Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study

Karsten Witt, Christine Daniels*, Julia Reiff, Paul Krack, Jens Volkmann, Markus O Pinsker, Martin Krause, Volker Tronnier, Manja Kloss, Alfons Schnitzler, Lars Wojtecki, Kai Bötzel, Adrian Danek, Rüdiger Hilker, Volker Sturm, Andreas Kupsch, Elfriede Karner, Günther Deuschl*

Summary

Background Deep brain stimulation (DBS) of the subthalamic nucleus (STN) reduces motor symptoms in patients with Parkinson's disease (PD) and improves their quality of life; however, the effect of DBS on cognitive functions and its psychiatric side-effects are still controversial. To assess the neuropsychiatric consequences of DBS in patients with PD we did an ancillary protocol as part of a randomised study that compared DBS with the best medical treatment.

Methods 156 patients with advanced Parkinson's disease and motor fluctuations were randomly assigned to have DBS of the STN or the best medical treatment for PD according to the German Society of Neurology guidelines. 123 patients had neuropsychological and psychiatric examinations to assess the changes between baseline and after 6 months. The primary outcome was the comparison of the effect of DBS with the best medical treatment on overall cognitive functioning (Mattis dementia rating scale). Secondary outcomes were the effects on executive function, depression, anxiety, psychiatric status, manic symptoms, and quality of life. Analysis was per protocol. The study is registered at ClinicalTrials.gov, number NCT00196911.

Findings 60 patients were randomly assigned to receive STN-DBS and 63 patients to have best medical treatment. After 6 months, impairments were seen in executive function (difference of changes [DBS–best medical treatment] in verbal fluency [semantic] –4·50 points, 95% CI –8·07 to –0·93, Cohen's *d*=–0·4; verbal fluency [phonemic] –3·06 points, –5·50 to –0·62, –0·5; Stroop 2 naming colour error rate –0·37 points, –0·73 to 0·00, –0·4; Stroop 3 word reading time –5·17 s, –8·82 to –1·52, –0·5; Stroop 4 colour naming time –13·00 s, –25·12 to –0·89, –0·4), irrespective of the improvement in quality of life (difference of changes in PDQ-39 10·16 points, 5·45 to 14·87, 0·6; SF-36 physical 16·55 points, 10·89 to 22·21, 0·9; SF-36 psychological 9·74 points, 2·18 to 17·29, 0·5). Anxiety was reduced in the DBS group compared with the medication group (difference of changes in Beck anxiety inventory 10·43 points, 6·08 to 14·78, 0·8). Ten patients in the DBS group and eight patients in the best medical treatment group had severe psychiatric adverse events.

Interpretation DBS of the STN does not reduce overall cognition or affectivity, although there is a selective decrease in frontal cognitive functions and an improvement in anxiety in patients after the treatment. These changes do not affect improvements in quality of life. DBS of the STN is safe with respect to neuropsychological and psychiatric effects in carefully selected patients during a 6-month follow-up period.

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Introduction

Deep brain stimulation (DBS) is an established therapy to treat the motor symptoms of Parkinson's disease (PD).[1] Although the beneficial effects of bilateral DBS of the subthalamic nucleus (STN) on motor symptoms and quality of life have been shown in patients with advanced PD,[2] its effects on cognitive and psychiatric symptoms are controversial. Some authors have concluded DBS to be safe;[3,4] however, other investigators reported cognitive deterioration, particularly in elderly patients.[5] A common symptom of DBS is a decrease in verbal fluency,[6] and the authors of neuropsychological studies have reported a decline in verbal memory,[7–11] psychomotor speed,[5] and visuospatial memory[5,7] after DBS. Some case series even showed a deterioration in global cognitive function that suggests incipient dementia, particularly in the elderly.[5] Improvements in cognitive functions, such as enhanced mental flexibility[7] and visuomotor sequencing, have also been reported after DBS.[3,4] However, only four studies included a control group of patients with PD who did not receive DBS.[7,12–14] Because most of the studies had small sample sizes, they had inadequate power to detect even large effects,[15] which emphasises the need for a controlled study with a large enough sample to test the effects of DBS in the neuropsychological domain. Postoperative psychiatric symptoms are common but are often present before surgery because PD is a neuropsychiatric disease;[16,17] depression has been reported in 1·5% to 25·0% of patients after surgery.[1,16,18] Improvement in depressive symptoms has been reported on a group level;[3] however, hypomania has been found in 4% to 15% of patients,[19] and a postoperative suicide rate of 0·5% to 2·9% has been

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*Contributed equally

Christian-Albrechts-University, Kiel, Germany (K Witt PhD, C Daniels MD, J Reiff MD, Paul Krack PhD, J Volkmann PhD, M O Pinsker MD, G Deuschl PhD); **Ludwig-Maximilians University, Munich, Germany** (K Bötzel PhD, A Danek PhD); **Charité Hospital, Humboldt University, Berlin, Germany** (A Kupsch PhD); **Cologne University, Cologne, Germany** (R Hilker PhD, V Sturm PhD); **Heidelberg University, Heidelberg, Germany** (M Krause PhD, V Tronnier PhD, M Kloss MD); **Heinrich Heine University, Dusseldorf, Germany** (A Schnitzler PhD, L Wojtecki MD); **and Innsbruck Medical University, Innsbruck, Austria** (E Karner MPsych)

Correspondence to: Günther Deuschl, Department of Neurology, University of Schleswig-Holstein, Campus Kiel, Schittenhelmstrasse 10, D-24105 Kiel, Germany **g.deuschl@neurologie.uni-kiel.de**

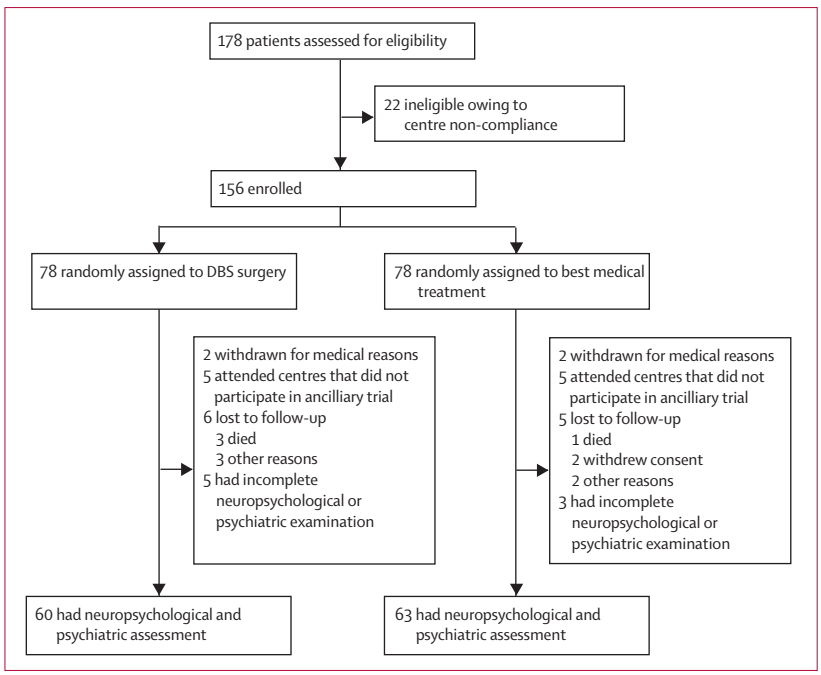

Figure 1: **Trial profile**

	DBS (n=60)	BMT (n=63)
M:F	36:24	41:22
Age (years)	60·2 (7·9)	59·4 (7·5)
Duration of disease (years)	13·8 (6·3)	14·0 (6·1)
Hoehn and Yahr stage (off)	3·62 (0·85)	3·77 (0·86)
Hoehn and Yahr stage (on)	2·29 (0·72)	2·30 (0·72)
Levodopa equivalents (mg/day)	1203 (535)	1142 (463)

Data are number of patients or mean (SD). DBS=deep brain stimulation. BMT=best medical treatment. M=male. F=female. Off=off medication state. On=on medication state.

Table 1: **Characteristics of patients at baseline**

reported.[1,16] Psychiatric symptoms are common in patients who have had DBS and might be due to the exacerbation of underlying psychiatric disease, to DBS, or to the drug regimen; however, the sample sizes in these studies were small, most did not have a control group, and none of the studies was randomised.

Cognitive impairments and depression have a major effect on quality of life,[20] even when the motor signs of PD are improved by DBS. This prospective, controlled, multicentre trial was an ancillary study to a randomised trial[2] that compared DBS with best medical treatment in patients with advanced PD over 6 months to investigate the postoperative changes in cognitive function and psychiatric symptoms and assess their effects on quality of life.

Methods

Patients

156 patients were enrolled in the study,[2] and 123 patients completed the neuropsychiatric assessments (figure 1). The screening procedure has been reported elsewhere.[2] Inclusion criteria were the clinical diagnosis of idiopathic PD in accordance with the British Parkinson's Disease Society brain bank criteria[21] for at least 5 years, age younger than 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[22] sum score ≤130), a major psychiatric illness—such as a history of or current psychosis or a history of or current severe depression diagnosed by a psychiatrist—or surgical contraindications. The study protocol was approved by the ethics committee at each participating centre, and all patients gave written informed consent. Patients were enrolled in pairs: one patient in each pair was randomly assigned to receive DBS surgery within 6 weeks after enrolment and the other patient to receive best medical treatment. Table 1 summarises of the characteristics of patients at baseline.

Procedures

Random assignment, monitoring, and data collection were done by the Coordinating Centre for Clinical Trials at the Philips University, Marburg, Germany, in accordance with good clinical practice.[2] Patients who were assigned to receive DBS had bilateral stereotactic surgery.[2] The permanent electrode (model 3389 DBS, Medtronic, Minneapolis, MN, USA) was connected to the pulse generator (Kinetra, Medtronic). Postoperatively, the optimum stimulation and antiparkinsonian medication were adjusted as needed. The standard pulse setting was 60 µs at 130 Hz, with the voltage adjusted for each patient. Neurologists who were specialists in movement disorders at each of the participating centres ensured that all patients assigned to the best medical treatment group received antiparkinsonian medication in accordance with the German Society of Neurology guidelines.[23] Levodopa equivalence doses were calculated, to compare the amount of medication given to each patient.[2] Neuropsychological and psychiatric assessments were done on medication at baseline, and under ongoing neurostimulation or on medication at 6 months. Neurologists and neuropsychologists were trained to examine the patients with the battery of tests. To assess the predefined primary outcome criterion—the effect of DBS or best medical treatment on overall cognitive functioning—we used the Mattis dementia rating scale. The sum score ranges from 0 to 144, with lower scores indicative of worse cognitive performance. Secondary outcome criteria were specific neuropsychological and psychiatric changes after DBS and their effect on quality of life. Experienced psychiatric consultants did the neuropsychiatric diagnostic procedure. These examiners were not blinded to the patient's treatment.

As a general requirement, tests that focused on the cognitive functions that are often affected in PD were selected; the motor components of these tests were minimised to detect cognitive changes rather than changes in the motor domain. Parallel versions of all tests (excluding

the Mattis dementia rating scale) were administered to minimise test and retest effects. Parallel versions of these tasks were grouped into forms A or B, and the patients' screening number determined the order of the tests (patients with even screening numbers had test form A at baseline and test form B at follow-up, whereas those with odd screening numbers had the opposite order).

Although global cognitive functions were tested with the Mattis dementia rating scale,[22] further analyses were done on the scale components (attention, initiation/perseveration, construction, conceptualisation, and memory). Verbal memory was assessed with a German version of Rey's auditory verbal learning test[24,25] (the sum of the correct words in the first five runs, the number of words correct in the first recall of the first run, and the number of words correct in the second word list gave the score for short-term verbal memory abilities). The results of a postinterference recall trial were analysed to measure retroactive interference. Delayed recall showed long-term verbal memory performance (late recognition). Parallel versions of Rey's auditory verbal learning test were used.[24] Forward and backward digit span were assessed with the Wechsler adult intelligence scale[26] and were analysed separately. Visuospatial abilities were assessed with the revised Benton visual retention test administration M,[27] which was also done as two parallel versions (the sum scores range between 0 and 15, where higher scores indicate better performance). Attention and response inhibition were assessed with a shortened version of the Stroop test[27] that consisted of four trials, each containing 36 items: reading colour words (blue, yellow, green, and red) printed in black ink; naming the colour of dots; reading colour words (blue, yellow, green, and red) printed in ink of incongruent colours (interference condition); and naming the ink colour of the written words printed in incongruent colours (interference condition). The number of errors and the time needed to complete the test were scored separately for each trial. Another aspect of executive function was assessed with verbal fluency tests, which included two semantic and two phonemic categories that each lasted for 1 min. The categories were male first names and plants or female first names and animals for semantic fluency and either R and K or P and F as first letters for phonematic fluency. The sum of correct answers in the two runs of the semantic and phonematic categories were scored separately.

	DBS	BMT	p	Difference of changes DBS–BMT*	Cohen's *d*
PDQ-39 score	40·78 (14·13)	38·69 (16·25)			
Change in PDQ-39 score	9·89 (14·87), 5·98 to 13·80; 5·06	−0·27 (9·83), −2·98 to 2·44; −0·20	<0·0001	10·16, 5·45 to 14·87	0·6
SF-36 physical well-being score	32·3 (14·4)	35·7 (19·0)			
Change in SF-36 physical well-being score	14·1 (17·5), 9·64 to 18·53; 6·64	−2·5 (14·1), −6·05 to 1·13; −1·37	<0·0001	16·55, 10·89 to 22·21	0·9
SF-36 psychological well-being score	47·3 (19·0)	47·6 (21·7)			
Change in SF-36 psychological well-being score	8·6 (23·7), 2·41 to 14·86; 2·77	−1·1 (16·8), −5·51 to 3·30; −0·50	0·021	9·74, 2·18 to 17·29	0·5
UPDRS I total score	2·64 (2·53)	2·54 (2·29)			
Change in UPDRS I total score	0·66 (2·64), 0·02 to 1·31; 2·06	0·08 (1·80), −0·36 to 0·52; 0·37	0·34	0·58, −0·19 to 1·35	0·24
UPDRS II off total score	22·31 (7·53)	21·72 (6·52)			
Change in UPDRS II off total score	8·87 (8·82), 6·71 to 11·02; 8·23	−1·27 (6·47), −2·85 to 0·32; −1·59	<0·0001	10·13, 7·48 to 12·78	1·4
UPDRS II on total score	8·81 (5·50)	8·02 (5·94)			
Change in UPDRS II on total score	1·54 (5·33), 0·24 to 2·84; 2·36	−1·16 (5·38), −2·48 to 0·15; −1·77	0·004	2·7, 0·87 to 4·53	0·5
UPDRS III off total score	47·9 (13·13)	47·3 (11·92)			
Change in UPDRS III off total score	21·16 (14·51), 17·51 to 24·82; 11·58	0·45 (9·87), −2·04 to 2·93; 0·36	<0·0001	20·71, 16·33 to 25·10	1·7
UPDRS III on total score	18·7 (9·7)	17·3 (9·0)			
Change in UPDRS III on total score	4·65 (9·91), 2·22 to 7·09; 3·82	−0·56 (7·99), −2·51 to 1·39; −0·57	0·004	5·21, 2·12 to 8·30	1·5
UPDRS IV total score	9·10 (4·10)	8·61 (3·61)			
Change in UPDRS IV total score	6·06 (4·64), 4·92 to 7·20; 10·60	0·44 (3·09), −0·32 to 1·20; 1·16	0·005	5·62, 4·26 to 6·98	0·6
Dysarthria score UPDRS II on total score	0·71 (0·72)	0·82 (0·80)			
Change in dysarthria score UPDRS II on total score	−0·07 (0·87), −0·28 to 0·15; −0·64	0·02 (0·32), −0·21 to 0·26; 0·19	0·52	−0·09, −0·41 to 0·23	−0·1
Dysarthria score UPDRS III on total score	0·88 (0·70)	0·85 (0·72)			
Change in dysarthria score UPDRS III on total score	−0·08 (0·91), −0·3 to 0·1; −0·67	−0·17 (0·92), −0·4 to 0·1; −1·43	0·24	0·10, −0·23 to 0·42	0·1
Levodopa equivalents (mg/day)	1203 (535)	1142 (463)			
Change in levodopa equivalents	606 (555), 469 to 744; 8·81	67 (377), −26 to 160; 1·43	<0·0001	539, 375 to 704	1·1

Data are mean (SD) for scores and mean (SD), 95% CI; reliable change index (RCI) for changes between baseline (before DBS) and 6 months. Positive change scores indicate clinical improvement. The Mann-Whitney *U* test was used to determine unadjusted two-sided p values for the group comparisons. *The difference scores (ie, the differences in the mean change scores of both groups) are given as mean, 95% CI. Cohen's *d* was calculated to show the between-groups effect sizes. Positive Cohen's *d* scores show an improvement in the DBS group compared with BMT. DBS=deep brain stimulation. BMT=best medical treatment. PDQ=Parkinson's disease questionnaire. UPDRS=unified Parkinson's disease rating scale.

Table 2: **Differences in quality of life scores, UPDRS scores, and levodopa equivalents between baseline and 6 months**

Signs and symptoms of depression were assessed with the Beck depression inventory,[28] a self-rating assessment with scores that range from 0 to 63 (high scores indicate more severe depression), and the Montgomery-Asberg depression rating scale,[29] a clinician-rated depression scale, with scores ranging from 0 to 60 (high scores indicate more severe depression). Anxiety was rated with the Beck anxiety inventory,[30] a self-rating assessment, with scores that range from 0 to 63 (high scores indicate more severe anxiety). The brief psychiatric rating scale[31] was used as a further psychiatric assessment of a wider range of symptoms, including psychosis (the total score of 18 clinician-rated items can range from 18 to 126, where high scores indicate poor mental health). Subscores of the brief psychiatric rating scale (anxiety and depression, anergia, thought disorders, activity, and hostility) were analysed separately. The Snaith-Hamilton pleasure scale[32] was used to assess hedonic tone;[32,33] this is a 14-item, self-rating scale that covers four domains of hedonic experience (interest and pastimes, social interaction, sensory experience, and food and drink). The sum score ranges between 0 and 14 (high scores indicate low hedonic tone). The Bech-Rafaelsen mania scale[34] was used as an 11-item rating scale to assess the symptoms of mania; the sum scores range from 0 to 44 (high scores indicate profound manic symptoms). Apathy was assessed with the apathy item of the unified Parkinson's disease rating scale part I, a single-item rating scale that ranges from 0 to 4 (high scores indicate more apathy).

Quality of life was assessed with the Parkinson's disease questionnaire (PDQ-39).[35,36] The PDQ-39 is a 39-item questionnaire with a total score that ranges from 0 to 100; high scores indicate worse function. Eight subscores (mobility, daily activities, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) and one sum score were calculated. Item 34 (difficulties speaking) was analysed separately to investigate patients' awareness of impaired speech production, with the frequency of speech difficulties rated between 1 (never) and 5 (all the time). The health-related quality of life physical and mental summary scores (in accordance with the medical outcome study 36-item short-form general health survey [SF-36]) were calculated by norm-based scoring (high scores indicate better quality of life).[37] Motor function was assessed with the unified Parkinson's disease rating scale part III,[38] with scores that range from 0 to 108 (high scores indicate worse condition).

	DBS (n=60)	BMT (n=63)	p	Difference of changes DBS–BMT*	Cohen's *d*
MDRS total score	139·6 (3·8)	140·0 (3·5)			
Change in MDRS total score	–1·8 (4·8), –3·04 to –0·64; –3·07	–0·7 (4·0), –1·66 to 0·35; –1·29	0·25	–1·19, –2·74 to 0·36	–0·3
MDRS attention subscale score	36·1 (0·9)	36·2 (0·9)			
Change in MDRS attention subscale score	–0·1 (1·1), –0·36 to 0·17; –0·71	0·1 (1·2), –0·19 to 0·38; 0·26	0·50	–0·19, –0·58 to 0·20	–0·2
MDRS initiation/perseveration subscale score	36·0 (2·1)	35·8 (2·0)			
Change in MDRS initiation/perseveration subscale score	–1·6 (2·8), –2·31 to –0·89; –4·50	–0·4 (2·2), –0·93 to 0·20; –1·29	0·02	–1·24 –2·14 to –0·34	–0·5
MDRS construction subscale score	5·9 (0·3)	6·0 (0·3)			
Change in MDRS construction subscale score	–0·6 (0·4), –0·15 to 0·03; –1·43	–0·2 (1·1), –0·46 to 0·11; –1·24	0·79	–0·11, –0·18 to 0·40	–0·1
MDRS conceptualisation subscale score	38·5 (1·2)	38·4 (1·2)			
Change in MDRS conceptualisation subscale score	–0·2 (2·6), –0·90 to 0·43; –0·72	–0·2 (1·8), –0·68 to 0·24; –0·96	0·81	0·02 –0·78 to 0·82	0·2
MDRS memory subscale score	23·0 (1·8)	23·6 (1·5)			
Change in MDRS memory subscale score	0·2 (2·3), –0·42 to 0·74; 0·55	–0·04 (1·6), –0·44 to 0·34; –0·24	0·46	0·21, –0·49 to 0·90	0·2
MDRS total score excluding verbal fluency subscore	120·5 (2·8)	121·1 (2·6)			
Change in MDRS total score excluding verbal fluency score	–0·5 (3·8), –1·41 to 0·49; –0·97	–0·6 (3·3), –1·44 to 0·24; –1·50	0·47	0·14, –1·11 to 1·40	0·04
RAVLT score (sum of runs 1 to 5)	40·2 (10·8)	43·3 (10·7)			
Change in RAVLT score (sum of runs 1 to 5)	–1·8 (7·9), –3·78 to 0·28; –1·72	–0·9 (9·1), –3·21 to 1·47; –0·74	0·45	–0·88 –3·95 to 2·18	–0·1
RAVLT score (runs 1+6)	9·8 (3·1)	9·5 (2·9)			
Change in RAVLT score (runs 1+6)	–0·4 (3·0), –1·18 to 0·46; –1·02	0·3 (3·4), –0·53 to 1·17; 0·76	0·28	–0·72, –1·87 to 0·42	–0·03
RAVLT score (run 7 [interference])	7·2 (3·0)	8·1 (3·4)			
Change in RAVLT score (run 7 [interference])	–0·4 (3·2), –1·17 to 0·47; –0·86	–0·2 (3·1), –0·97 to 0·61; –0·46	0·27	–0·17, –1·29 to 0·95	–0·2
RAVLT score (run 8 [late recognition])	6·4 (3·7)	7·7 (3·5)			
Change in RAVLT score (run 8 [late recognition])	0·4 (3·2), –0·47 to 1·18; 0·86	–0·4 (2·9), –1·12 to 0·39; –0·98	0·24	0·72, –0·38 to 1·83	0·2
Digit span (forward) score	6·6 (1·9)	6·9 (2·0)			
Change in digit span (forward) score	0·1 (1·8), –0·37 to 0·57; 0·43	–0·2 (2·2), –0·79 to 0·32; 0·86	0·57	–0·34, –1·06 to 0·38	–0·2
Digit span (backward) score	4·8 (1·8)	5·0 (1·9)			
Change in digit span (backward) score	–0·2 (1·6), –0·64 to 0·17; –1·15	0·1 (1·9), –0·38 to 0·60; 0·46	0·28	0·34, –0·29 to 0·97	–0·2
Benton test (total) score	11·5 (2·1)	11·7 (2·0)			
Change in Benton test (total) score	–0·4 (2·3), –1·0 to 0·2; –1·35	–0·5 (2·2), –1·0 to 0·1; –1·69	0·90	0·08, –0·74 to 0·89	0·03

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	DBS	BMT	p	Difference of changes DBS–BMT*	Cohen's *d*
(Continued from previous page)					
Verbal fluency score (semantic)	34·3 (10·3)	36·2 (8·5)			
Change in verbal fluency score (semantic)	–5·6 (9·7), –8·09 to –3·08; –4·45	–1·1 (10·1), –3·68 to 1·51; –0·83	0·03	–4·50, –8·07 to –0·93	–0·4
Verbal fluency score (phonemic)	21·0 (9·2)	21·9 (7·2)			
Change in verbal fluency score (phonemic)	–3·3 (7·0), –5·12 to –1·48; –3·63	–0·2 (6·6), –1·91 to 1·42; –0·29	0·02	–3·06, –5·50 to –0·62	–0·5
Stroop 1 word reading time (s)	17·0 (6·7)	16·8 (5·2)			
Change in Stroop 1 word reading time (s)	–0·5 (8·9), –2·32 to 1·23; –0·61	0·3 (6·0), –1·27 to 1·81; 0·35	0·07	–0·81, –3·14 to 1·52	–0·1
Stroop 1 word reading score (error rate)	0·02 (0·1)	0·02 (0·1)			
Change in Stroop 1 word reading score (error rate)	–0·3 (1·8), –0·79 to 0·16; –1·34	0·0 (0·2), –0·05 to 0·05; 0·00	0·05	–0·32, –0·79 to 0·16	–0·2
Stroop 2 word reading time (s)	22·9 (5·3)	24·3 (7·2)			
Change in Stroop 2 word reading time (s)	–3·4 (7·7), –5·40 to 1·38; –3·38	0·7 (7·1), –1·11 to 2·55; 0·79	0·05	–4·12, –6·81 to –1·42	–0·5
Stroop 2 word reading score (error rate)	0·1 (0·4)	0·2 (0·5)			
Change in Stroop 2 word reading score (error rate)	–0·3 (1·3), –0·64 to 0·04; –1·76	0·1 (0·5), –0·07 to 0·20; 0·94	0·001	–0·37, –0·73 to 0·00	–0·4
Stroop 3 word reading time (s)	22·1 (10·0)	22·5 (10·4)			
Change in Stroop 3 word reading time (s)	–4·8 (10·7), –7·54 to 2·02; –3·46	0·4 (9·5), –2·05 to 2·83; 0·32	0·001	–5·17, –8·82 to –1·52	–0·5
Stroop 3 word reading score (error rate)	0·4 (0·8)	0·3 (0·7)			
Change in Stroop 3 word reading score (error rate)	–0·2 (1·0), –0·41 to 0·11; –1·14	–0·2 (1·0), –0·47 to 0·02; –1·88	0·60	0·08, –0·28 to 0·44	0·1
Stroop 4 colour naming time (s)	61·9 (23·8)	60·3 (27·2)			
Change in Stroop 4 colour naming time (s)	–12·5 (40·9), –23·02 to 1·89; –2·36	0·5 (23·9), –5·57 to 6·67; 0·18	0·02	–13·00, –25·12 to –0·89	–0·4
Stroop 4 colour naming (error rate) score	2·0 (3·0)	1·3 (2·1)			
Change in Stroop 4 colour naming (error rate) score	–0·8 (3·7), –1·76 to 0·16; –0·67	–0·03 (2·5), –0·68 to 0·61; –0·11	0·38	–0·77, –1·91 to 0·38	–0·2

Data are mean (SD) for scores and mean (SD), 95% CI; reliable change index (RCI) for changes between baseline (before DBS) and 6 months. Positive change scores indicate clinical improvement. The Mann-Whitney *U* test was used to determine unadjusted two-sided p values for the group comparisons. *The difference scores (ie, the differences in the mean change scores of both groups) are given as mean, 95% CI. Cohen's *d* was calculated to show the between-groups effect sizes. Positive Cohen's *d* scores show an improvement in the DBS group compared with BMT. DBS=deep brain stimulation. BMT=best medical treatment. MDRS=Mattis dementia rating scale. RAVLT=Rey's auditory verbal learning test. Stroop 1=section 1 of Stroop test: reading words written in black ink. Stroop 2=section 2 of Stroop test: naming colour dots for simple colour naming. Stroop 3=section 3 of Stroop test: interference condition reading words (blue, yellow, green, red) printed in ink of incongruent colours. Stroop 4=section 4 of Stroop test: interference condition naming the ink colour of the written words printed in incongruent colours.

Table 3: **Differences in cognitive test scores at baseline and at 6 months**

Any new symptom or worsening of a pre-existing cognitive or psychiatric symptom was classified as an adverse event. The frequency and severity of adverse events were recorded for the intention-to treat-group.

The study is registered at ClinicalTrials.gov, number NCT00196911.

Statistical analysis

The differences in scores between baseline and the 6-month follow-up were calculated for each test. Because all the tests had interval or ordinal scales, non-parametric tests (Mann-Whitney *U* and Spearman's correlation) were used to compare the between-treatment results. Fisher's exact test was used to analyse the proportions of patients in multiple cases, whenever this statistic is appropriate (eg, patients who used test form A and B at baseline, patients who worsened more than 2 SD in the Mattis dementia rating scale score or who had psychiatric side-effects). We did not correct the level of significance for multiple comparisons; however, we were mindful of the consecutively higher probability of a type 1 error. We analysed the differences in test results in two directions: between two timepoints (test score at follow-up minus test score at baseline) and between groups (mean change in score in the DBS group minus mean change in score in the best medical treatment group).

In the between-time-points analyses, the change is the change in scores for the DBS and best medical treatment groups separately. The relevance of this change is shown by the reliable change index (RCI), which is calculated with the formula RCI=(test score at follow-up–test score at baseline)/SD_{diff}, where SD_{diff} is the standard error of the difference score.[39] Upper and lower cut-off values of 1·645 or –1·645, respectively, indicated reliable change.

In the between-groups analyses, the effect sizes of changes between the DBS and the best medical treatment groups were assessed with Cohen's *d*, an index of the magnitude of a treatment effect.[40] Cohen's *d* is the difference between the means (mean change score in DBS group minus mean change score in best medical treatment group) divided by the pooled SD of both groups at baseline. Cohen's *d* can define effect sizes that are small (*d*=0·2 to 0·49), medium (*d*=0·5 to 0·79), and large (*d*≥0·8).[40]

Neuropsychological and neuropsychiatric variables were correlated with the change in levodopa equivalence dose to assess the effect of this change on cognitive and neuropsychiatric changes. Furthermore, we split the DBS patients into two groups: group A, who had impaired test performance, which was defined by a decrease in test

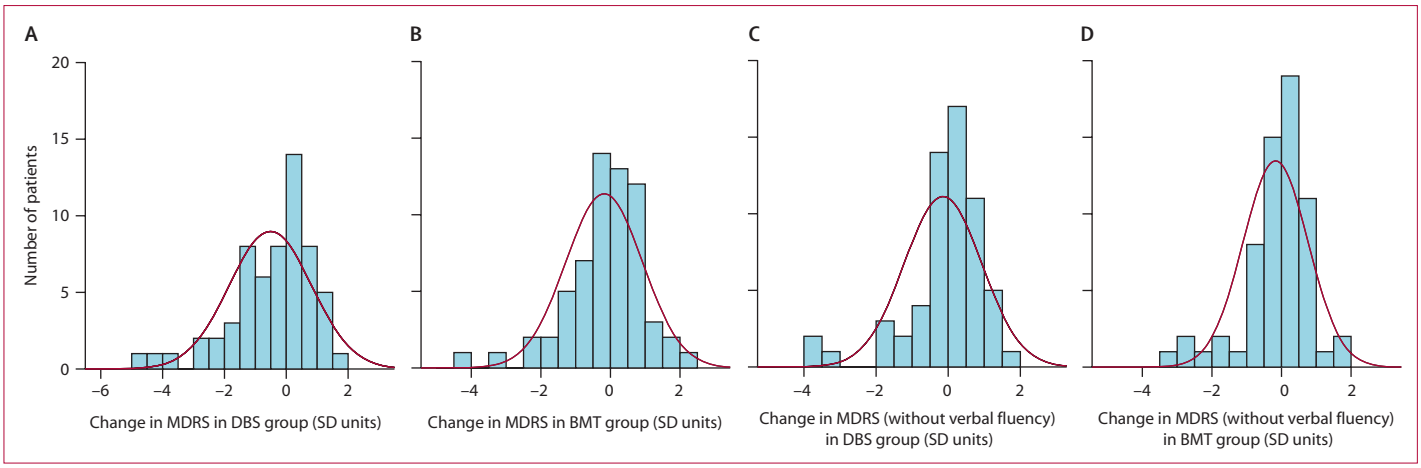

Figure 2: **Changes in SD of MDRS scores between baseline (before DBS) and 6 months**
(A,C) Changes in the DBS group. (B,D) Changes in the best medical treatment group. A and B include verbal fluency; C and D do not include verbal fluency. MDRS=Mattis dementia rating scale. BMT=best medical treatment.

performance of more than 1 SD of the pooled SD at baseline, and group B, who were stable performers, defined by a decrease of less than 1 SD or an improvement in test performance. The quality of life scores were compared between groups A and B, and Spearman's correlation coefficients were calculated for changes in test scores (verbal fluency and Stroop test) and changes in PDQ-36 and SF-36 scores between the groups to detect a relation between cognitive deterioration and quality of life in the DBS group. The level of significance was defined as less than 0·05.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all data in this study and had the final responsibility for the decision to submit for publication.

Results

Changes in motor performance (UPDRS) and quality of life (PDQ-39 and SF-36) are shown in table 2. DBS led to a significant improvement in motor functions and quality of life compared with best medical treatment.[2] There was no difference (p=0·25) in the number of patients who completed test form A or B at baseline: test form A was completed by 64 patients (28 patients in the DBS group and 36 patients in the best medical treatment group) and test form B was completed by 59 patients (32 patients in the DBS group and 27 patients in the best medical treatment group).

See Online for webtable

The difference in scores for overall cognition between groups was not significant (table 3, figure 2). There was, however, a difference in the Mattis dementia rating scale initiation/perseveration subscore due to the verbal fluency item. This finding was consistent with significantly greater negative changes in the semantic and phonemic fluency scores of the verbal fluency test in the DBS group, which was applied separately from the Mattis dementia rating scale. Additionally, the DBS group had significantly greater negative changes in reading time under the interference conditions of the Stroop test than did the best medical treatment group. The error rate in the Stroop test was significantly higher in the DBS group. The effect sizes of the Stroop test were small (error rate and reading times) but verbal fluency reached a medium-sized effect that was significant (table 3). Changes in verbal fluency and performance in the Stroop test were not associated with changes in the scores in the psychiatric scales (Beck depression inventory, Montgomery-Asberg depression rating scale, and the brief psychiatric rating scale), dysarthria, attention (Mattis dementia rating scale attention subscore and digit span), changes in the unified Parkinson's disease rating scale part III, and the levodopa equivalence dose. Changes in dysarthria score (unified Parkinson's disease rating scale part III) did not differ between the DBS and BMT groups (table 2). The changes in the other neuropsychological tests (digit span, Benton visual retention test, and Rey's auditory verbal learning test) after DBS were not significantly different compared with best medical treatment.

No differences in quality of life (PDQ-39 and SF-36) were found when the patients who had DBS were segregated according to whether verbal fluency was impaired or stable (webtable). Furthermore, there were no differences in the cognition and communication subitems of the PDQ-39 (webtable). There was no significant association between changes in verbal fluency and Stroop test performance and between changes in PDQ-39 and SF-36 scores in the patients who had DBS.

To assess the possible general effects of DBS on cognition we further analysed the scores of the Mattis dementia rating scale despite the absence of a significant between-group difference. When the verbal fluency component was

	DBS group	BMT group	p	Difference of changes DBS–BMT*	Cohen's *d*
BDI score	12·0 (5·8)	12·1 (5·3)			
Change in BDI score	1·9 (6·7), 0·20 to 3·53; 2·23	0·4 (5·7), –1·01 to 1·81; 0·57	0·06	1·26, –0·91 to 3·42	+0·2
MADRS	8·7 (5·3)	7·4 (5·2)			
Change in MADRS score	0·6 (7·2), –1·21 to 2·49; 0·69	–1·34 (5·5), –2·71 to 0·02; –1·97	0·07	1·98, –0·30 to 4·26	+0·3
BAI score	21·9 (11·4)	20·6 (11·5)			
Change in BAI score	9·0 (11·6), 6·08 to 11·95; 6·14	–0·6 (11·3), –3·39 to 2·19; –0·72	<0·0001	10·43, 6·08 to 14·78	+0·8
BPRS total score	27·8 (5·2)	27·0 (6·3)			
Change in BPRS total score	3·2 (6·7), 1·48 to 4·91; 3·73	0·8 (6·4), –0·78 to 2·43; 1·03	0·07	2·37, 0·04 to 4·69	+0·4
BPRS (anxiety and depression) score	10·1 (3·0)	9·9 (3·4)			
Change in BPRS (anxiety and depression) score	1·4 (4·2), 0·30 to 2·46; 2·56	0·1 (4·3), –0·93 to 1·21; 0·26	0·15	1·24, –0·27 to 2·74	+0·07
BPRS anergia score	6·1 (2·0)	5·6 (1·9)			
Change in BPRS anergia score	1·1 (2·1), 0·51 to 1·59; –3·87	0·3 (1·6), –0·05 to 0·73; –5·10	0·52	0·71, 0·04 to 1·37	+0·4
BPRS thought disorders score	4·2 (0·8)	4·3 (0·9)			
Change in BPRS thought disorders score	0·1 (1·2), –0·26 to 0·35; 0·33	0·0 (0·5), –0·11 to 0·15; 0·31	0·62	0·03, –0·30 to 0·36	+0·03
BPRS activity score	4·3 (2·0)	4·2 (2·1)			
Change in BPRS activity score	0·7 (2·0), 0·22 to 1·23; 2·86	0·4 (2·0), 0·11 to 0·86; –1·56	0·47	0·35, –0·35 to 1·04	+0·2
BPRS hostility score	3·1 (0·5)	3·1 (0·3)			
Change in BPRS hostility score	0·0 (0·6), –0·15 to 0·15; 0·00	–0·1 (0·5), –0·17 to 0·07; 0·82	0·99	0·05, –1·14 to 0·24	+0·1
SHAPS score	0·8 (1·6)	0·8 (1·3)			
Change in SHAPS score	–0·03 (1·3), –0·35 to 0·28; –0·20	0·3 (1·3), –0·02 to 0·61; 1·85	0·26	–0·32, –0·77 to 0·12	–0·3
BRMS score	1·4 (2·6)	1·2 (2·4)			
Change in BRMS score	0·6 (2·7), –0·07 to 1·29; –1·96	0·3 (1·5), –0·05 to 0·75; –1·75	0·82	0·26, –0·52 to 1·04	+0·1
Apathy score (item 1 UPDRS 1)	0·85	0·96			
Change in apathy score (item 1 UPDRS 1)	0·0, –0·3 to 0·3; –0·11	0·3, 0·0 to 0·5; 2·07	0·22	–0·27, –0·63 to 0·09	–0·1

Data are mean (SD) for scores and mean (SD), 95% CI; reliable change index (RCI) for changes between baseline (before DBS) and 6 months. Positive change scores indicate clinical improvement. The Mann-Whitney *U* test was used to determine unadjusted two-sided p values for the group comparisons. *The difference scores (ie, the differences in the mean change scores of both groups) are given as mean, 95% CI. Cohen's *d* was calculated to show the between-groups effect sizes. Positive Cohen's *d* scores show an improvement in the DBS group compared with BMT. DBS=deep brain stimulation. BMT=best medical treatment. BDI=Beck depression inventory. MADRS=Montgomery-Asberg depression rating scale. BAI=Beck anxiety inventory. BPRS=brief psychiatric rating scale. SHAPS=Snaith-Hamilton pleasure scale. BRMS=Bech-Rafaelsen mania scale. UPDRS=unified Parkinson's disease rating scale.

Table 4: **Differences in psychiatric test scores at baseline and 6 months**

removed from the initiation/perseveration subscore of the scale, the difference that remained was almost zero (table 3). The Mattis dementia rating scale total score was decreased by more than 2 SD in seven (12%) of the patients who had DBS compared with four (6%) of the patients who received best medical treatment (p=0·35; figure 2). After exclusion of the verbal fluency component from the Mattis dementia rating scale, three patients who had DBS (5%) and four patients who had best medical treatment (6%) had a reduction of more than 2 SD (p=0·70; figure 2).

The baseline neuropsychiatric scores and the corresponding changes at 6 months are shown in table 4. Anxiety (Beck anxiety inventory) was significantly reduced in the DBS group but remained unchanged in the best medical treatment group. The effect size indicates a large change, and there was a slight antidepressant effect in the DBS group, which is indicated by an improvement in mood on the Beck depression inventory and the Montgomery-Asberg depression rating scale. Because none of the scores in the psychiatric scales declined significantly after DBS, we did not correlate the changes with quality of life measurements. The changes in levodopa equivalence doses were not associated with any changes in neuropsychiatric scale scores in the DBS group.

	DBS (n=78)	BMT (n=78)
Suicide	1	..
Death in a psychotic episode	..	1
Depression	4	..
Psychosis	4	7
Severe loss of affect (apathy)	1	..

Table 5: **Serious adverse events in the psychiatric domain reported after DBS or best medical treatment**

Ten patients in the DBS group (13%) and eight patients in the BMT group (10%) had severe psychiatric adverse events (table 5). The depressive episodes reported by four patients in the DBS group had remitted by the 6-month follow-up examination.

Discussion

The design of our study enabled a prospective comparison of DBS with best medical treatment in two large groups of patients with advanced PD. We found that global

cognitive function, verbal memory, working memory, and attention were unchanged after DBS; however, significant impairments were seen in verbal fluency and performance in the Stroop test. Cognitive impairments after DBS had no effect on the quality of life, and there was no significant decline in the scores of psychiatric scales at the group level. Depression was more commonly seen after DBS, and medically induced psychosis was more common in the best medical treatment group.

Impaired verbal fluency after DBS has been a consistent finding in case series, but the findings of these studies were mostly based on a comparison between preintervention and postintervention performance.[6] On the basis of our results, we conclude that impaired verbal fluency is not related to disease progression but rather to the intervention. The moderate decline in semantic and phonemic verbal fluency after DBS is in the range reported by Parsons and co-authors,[6] who reviewed 28 studies of the cognitive effect of DBS on the STN in 612 patients.[6] The decline in performance in the Stroop test after DBS was most prominent in the interference condition. The cluster of impairment in verbal fluency and Stroop test performance in the interference condition can be interpreted as impairments of executive functioning, particularly because there was no decline in the results of the other tests. The changes seen in the DBS group might be related to the surgery, to DBS, or to the decrease in medication, although we found no correlations between the changes in neuropsychiatric test results and levodopa equivalents. The decline in executive functions after DBS of the STN might be due to an effect on the loops of the basal ganglia; Frank and co-authors[41] showed the influence of DBS of the STN on decision-making, which suggests that the indirect pathway of the basal ganglial loops is involved in cognitive aspects of response selection.[41] This hypothesis should be investigated in future studies by comparison of the test scores after acute changes in stimulation and medication.

No significant differences were seen between the two groups nor in the within-group analysis in the number of patients whose global cognitive functioning deteriorated. The non-significant change in Mattis dementia rating scale total score in the DBS group due to lower verbal fluency scores (figure 2) underscores the absence of a negative effect of neurostimulation on global cognitive functioning, and is in line with the findings of a previous meta-analysis,[6] which also failed to find significant changes in global cognitive functioning after DBS. By contrast, the authors of the meta-analysis[6] and of non-randomised studies[5,7–11,14] reported a decline in verbal memory performance after DBS, particularly in delayed recall; however, we were unable to confirm this finding (table 3). In our study, the performance of the patients with DBS in the Rey's auditory verbal learning test did not deteriorate, nor did their scores in the immediate or the delayed recall condition. The different results of the other studies might be explained by the absence of randomised control groups or by the specific selection criteria.

One related and serious concern is that even modest postsurgical cognitive impairment can shift patients with borderline or mild impairment into the moderate-to-severe range of cognitive dysfunction.[6] This becomes particularly relevant for changes in verbal fluency because an effect of impaired verbal fluency on daily activities has been reported in non-demented patients with PD;[20,42] furthermore, this group has shown small-to-medium impairments in verbal fluency.[43] If DBS further impairs verbal fluency, an additive effect could be suspected; however, our results do not support this argument (figure 2).

Executive dysfunction in the DBS group had no effect on the benefits of DBS on quality of life, even for the communication and cognition subitems of the PDQ-39. The dramatic improvement in motor function and the pronounced reduction in dyskinesias after DBS account for most of the improvement in quality of life.[2] We conclude from this analysis that the moderate decline in cognitive function after DBS of the STN does not lead to a decline in quality of life.

The overall occurrence of severe psychiatric side-effects was 12·8% in the DBS group and 10·3% in the best medical treatment group. Overall there was an improvement in depression scores after DBS but the effect size was small (table 4), which is in agreement with other published reports.[7,44] The improvement in the Beck anxiety inventory scores after DBS has the greatest effect size (Cohen's d=0·8) of all the changes in the psychiatric domain. However, caution is warranted in the interpretation of such a large change after DBS because the Beck anxiety inventory includes several items with a strong somatic connection (eg, inability to relax, unsteady gait, tremor of the hands, feeling shaky, gastrointestinal symptoms, and faintness) that improve considerably after DBS. The brief psychiatric rating scale includes the clinician-rated items anxiety and depression, which were not different between the two groups. This argues against a dramatic effect of DBS on the symptoms of anxiety; however, the change in the Beck anxiety inventory score could also show a true effect that otherwise goes unnoticed by physicians. The patients in this study had severe motor fluctuations, which were mostly seen with off-state-related anxiety; however, because off time is reduced by 80% after DBS,[2] the reduction in anxiety might only be seen in the patient-based questionnaire of the Beck anxiety inventory.

One patient committed suicide after DBS and one patient in the best medical treatment group died after he caused an automobile accident during a psychotic episode (table 5). Both complications might or might not be indirectly related to the treatments; psychosis was more common in the best medical treatment group (seven *vs* four), which indicates a higher risk of medication-induced psychosis than the DBS group, who were on reduced medication. Transient depressive episodes after DBS have been seen in between 1·5% and 25·0% of patients.[1,18,19,45–49] Withdrawal of dopaminergic

medication might contribute to this postoperative depression.[19] The same mechanism has also been discussed as a cause of apathy, which is one of the most commonly reported adverse behavioural effects of DBS.[19] One patient had a severe loss of affectivity, which was comparable with apathy. However, the apathy score for the DBS group did not change significantly between baseline and at 6 months, despite a reduction in dopaminergic medication of about 50%. The results of our controlled study are, therefore, a strong argument against a systematic apathy-inducing effect of DBS. However, we assessed only the first 6 months postsurgery, whereas some authors have reported an increase in apathy in long-term follow-up at 1 year and 3 years.[50,51] Mania in the first weeks after implantation of the DBS device has been reported, and the authors of open-case series have reported a high proportion of hypomanic states (4% to 15%).[1,8,45,52] Because the serious psychiatric side-effects after surgery are published in case-report format, their frequency might be overestimated.[16,50,53] We found no occurrence of mania in our study, and the absence of high mania scores (table 4) diminishes the risk of this side-effect. The frequency of psychiatric side-effects also depends on the postoperative management of these patients; there are potential interactions with dopaminergic medication and stimulation.[19,54] Most psychiatric side-effects were transient, and systematic psychiatric evaluation did not find any psychiatric deterioration, which suggests that side-effects can, indeed, be managed. In summary, the patients in the best medical treatment group mostly had hyperdopaminergic side-effects (medication-induced psychosis), whereas patients treated with DBS more commonly had side-effects due to hypodopaminergic stimulation.

There are some limitations in our study design. There was no sham surgery group or a placebo control; because of the potential side-effects, the use of sham surgery controls is ethically dubious.[55] Placebo stimulation in a blinded condition is also not practical because DBS interferes with antiparkinsonian medication and the large reduction in medication that is necessary to reduce motor complications would unmask the stimulation condition.[2] A further problem is that we did not correct the level of significance for multiple comparisons; this was owing to the high probability of type II errors, which might mask possible adverse effects of the surgery. This implies that we accept the higher probability of type I errors. The range of cognitive functions tested is restricted; however, the number of tasks with multiple parallel versions for repeated testing and the time available to test patients in such a large trial are restricted. Nevertheless, we do not believe that these limitations have substantially distorted the main results of our study.

Despite the fact that we were able to show the safety of DBS for the cognitive and psychiatric domains in a randomised, multicentre setting, some important questions are unanswered. What is the cut-off score for patients who have moderate cognitive impairments before surgery? We were also not able to establish which specific changes in the cognitive and the psychiatric domains after DBS are related to old age, because only 15 of 123 of our patients (12%) were older than 70 years. Further efforts will be needed to identify the presurgical specific risk factors that might predict the individual cognitive and behavioural changes incurred by DBS. The results of recent investigations suggest that patients with PD and mild cognitive impairment of the non-memory type (including patients with slight executive dysfunction) have a high risk of dementia in the course of the disease.[56,57] Long-term follow-up studies report an incidence of dementia that is compatible with the natural progression of the disease.[1,58]

Contributors

KW, CD, PK, and GD were responsible for the concept and the design of the study. CD, JR, MOP, MK, VT, MKl, AS, LW, KB, AD, RH, VS, AK, and EK acquired the data, which was analysed and interpreted by KW, CD, PK, and GD. KW, CD, and GD drafted all or parts of the article, which was reviewed by PK, MOP, JV, JR, AK, AD, MK, VT, MKl, AS, LW, KB, RH, VS, and EK. KW and CD contributed their statistical expertise. GD obtained the funding and supervised the study.

Conflicts of interest

KB, GD, PK, MK, AK, MP, AS, VS, VT, JV, and LW have received speaking fees from Medtronic. GD, VT, JV, and LW have received consulting fees from Medtronic. GD, AK, MK, and JV have received research grants from Medtronic. VS owns stock options in Medtronic. The other authors have no conflicts of interest.

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