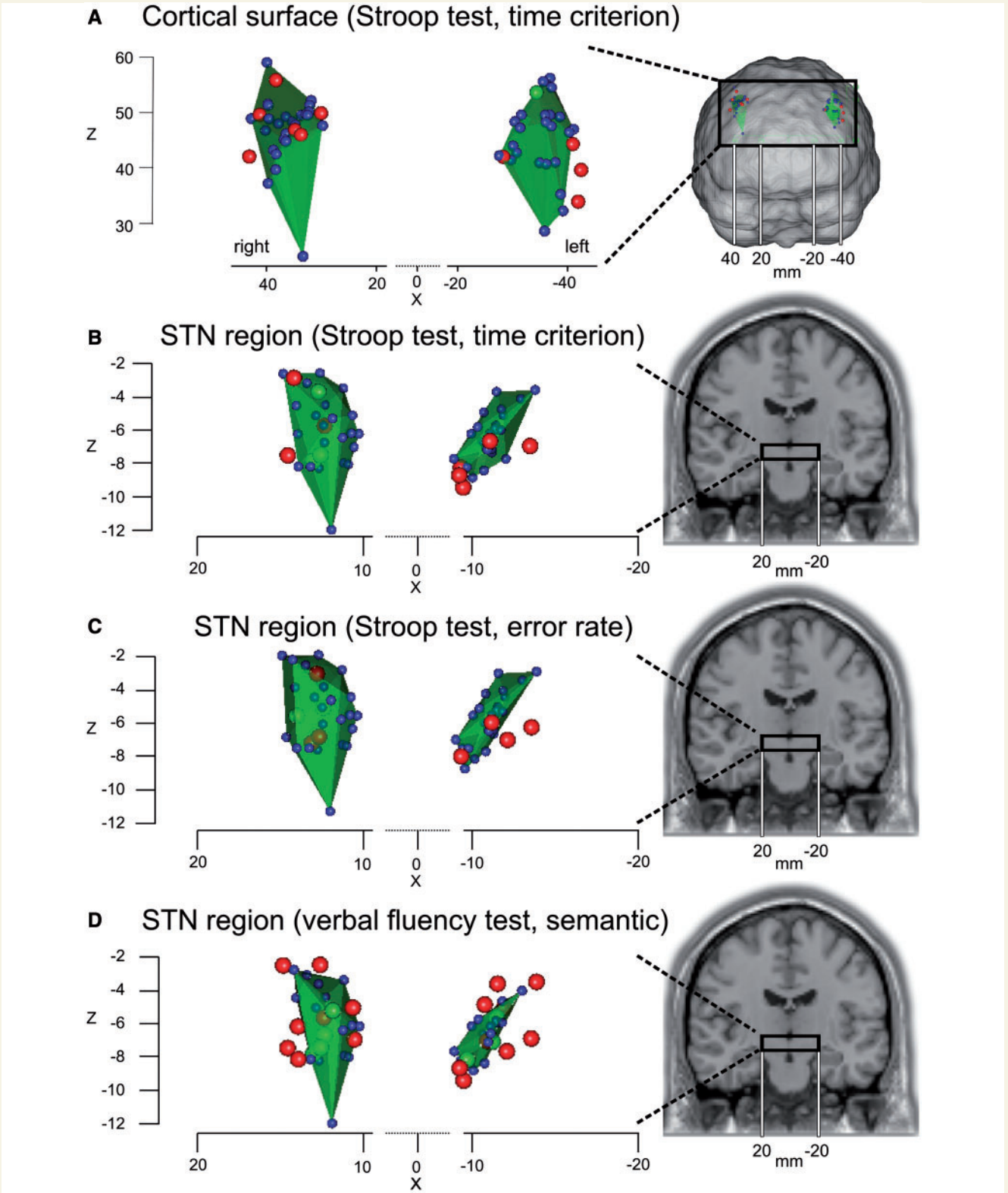

Figure 1 (**A**) The cortical entry points of stable performers (blue circles) built an area (green) on the cortical surface. Most of the cortical entry points of patients who worsened (red circles) on the time criterion of the Stroop test lay within the area of stable performers on the right hemisphere, but surrounded the area of stable performers on the left hemisphere. (**B–D**) On the level of the position of the active electrode stable performers (blue circles) build a volume (green). The active position of patients who worsened in Stroop test performance (**B** and **C**) or semantic verbal fluency (**D**) lay outside the volume of stable performers (red circles with a ventral position, shadowed red circles in a dorsal position and green circles within the area of stable performers). On the left STN area most of patients who worsened showed a ventral electrode position.

Table 3 Analysis of cortical entry point positions (left) and lesioned volume of the caudate nucleus and globus pallidus (right) of patients who decline and stable patients after STN-DBS

	Cortical entry point				Lesioned basal ganglia volume (ml)	
	Left		Right			
	No. of electrodes in area/out of area	*P*	No. of electrodes in area/out of area	*P*	Caudate nuceli decline/stable	Globus pallidus decline/stable
MDRS total score	2/4	0.07	5/2	0.54	**0.096/0.049 *P* = 0.02**	**0.027/0.050 *P* = 0.02**
Backward digit span task	2/3	0.12	1/4	0.13	**0.105/0.049 *P* < 0.04**	0.053/0.993
Semantic verbal fluency	4/8	0.08	7/5	0.33	0.066/0.054 ns	0.048/0.071 ns
Phonematic verbal fluency	4/3	0.22	4/3	0.31	0.084/0.051 ns	0.079/0.057 ns
Stroop interference condition/ colour naming time	1/4	0.11	0/6	**0.02**	0.068/0.056 ns	0.053/0.065 ns
Error rate	2/2	0.26	1/4	0.34	0.156/0.055 ns	0.061/0.092 ns

The number of cortical entry positions of the group with declining performance outside and inside of the area determined from the cortical entry positions of the stable/improved performers were reported. The statistics of the permutation analysis is given as percentage of cortical entry positions outside the area of stable performers and *P*-level of permutation-statistics.

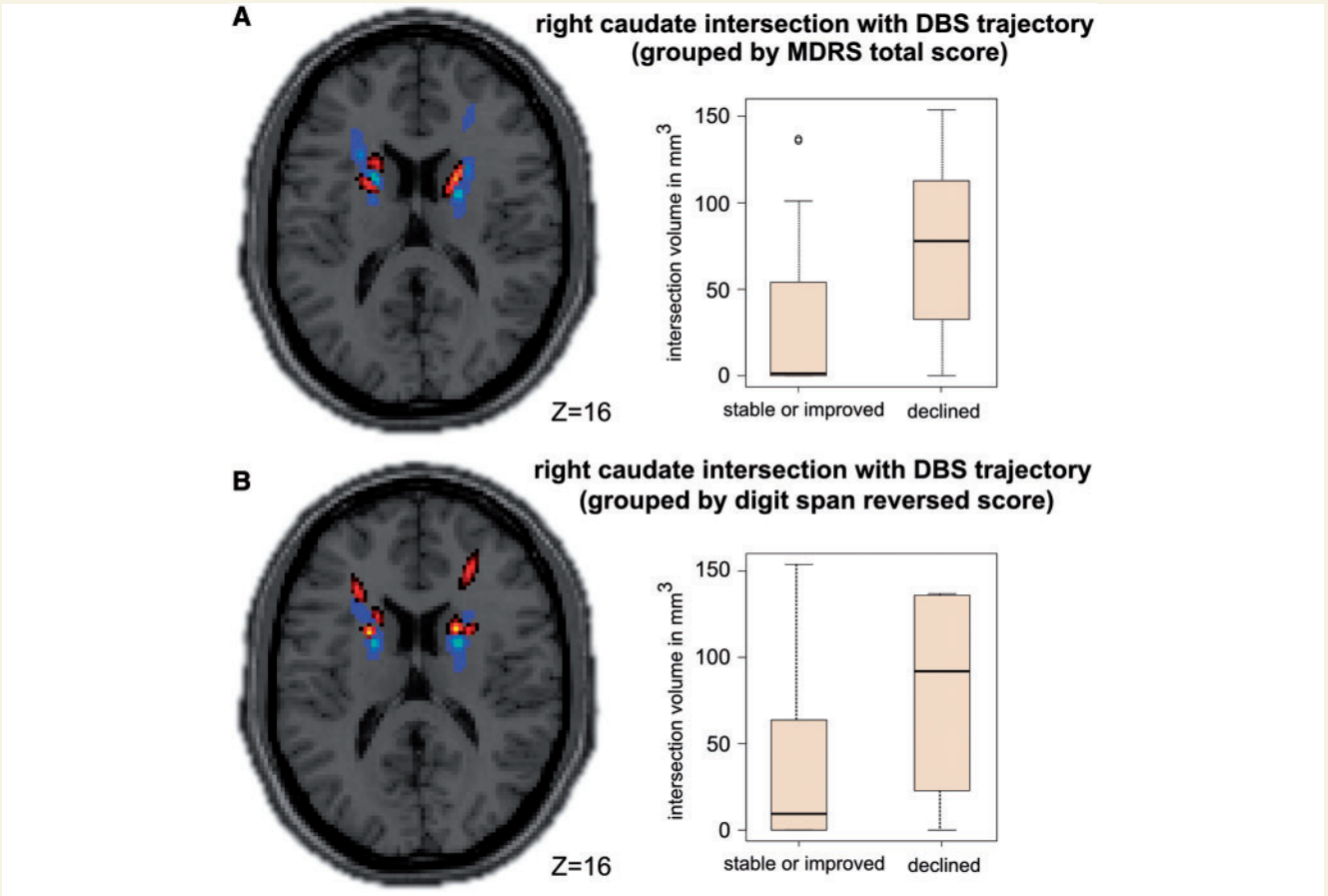

Figure 2 Electrode trajectories on the level of the caudate nuclei. Presented are voxels that were affected by electrode trajectory of patients that decline in cognitive functions after STN-DBS (red) and patients that showed a stable or an even improved cognitive function after STN-DBS (blue). Patients who decline on global cognition (MDRS, **A**) and patients who decline in working memory performance (backward digit span task, **B**) showed an electrode trajectory that passed the caudate nuclei.

Table 4 Analysis of STN electrode position and stimulation amplitude of patients who decline and stable patients after STN-DBS

	STN target position				Stimulation amplitude			
	Left		Right		Left		Right	
	No. of electrodes in area/out of area	*P*	No. of electrodes in area/out of area	*P*	Decline/stable V, mean (SD)	*P*	Decline/stable V, mean (SD)	*P*
MDRS total score	2/4	0.07	3/4	0.20	2.8 (0.9)/2.6 (0.7)	0.51	2.3 (0.7)/2.9 (0.8)	0.11
Backward digit span task	1/4	**0.04**	2/3	0.35	3.2(0.6)/2.6 (0.7)	0.05	2.6 (0.9)/2.7 (0.8)	0.73
Semantic verbal fluency	3/9	**0.04**	4/8	0.12	3.0 (0.5)/2.5 (0.7)	**0.03**	2.6 (0.8)/2.7 (0.8)	0.68
Phonematic verbal fluency	6/1	0.9	3/4	0.27	2.8 (0.9)/2.7 (0.7)	0.76	2.7 (0.9)/2.8 (0.8)	0.80
Stroop interference condition/ colour naming time	0/5	**0.006**	4/2	0.56	3.0 (0.6)/2.6 (0.7)	0.21	2.7 (0.5)/2.8 (0.9)	0.82
Error rate	0/4	**0.002**	5/0	1.00	3.0 (0.6)/2.6 (0.7)	0.26	2,8 (0.8)/2.8 (0.8)	0.26

The number of electrode position of group of declining performers outside and inside of the area determined from the STN region of the stable/improved performers were reported. The statistics of the permutation analysis is given as percentage of STN positions outside the area of stable performers and *P*-level of permutation-statistics.

active electrode outside the area of the electrodes of stable performers of the left side of the brain. It has been shown previously that STN-DBS influences performance in both tasks (Parsons *et al*., 2006; Witt *et al*., 2008). For verbal fluency performance, there was strong evidence that detrimental effects were caused by the surgical intervention rather than stimulation itself (Jahanshahi *et al*., 2000; Pillon *et al*., 2000; Morrison *et al*., 2004; Witt *et al*., 2004; Okun *et al*., 2012). This observation resembles long-lasting implant effects in the motor domain. The lesion caused by the insertion of the stimulating lead is held responsible for a slight and often transient improvement in motor functions (Mann *et al*., 2009). Significantly more patients with a decline in semantic verbal fluency performance showed an active electrode outside the stimulated area of stable performers underlining the importance of precise targeting within the subthalamic area. Mikos *et al*. (2011) combined individual imaging data and electrophysiological data during the electrode placement which enabled a patient-specific analysis of the relationship between the volume of tissue activated during STN-DBS and verbal fluency. Their analysis revealed that the volume of activated STN tissue influenced by the most ventral electrode contacts was significantly correlated with verbal fluency performance. Furthermore ventral STN stimulation can also result in affective problems (Okun *et al*., 2009). Notably, the higher stimulation amplitude in patients who decline in verbal fluency performance confirms the assumption that the combination of the electrode position and stimulation amplitude is responsible for the decline in verbal fluency performance. In the present study the active electrodes of all five patients declining in Stroop task performance exhibited were located more ventrally within the subthalamic area than those of stable performers and, notably the stimulation amplitude was significant higher in patients who decline in Stroop test performance. This ventral position increased the likelihood of limbic and associative STN segments to be affected by electric stimulation. The cortico-subcortical loops passing through the limbic and the associative part of the STN are connected with the anterior cingulate cortex and the dorsolateral prefrontal cortex (Alexander and Crutcher, 1990; Parent and Hazrati, 1995). The anterior cingulate cortex shows increased activity during erroneous responses and under conditions of increased response competition (e.g. in the interference condition of the Stroop test) (Carter *et al*., 1998). In this way the anterior cingulate cortex plays an important role in performance monitoring detecting erroneous responses. STN-DBS alters cerebral blood flow in the anterior cingulate cortex (Schroeder *et al*., 2002). Changes in regional cerebral blood flow in the anterior cingulate cortex induced by STN-DBS are correlated with impaired response inhibition (Campbell *et al*., 2008). Therefore, our data corroborate the hypothesis that stimulation of the ventral, limbic part of the STN impairs function of the anterior cingulate cortex circuit and causes subtle negative effects on the interference condition of the Stroop test. Since the group of decliners show significantly higher stimulation amplitudes for an optimal motor outcome, we suggest that this decline is also an effect of stimulation and not exclusively an effect of the lesion itself. Of note, we found significant results in the permutation analysis only for the left hemisphere. This may indicate hemispheric specialization but could also be related to a simple methodological issue. In our surgical approach the left electrode was always placed first and the variability of the final electrode location was lower in the left than in the right hemisphere, probably due to an increasing brain shift throughout the course of the procedure. This difference in spatial variability could impact on the statistical power to detect outliers.

Several limitations of our study need to be discussed. First, we did not carry out diffusion tensor imaging at baseline limiting our ability to assess the impact on white matter tracts. However, it is unlikely that our main finding of a caudate lesion impacting on neuropsychological outcomes can be explained by an additional damage of specific fibre tracts. Secondly, because STN-DBS significantly improved motor symptoms in all patients we assumed a correct electrode positioning within the subthalamic area on clinical grounds. However, a patient-specific analysis combining individual imaging and electrophysiological data may provide more detailed information about the optimal contact location within the STN, which is lost in the normalization procedure of our group-based approach. Third, our study was not powered to

combine preoperative baseline data, imaging data of the electrode trajectories and the active electrode position in a single statistical analysis. Therefore, the present study analysed only combinations of baseline factors associated with the electrode trajectories (volume of lesioned tissue of subcortical nuclei). Fourth, after DBS surgery often an oedema surrounded the electrode which might turn into a gliosis in the chronic stage. In the present study we scanned the patients only once shortly after surgery. Therefore we can not determine the role of these changes on cognitive functions. This point should be addressed in longitudinal studies with multiple MRI scans. Fifth, with respect to the impact of the caudate lesion on the neuropsychological changes, we are not able to exactly differentiate between effects of a lesion caused by the guide tubes or the microelectrodes. The guide tubes were placed 3 cm before the MRI-based target point and thereby reached the caudate nucleus whenever the planed trajectory passes the caudate nucleus. In contrast the number of test electrodes is not correlated with the neuropsychological changes. Given the fact that the guide tubes or the microelectrodes passing the caudate nucleus cause decline in neuropsychological functioning a trajectory affecting the caudate nucleus should be avoided whenever possible.

In conclusion, the present study suggests that the caudate nuclei must be spared by the electrode trajectory and that alternative, more antero-lateral paths are cognitively safer. In addition, we identified older age as a risk modifier for a cognitive decline after a caudate penetration by the stimulating lead. This study also stresses the role of precise targeting of the active electrode contact within the subthalamic nucleus to avoid subtle negative effects on semantic verbal fluency and response inhibition behaviour.

Acknowledgements

We thank Carmen Schade-Brittinger and the Koordinationszentrum für Klinische Studien, Marburg, for data management. Dr. Bettina Möller contributed to data collection.

Funding

This study was supported by the German Ministry of Research and Technology to G.D. (Kompetenznetz Parkinson, FK:01GI0201), the German Research Council to G.D. (SFB 855, TP D2) and the International Parkinson Fond Europe to K.W. and C.D.

Supplementary material

Supplementary material is available at *Brain* online.

Conflict of interest

KW has received lecture fees from Medtronic and has been serving as consultant for UCB. He is a government employee and he receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health and International Parkinson Fonds Europe. OG is a government employee. CD is a government employee and received funding for her research from International Parkinson Fonds Europe. DF is a government employee. TVE is a government employee. Apart from intramural funding from his affiliated institution, he received a grant from the Leibniz Association and serves as a consultant for the CHDI foundation. JV has received honoraria from Medtronic, Boston Scientific, St. Jude, TEVA, UCB, Novartis, Orion and GlaxoSmithKline. He has been serving as a consultant for Medtronic, Boston Scientific and Novartis. He received grants from Medtronic and AbbVie. GD has received lecture fees from TEVA, Lundbeck, Medtronic and Desitin and has been serving as a consultant for TEVA, Medtronic, Novartis, Sapiens, Medtronic. He received royalties from Thieme publishers. He is a government employee and he receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Health and Medtronic.

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