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Impact of sub-thalamic nucleus deep brain stimulation on dual tasking gait in Parkinson's disease

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Abstract

Background: The beneficial effects of bilateral sub-thalamic nucleus deep brain stimulation on motor function and gait in advanced Parkinson's disease are established. Less is known about the effect of stimulation on cognitive function and the capacity to walk while dual tasking, an ability that has been related to fall risk. Everyday walking takes place in complex environments that often require multi-tasking. Hence, dual tasking gait performance reflects everyday ambulation as well as gait automaticity. The purpose of this study was to examine the impact of sub-thalamic nucleus deep brain stimulation on dual task walking in patients with advanced Parkinson's disease.

Methods: Gait was assessed using a performance-based test and by quantifying single-task and dual task walking conditions in 28 patients with advanced Parkinson's disease. These tests were conducted in 4 conditions: "OFF" medication, with the stimulator turned on and off, and "ON" medication, with the stimulator turned on and off. A previously validated, computerized neuro-psychological battery assessed executive function, attention and memory "OFF" and "ON" deep brain stimulation, after subjects took their anti-Parkinsonian medications.

Results: Stimulation improved motor function and the spatiotemporal parameters of gait (e.g., gait speed) during both single-task and dual task walking conditions. Attention improved, but executive function did not. The dual task effect on gait did not change in response to stimulation. For example, during serial 3 subtractions, gait speed was reduced by -0.20 ± 0.14 m/sec while OFF DBS and OFF meds and by −0.22 ± 0.14 m/sec when the DBS was turned on (p = 0.648). Similarly, ON medication, serial 3 subtractions reduced gait speed by −0.20 ± 0.16 m/sec OFF DBS and by -0.22 ± 0.09 m/sec ON DBS (p = 0.543).

Conclusions: Bilateral sub-thalamic nucleus deep brain stimulation improves motor symptoms, certain features of gait and even some aspects of cognitive function. However, stimulation apparently fails to reduce the negative impact of a dual task on walking abilities. These findings provide new insight into the effects of deep brain stimulation on gait during cognitively challenging conditions and everyday walking.

Keywords: Dual task, Falls, Executive control, Parkinson's disease, Cognitive impairment, Gait, DBS

Background

In patients with advanced Parkinson's disease, sub-thalamic nucleus (STN) deep brain stimulation (DBS) reduces tremor, rigidity and bradykinesia, allows for a significant decrease in anti-Parkinsonian medications, and diminishes dyskinesias [1-4]. Indeed, pre-surgery Unified Parkinson's Disease Rating Scale (UPDRS) motor scores may often be improved by two-thirds in response to DBS [2-5]. DBS also enhances postural control and increases gait speed and stride length, both off and on anti-Parkinsonian medications [6-9]. From this perspective, DBS appears to provide good relief for key motor symptoms of advanced PD.

The effects of DBS on the ability to walk while performing a dual task (DT) have not been previously studied. Everyday walking typically takes place in complex environments and challenging situations that demand

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appropriate allocation of attention between gait and simultaneously-performed additional tasks such as talking on a cellphone [10,11]. Thus, whereas single-task walking represents the capabilities of a patient, DT walking abilities more closely reflect functional ambulation in cognitively-demanding conditions. DT walking abilities also provide a window into the automaticity of movement [10,12]. Over-learned movements do not depend on attention or cognitive input and are generally impervious to the effects of dual tasking. For example, healthy young adults can walk and perform other tasks with little impact on their gait. Conversely, when gait is impaired or relies on cognitive input, a DT will cause marked changes in the walking pattern. The simultaneous performance of a DT generally causes patients with PD to walk more slowly, with shorter strides, and with a much larger effect of the DT on gait than seen in healthy controls [11,13-16]. Pilot studies have demonstrated that interventions may enhance DT abilities even in PD [17-20], however, the effects of STN DBS on DT gait have not yet been investigated.

A priori, there are several ways to view the impact of DBS on DT walking. One possibility is that the negative DT effects, i.e., the DT costs, might be reduced as a result of DBS due to the improved motor function. If walking becomes a more automatic process after DBS and walking capacity improves, then it should be more resistant and impervious to the negative effects of DT. In other words, DBS should improve functional reserve so that it is less vulnerable to the effects of a DT. Alternatively, although gait improvement does occur in response to DBS, not all aspects of gait respond similarly to DBS [21-25]; for example, freezing of gait typically does not respond well to traditional STN DBS [26]. From this perspective, perhaps those gait properties that are more critical to DT abilities will not be enhanced. The effects of DBS on cognitive function are inconsistent, with some studies even reporting a decline in executive function following DBS [2,27,28]. Since DT abilities are also related to cognitive abilities, especially executive function [10,29], it could be speculated that DBS might not ameliorate the DT costs.

The primary purpose of the present study was to address these questions by quantifying the DT effects on gait in patients with PD while ON and OFF DBS. We hypothesized that STN DBS (ON DBS) reduces the DT costs of gait, compared to the costs observed when the stimulator is off (OFF DBS). To investigate the effects of DBS in a state that more closely reflects the underlying pathology, we examined the subjects during the OFF medication state. To evaluate conditions that reflect everyday function, patients were also assessed in the ON state (ON, OFF meds and ON and OFF DBS). Analysis focused on two properties of gait: 1) average stride length (and the closely related average gait speed). Stride length and gait speed are widely accepted

measures of mobility in general [30], and in PD specifically [31,32]. 2) measures of gait variability. These gait features reflect the rhythmicity and consistency of the gait pattern, are altered in PD, are related to disease severity, and are related to fall risk [15,33-37]. Because of the potential role of cognitive function in DT costs, we also quantified the effects of DBS on this domain to gain insight into the relationship between the STN, cognitive function, and DT abilities in patients with advanced PD.

Methods

Participants

Subjects were included if they fulfilled UK Brain Bank criteria for PD [38], if they had undergone bilateral STN DBS surgery at least two months prior to the study for treatment of PD symptoms, if their stimulation settings were stable, and if they could walk independently without any walking aids, with the DBS on. Standard clinical criteria were used to evaluate the subjects for their suitability for STN DBS surgery. Selection criteria that were applied are those that have become widely accepted in many parts of the world. This includes, for example, at least a 30% improvement in UPDRS scores in response to an l-dopa challenge; a diagnosis of idiopathic PD for at least 4 or more years; complications of medication including ON-OFF fluctuations and/or dyskinesias; normal brain MRI; and otherwise generally healthy. Psychiatric exclusions include sub-optimally controlled depression. Psychotic patients are automatically excluded. To be approved for DBS surgery, the patients undergo a battery of cognitive tests. Addenbrooke's Cognitive Examination (ACE) is used as a cognitive screen (subjects are included if they score over 70), along with the Frontal Assessment Battery (FAB), for which we generally will require a score of at least 12. The Hamilton Depression Rating Scale (HDRS) is used to screen for depression; subjects who score more than 15 will be excluded or sent for more detailed evaluation. Frank dementia is obviously an exclusion factor. Between 50% and 70% of patients who are referred to our center for surgery meet accepted inclusion criteria. The institutional review board (IRB) of Hadassah University Hospital approved this study and informed written consent was obtained.

Protocol

Subjects arrived for the assessment in the morning, at least 12 hours after taking their last anti-Parkinsonian medication dose, i.e., in an OFF meds/ON DBS state, when medication effects are minimal [39,40]. While OFF medications, they were familiarized with the gait and dual tasks. Subjects then completed gait testing, the Timed Up and Go test, and the motor part of the UPDRS, both ON and OFF DBS. Subjects then took their usual morning dose of anti-Parkinsonian medications. After reaching a

self-declared ON medication state (typically 30–60 minutes later), gait, the Timed Up and Go, and the motor part of the UPDRS were re-evaluated. A neuropsychological battery quantified cognitive function both ON and OFF DBS, while ON meds. The order of testing (ON vs. OFF DBS), was randomized both while OFF medications and while ON medications. With ample breaks, the entire protocol typically took about 3 hours to complete.

Gait tasks

Gait was studied in three conditions: 1) "single-task", usual-walking at a self-selected comfortable speed (ST walking), 2) walking while subtracting serial 3s from a predefined 3 digit number (DT-S3) and 3) walking while performing a verbal fluency task (DT-VF) (without explicit instructions regarding prioritization); they were asked to recite words that began with a specific letter (the letter was randomized across conditions), using a previously validated protocol [41,42]. To determine if the effects of DBS on DT gait were dependent on the specifics of the dual task, both the arithmetic and fluency tasks were used. The order of testing (ST, DT-S3, and DT-VF) was randomized. Under each condition, subjects walked up and down an 18 meter-long, 2-meter wide hallway at their self-selected speed for one minute.

Secondary tasks

In each medication/DBS condition, serial subtraction (using a different 3 digit starting number) was also performed for one minute in the seated position to allow for quantification of the effects of walking on these cognitive tasks. The order of testing, i.e., seated vs. walking, was randomized. To minimize testing time, verbal fluency was not tested in the seated position. For both secondary tasks, the number of errors and number of words or subtractions were scored to evaluate performance on the serial subtraction and verbal fluency tests.

For each walking condition, several gait measures were derived from force sensitive shoe insoles and a stopwatch, using previously described and validated methods [14,15,19]. Briefly, steady-state gait speed was calculated by measuring the time to complete the middle 10 meters of each lap, averaged over all laps for each walk. Additional gait parameters that were evaluated included: average stride length, average stride time, average swing time, and gait variability, as measured by stride time variability and swing time variability [14,15,19]. Stride time was defined as the time from initial foot contact to the next initial foot contact. Swing time, presented as a percent of the gait cycle, was defined as the time of single support; it is determined by the time from toe-off to heel-strike, divided by the stride time ($\times 100$) and presented as a percent of the gait cycle (for healthy young adults, swing time % is about 40% of the gait cycle).

Variability was defined using the coefficient of variation, e.g., $100 \times$ (standard deviation of stride time)/(average stride time). Using previously described methods, the data at each turn (that took place when the subject reached the end of a lap) and any data during freezing of gait episodes, were excluded from the analysis. Any freezing of gait episode was counted in each walking condition. To compare the DT effects across DBS and medication states, the DT cost measure was calculated as the difference between the single-task and DT walking conditions, for each gait parameter [10,11]. We also verified that the results were similar if DT costs were calculated as percent change instead of the difference. Since both methods of estimating DT costs produced similar findings, only the results based on the differences are reported.

Assessment of PD symptoms and cognitive function

PD status and disease severity were evaluated using the motor portion of the UPDRS [43]. Mean L-dopa daily dose was quantified as previously described [44]. The Timed Up and Go test assessed functional mobility [45,46] (standard instructions were followed; there was no dual task during this test). A computerized neuropsychological test battery (Mindstreams®, NeuroTrax Corp., NJ), previously validated in patients with PD [15,47] quantified executive function, memory and attention (largely sustained attention) [48,49]. The executive function battery included computerized versions of the Go-No-Go and the Stroop interference tests. The test battery generates composite indices of each cognitive domain [48-50] on an IQ-like scale, with 100 representing the estimated population mean normalized for age and education.

Statistical analysis

Descriptive statistics are reported as mean ± standard deviation. Many of the dependent variables were not normally distributed; hence, non-parametric analyses were applied since they make no assumptions about the distribution of the data and are not sensitive to extreme values. To assess the effects of DBS on gait, Friedman's tests (the non-parametric parallel to repeated measures ANOVA) were first applied for each gait parameter (e.g., gait speed) to determine if any of the walking conditions differed from one another (i.e., ST,

Table 1 Subject characteristics (n = 28)

Age (years)	61.46 ± 8.13
Gender	3 females
Disease duration (years)	13.2 ± 5.0
Mini Mental State Exam	27.9 ± 1.7
Time after surgery (months)	25.4 ± 13.1
UPDRS motor scores (OFF DBS/OFF meds)	38.53 ± 13.53

Table 2 Effects of DBS on motor symptoms and single-task, usual-walking gait

	OFF meds			ON meds		
	OFF DBS	ON DBS	P-value OFF vs. ON DBS	OFF DBS	ON DBS	P-value OFF vs. ON DBS
UPDRS Motor part	38.53 ± 13.53	17.5 ± 8.20	<0.001	36.20 ± 13.84	13.40 ± 7.82*	<0.001
Timed Up and Go (sec)	14.97 ± 5.69	12.62 ± 4.42	0.001	13.28 ± 3.27	11.46 ± 2.35*	0.007
Gait speed (m/s)	1.01 ± 0.30	1.09 ± 0.31	0.009	1.13 ± 0.19	1.21 ± 0.18*	0.053
Stride length (m)	1.09 ± 0.29	1.16 ± 0.30	0.005	1.27 ± 0.14	1.32 ± 0.15*	0.049
Stride time (sec)	1.10 ± 0.12	1.090 ± .10	0.502	1.09 ± 0.10	1.09 ± 0.10	0.653
Stride time variability (%)	2.82 ± 1.42	2.33 ± 1.24	0.093	2.19 ± 0.91	1.84 ± 0.46*	0.407
Swing time (%)	36.19 ± 3.09	36.18 ± 2.68	0.654	36.66 ± 2.87	36.90 ± 2.05	0.199
Swing time variability (%)	5.35 ± 3.10	4.65 ± 2.81	0.156	4.68 ± 2.02	3.94 ± 1.20	0.035

*indicates a significant difference between OFF meds/OFF DBS vs. ON meds/ON DBS.

DT-S3, DT-VF). If differences were observed (p < 0.05), Wilcoxon Signed Rank tests were applied to determine which conditions differed. Similar analyses were applied to the cognitive measures, other patient characteristics, and to the DT costs. P-values reported are based on two-tailed comparisons. The significance level was set at 0.05. Statistical analyses were performed using SPSS for Windows.

Results

Subject characteristics

In a consecutive sample spanning from October 2007 to November 2008, 28 patients with PD met the inclusion and exclusion criteria and agreed to participate. Patient characteristics are summarized in Table 1 and Table 2. Stimulation parameters included a mean rate of 161.96 ± 24.01 Hz for the left or the right side. The mean voltage was 3.08 ± 0.58 V for the right side and 3.12 ± 0.61 V for the left side. Pulse width was 90 μs for 10 electrodes (in 6 patients) and 60 μs for the other 46 electrodes. Mean L-dopa daily dose was 1180 ± 758 mg before surgery and 490 ± 269 mg after surgery (p < 0.001); with a median decrease in medication dose of 60% (Dopa-equivalent).

Effects of DBS on motor function and single-task walking

UPDRS motor scores improved significantly (p < 0.0001) with DBS stimulation (both ON and OFF meds), and when comparing the two extreme states (i.e., OFF meds/

OFF DBS vs. ON meds/ON DBS) as seen in Table 2. Similarly, Timed Up and Go times decreased (i.e., improved) in response to DBS, both ON meds (p = 0.007) and OFF meds (p = 0.001). Timed Up and Go duration in the ON meds/ON DBS condition was significantly lower than that in the OFF meds/OFF DBS condition.

Table 2 summarizes the single-task walking parameters in the 4 medication/DBS conditions. Gait speed improved in response to DBS in the OFF meds condition (p = 0.009). In the ON meds condition, gait speed also tended to improve, but this increase was not significant (p = 0.053). Gait speed and stride length in the ON meds/ON DBS condition were significantly greater than those in the OFF meds/OFF DBS condition. Stride time variability improved (i.e., decreased) in response to DBS in the OFF meds condition, however, this change did not reach the level of significance (p = 0.093). Swing time variability significantly improved in response to DBS in the ON meds condition (p = 0.035).

Effects of DBS on DT costs

Both dual tasks (serial subtractions and verbal fluency) had a significant negative impact on almost all gait parameters in all 4 conditions, compared to single-task walking (typically p < 0.0001 under every condition, for all gait parameters). For example, in the OFF meds/OFF DBS condition, gait speed was reduced from 1.01 ± 0.30 m/sec during single-task walking to 0.84 ± 0.29 m/sec

Table 3 Effects of DBS on dual task costs during serial 3 subtractions*

	OFF meds			ON meds		
	OFF DBS	ON DBS	P-value OFF vs. ON DBS	OFF DBS	ON DBS	P-value OFF vs. ON DBS
Gait speed (m/sec)	−0.20 ± 0.14	−0.22 ± 0.14	0.648	−0.20 ± 0.16	−0.22 ± 0.09	0.543
Stride length (m)	−0.16 ± 0.09	−0.16 ± 0.11	0.823	−0.17 ± 0.10	−0.15 ± 0.11	0.778
Stride time (sec)	0.08 ± 0.11	0.08 ± 0.10	0.433	0.07 ± 0.10	0.09 ± 0.10	0.398
Stride time variability (%)	0.62 ± 0.81	0.84 ± 0.95	0.067	2.09 ± 3.17	1.01 ± 0.91	0.243
Swing time (%)	−1.09 ± 1.07	−0.93 ± 0.91	0.247	−1.21 ± 1.63	−0.81 ± 1.00	0.904
Swing time variability (%)	1.70 ± 1.44	1.78 ± 1.48	0.502	2.33 ± 3.97	1.19 ± 1.62	0.355

*Entries are single-task - dual task values.

Table 4 Effects of DBS on dual costs during the verbal fluency task*

	OFF meds			ON meds		
	OFF DBS	**ON DBS**	**P-value OFF vs. ON DBS**	**OFF DBS**	**ON DBS**	**P-value OFF vs. ON DBS**
Gait speed (m/sec)	−0.21 ± 0.10	−0.20 ± 0.08	0.615	−0.22 ± 0.12	−0.22 ± 0.09	0.681
Stride length (m)	−0.17 ± 0.08	−0.16 ± 0.07	0.903	−0.16 ± 0.07	−0.15 ± 0.07	0.494
Stride time (sec)	0.10 ± 0.12	0.07 ± 0.07	0.181	0.10 ± 0.13	0.08 ± 0.10	0.520
Stride time variability (%)	0.61 ± 1.29	1.18 ± 1.73	0.192	1.61 ± 1.99	1.23 ± 1.46	0.687
Swing time (%)	−1.01 ± 1.20	−1.13 ± 1.03	0.689	−1.23 ± 1.30	−1.45 ± 2.66	0.658
Swing time variability (%)	1.82 ± 1.59	2.00 ± 2.44	0.958	2.60 ± 3.80	3.36 ± 8.63	0.573

*Entries are single-task - dual task values.

($p < 0.0001$) during serial 3 subtractions, and to 0.82 ± 0.28 m/sec ($p < 0.0001$) during the verbal fluency task. In the ON meds/ON DBS condition, gait speed was reduced from 1.08 ± 0.32 m/sec during single-task walking to 0.91 ± 0.29 m/sec during serial 3 subtractions ($p < 0.0001$), and to 0.87 ± 0.30 m/sec during the verbal fluency task ($p < 0.0001$).

As summarized in Tables 3 and 4, the DT cost of all gait parameters did not change with stimulation compared to the DT cost without stimulation, when subjects were ON or OFF medications (see also Figure 1). The DT costs in the two extreme conditions (i.e., OFF meds/ OFF DBS and the ON meds/ON DBS) were also not significantly different from each other for all gait parameters. As noted in the Methods, the lack of any

beneficial effect of DBS on DT costs was also observed if costs were determined as percent change. For example, for gait speed, the percent change in each of the 4 conditions, corresponding to those in Table 3, were: -20.67% and -23.20% (P = 0.848, DBS effect OFF meds) and −16.38% and −20.20% (P = 0.778, DBS effect ON meds) during serial subtractions. Table 4 summarizes the effects of DBS on dual costs during the verbal fluency task. As was the case for serial subtraction, the DT cost of all gait parameters did not change with stimulation compared to the DT cost without stimulation, during the verbal fluency task.

Performance of secondary tasks

Tables 5 and 6 summarize the performance of the secondary tasks in all 4 walking conditions. Briefly, in response to
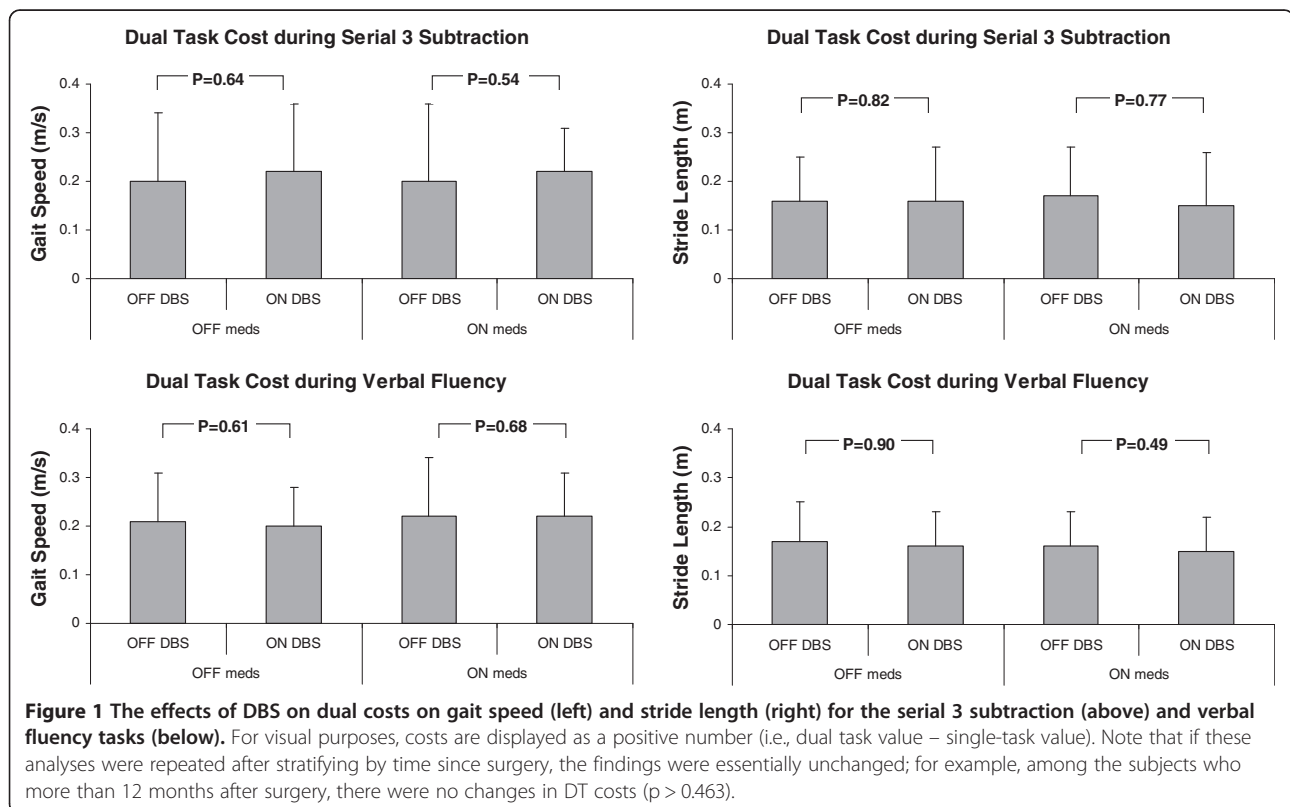

Figure 1 The effects of DBS on dual costs on gait speed (left) and stride length (right) for the serial 3 subtraction (above) and verbal fluency tasks (below). For visual purposes, costs are displayed as a positive number (i.e., dual task value – single-task value). Note that if these analyses were repeated after stratifying by time since surgery, the findings were essentially unchanged; for example, among the subjects who more than 12 months after surgery, there were no changes in DT costs (p > 0.463).

Table 5 Performance on secondary tasks: number of subtractions (S3) and verbal fluency (VF)

	OFF meds			ON meds*		
	OFF DBS	**ON DBS**	**P-value OFF vs. ON DBS**	**OFF DBS**	**ON DBS**	**P-value OFF vs. ON DBS**
S3 Sitting	16.09 ± 7.84	17.77 ± 8.23	0.055	16.77 ± 9.12	17.50 ± 8.56	0.830
S3 Walking	15.61 ± 7.77	15.66 ± 8.07	0.796	15.05 ± 7.75	17.94 ± 8.27	0.036
P-Value Sitting vs. Walking	0.659	0.001		0.157	0.311	
VF Walking	6.26 ± 3.14	6.47 ± 1.92	0.732	6.66 ± 2.19	6.77 ± 2.57	0.855

*Entries are the mean ± standard deviation number of words recited in each condition for verbal fluency and the mean ± standard deviation number of subtractions during the serial 3 subtraction task.

DBS, the number of serial subtractions performed during walking was unchanged OFF medications (p = 0.796). ON medications, the number of serial subtractions increased (p = 0.036). The number of mistakes made was not related to medication or DBS condition (see Table 6). Verbal fluency performance was also independent of medication and DBS condition.

Effects of DBS on freezing of gait

Freezing of gait (FOG) was observed in 9 subjects. FOG occurred in 12% of the walking tasks. The vast majority of the freezing (79%) took place during the turns at the end of each lap, i.e., only about 3% of the walks were interrupted by FOG in the middle of a lap. The number of FOG episodes was not significantly affected by DBS. For example, in the OFF medication condition (p > 0.18 overall), 3 episodes occurred during usual walking, both ON and OFF DBS. 4 episodes took place during serial 3 subtractions OFF DBS and 6 occurred ON DBS. Two FOG episodes occurred during the verbal fluency dual task off DBS, while 4 occurred when DBS was on.

Effects of DBS on cognitive function

Figure 2 shows the cognitive index scores both ON and OFF DBS (while ON meds). Attention improved in response to DBS and executive function improved, however, the increase was not statistically significant. Memory did not improve in response to DBS. Interestingly, improvements in the executive function index in response to DBS were associated with lower (i.e., better) DT costs for stride length during the verbal fluency task (r = 0.65, p = 0.032) (see Figure 3). Similarly, improvements in the executive function index in response to DBS were associated with

lower (i.e., better) DT costs for stride time variability during the serial 3 subtraction task (r = 0.66, p = 0.038).
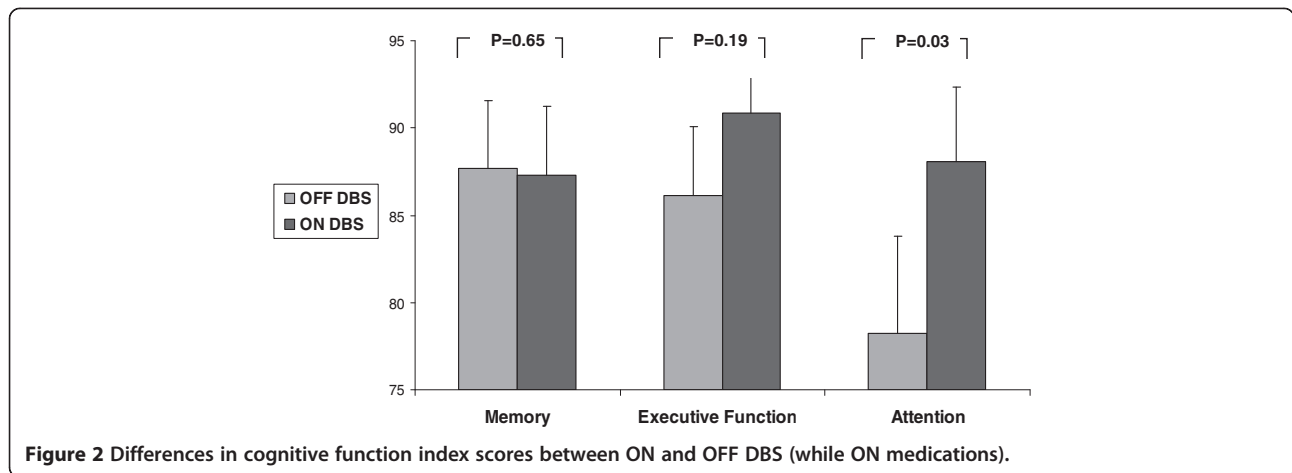
Discussion

STN DBS has previously been associated with improvements in motor function, stride length, gait speed and rhythmicity [6-9]. We, therefore, hypothesized that gait would be more consistent and automatic and less cognitively demanding when the stimulation was activated and that this effect would lead to a reduction in the DT costs of gait, compared to the costs observed when the stimulator is off. Our findings suggest that this hypothesis should be rejected. Although we found improvement in certain features of single-task gait and cognitive function with stimulation, the impact of DT on gait was unchanged in response to bilateral STN DBS.

One partial explanation might be that the effects of DBS on cognitive function were not sufficient or specific enough to elicit beneficial changes to DT walking. We found improvement in attention with STN stimulation, although executive function did not improve significantly. The attention index that we used largely reflects sustained attention, but not task switching or dual tasking. Executive function may be more closely associated with DT performance and complex everyday walking in PD [10,11,51]. While executive function did respond to DBS in some subjects and there was an association between improvement in this cognitive domain and DT costs (recall Figure 3), this finding was not consistently observed. Thus, this overall negative finding with respect to executive function might explain the lack of improvement in DT walking ability. Improvements in single-task gait alone are apparently not sufficient to lower the DT impact as some form of cognitive reserve

Table 6 Performance on secondary tasks: mistakes in the number of subtractions or while generating words

	OFF meds			ON meds		
	OFF DBS	**ON DBS**	**P-value OFF vs. ON DBS**	**OFF DBS**	**ON DBS**	**P-value OFF vs. ON DBS**
S3 Sitting	1.04 ± 1.09	0.90 ± 1.06	0.476	0.88 ± 1.13	0.94 ± 0.99	0.803
S3 Walking	1.33 ± 1.13	1.44 ± 1.38	0.750	1.31 ± 1.70	1.42 ± 1.64	0.677
P-Value Sitting vs. Walking	0.408	0.694		0.239	0.770	
VF Walking	0.52 ± 0.84	0.89 ± 0.87	0.109	0.27 ± 0.57	0.72 ± 1.12	0.190

S3: serial 3 subtractions; VF: verbal fluency.

Figure 2 Differences in cognitive function index scores between ON and OFF DBS (while ON medications).
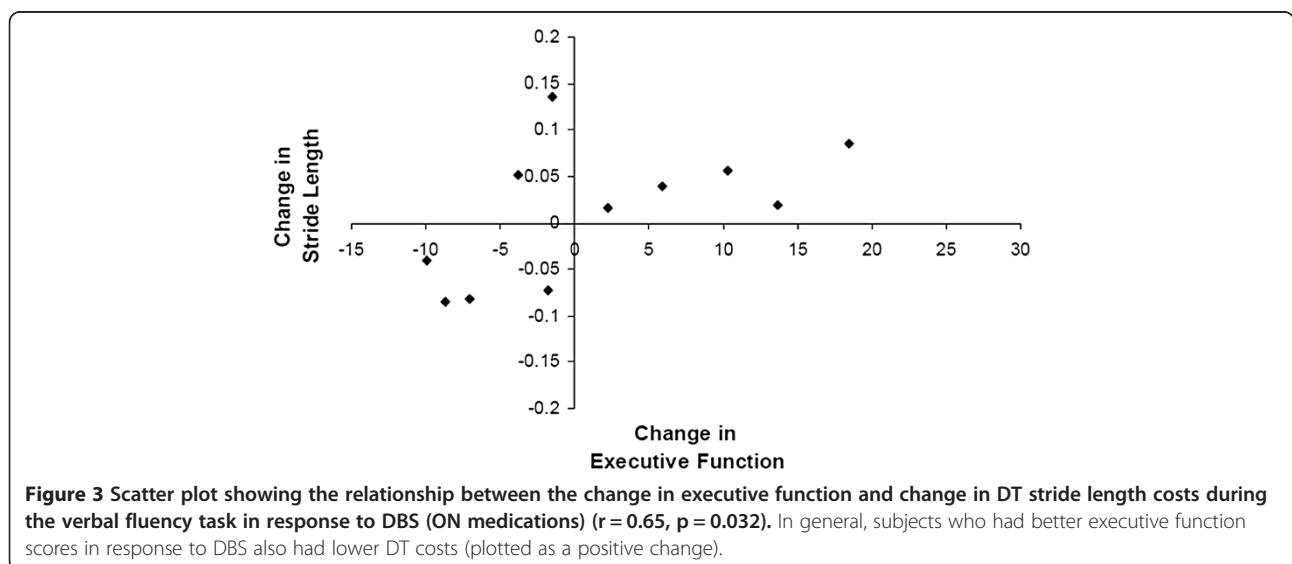
is apparently involved during DT walking in patients with PD [12]. This observation that only specific sub-domains of cognitive function improved in response to DBS is consistent with previous studies [27,52]. Interestingly, Alberts et al. [53] reported that bilateral STN DBS leads to a decreased ability to track forces when the dual task was complex (e.g., serial 3 subtractions), somewhat parallel to the influence of serial subtractions on gait in the present study.

The basal ganglia have multiple connections to frontal networks that regulate executive function and cognitive abilities [54,55]. The present findings are consistent with previous studies that suggested that STN DBS does not positively influence these circuits and their function [2,27,28]. In addition to the basal ganglia-thalamocortical motor circuits, output from the basal ganglia also ends in the pedunculopontine nucleus (PPN), an area which has been termed the brain's gait pace regulator [56-58]. Noting the ineffectiveness of STN DBS to reduce fall risk and

freezing of gait, consistent with the present findings, several authors speculated that PPN stimulation may be more successful for ameliorating axial symptoms like freezing and falls [26,44,58]. In the future, it would be interesting to test whether DT costs respond to PPN stimulation.

Clinical implications and limitations

Falls and freezing of gait, common causes of falls in PD, are, typically, unresponsive to STN DBS [21,28,58,59]. Weaver et al. even describe an increase in fall frequency post-DBS among patients with PD [60]. It is unclear if this increase is a direct effect of DBS or an indirect result [60]. Improved ambulation following DBS may lead to greater exposure to challenging situations and, hence, to an increased risk of falls. Among older adults and in patients with PD, many falls occur during ambulation and fall risk has been related to executive function, DT performance, gait variability, and usual-walking gait abilities [15,42,51,61-69]. In the present study, usual-

Figure 3 Scatter plot showing the relationship between the change in executive function and change in DT stride length costs during the verbal fluency task in response to DBS (ON medications) (r = 0.65, p = 0.032). In general, subjects who had better executive function scores in response to DBS also had lower DT costs (plotted as a positive change).

walking gait speed improved in response to DBS, however, these other fall risk factors were generally not responsive to DBS. If subjects walk faster after DBS, while their cognitive function and ability to cope with challenging conditions are unchanged, as reflected in the DT costs, perhaps they have a greater risk for falls. In this regard, it is interesting to note that the present findings suggest that just as patients with PD inappropriately focus their attention on the secondary, dual tasks and apply a "posture second" strategy [12,16], this poor judgment is not responsive to DBS.

This study has several limitations. For example, the assessment protocol was long (approximately 3 hours) and some subjects became tired toward the end. This may have resulted in an under-estimation of the effects of anti-Parkinsonian medication, as the assessments with medication were always conducted last, when the subjects were most likely to be tired. On the other hand, this situation may actually reflect everyday abilities. Similarly, we did not assess the response to a supra-maximal dose of l-dopa, something that might be of interest in the future, because we aimed to focus on testing that reflects the subject's typical abilities and medication dosing. We also did not make any statistical corrections for multiple comparisons. However, this analytical choice actually increased the likelihood that we might find support for lower DT costs in response to DBS; the results did not support this possibility, even though both dual tasks generally had robust (e.g., $p < 0.001$) negative effects on gait. Another limitation is that the assessor was not blinded to the condition. However, data analyses were performed offline using automated software routines that were blinded to the conditions. Finally, we did not include a healthy control group to compare the DT costs. However, previous studies reported higher DT costs among patients with PD compared to age-matched controls [11,15]. We, therefore, conjecture that the costs observed in the present study were also larger than those that could be expected to be seen in healthy controls.

Conclusions

The present investigation is, to our knowledge, the first explicit examination of DT walking in PD patients after STN DBS. The DT costs of multiple, distinct aspects of gait did not improve in response to STN DBS. The absence of change in this ability with STN stimulation indicates that this surgery does not positively impact on the automaticity of walking and suggests that PD patients may be unable to adequately cope with the multi-tasking challenges that are common during every-day walking. Several interventions have been proposed for reducing the impact of DT on gait in PD [17-20]; it would, in the future, be of interest to examine if these are effective in post-DBS patients.

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References
1. Lozano AM: **Deep brain stimulation for Parkinson's disease.** *Parkinsonism Relat Disord* 2001, **7**:199–203.
2. Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, *et al*: **Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up.** *Brain* 2005, **128**:2240–2249.
3. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, Daniels C, Deutschlander A, Dillmann U, Eisner W, *et al*: **A randomized trial of deep-brain stimulation for Parkinson's disease.** *N Engl J Med* 2006, **355**:896–908.
4. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, Lang AE, Deuschl G: **Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes.** *Mov Disord* 2006, **21**(Suppl 14):S290–S304.
5. Bejjani BP, Gervais D, Arnulf I, Papadopoulos S, Demeret S, Bonnet AM, Cornu P, Damier P, Agid Y: **Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation.** *J Neurol Neurosurg Psychiatry* 2000, **68**:595–600.
6. Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, Schrader B, Raethjen J, Wenzelburger R, Mehdorn HM, *et al*: **Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait.** *Neurology* 2001, **57**:144–146.
7. Crenna P, Carpinella I, Rabuffetti M, Rizzone M, Lopiano L, Lanotte M, Ferrarin M: **Impact of subthalamic nucleus stimulation on the initiation of gait in Parkinson's disease.** *Exp Brain Res* 2006, **172**:519–532.
8. Ferrarin M, Rizzone M, Bergamasco B, Lanotte M, Recalcati M, Pedotti A, Lopiano L: **Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease.** *Exp Brain Res* 2005, **160**:517–527.
9. Rocchi L, Chiari L, Cappello A, Gross A, Horak FB: **Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson's disease.** *Gait Posture* 2004, **19**:172–183.
10. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16**:1–14.

11. Yogev-Seligmann G, Hausdorff JM, Giladi N: The role of executive function and attention in gait. *Mov Disord* 2008, **23**:329–342.

12. Yogev-Seligmann G, Hausdorff JM, Giladi N: Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov Disord* 2012, **27**:765–770.

13. O'Shea S, Morris ME, Iansek R: Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther* 2002, **82**:888–897.

14. Hausdorff JM, Balash J, Giladi N: Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol* 2003, **16**:53–58.

15. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM: Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci* 2005, **22**:1248–1256.

16. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M: The "posture second" strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci* 2006, **248**:196–204.

17. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM: Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A Biol Sci Med Sci* 2011, **66**:234–240.

18. Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM: The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert Rev Neurother* 2011, **11**:1057–1075.

19. Yogev-Seligmann G, Giladi N, Brozgol M, Hausdorff JM: A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil* 2012, **93**:176–181.

20. Canning CG: The effect of directing attention during walking under dual-task conditions in Parkinson's disease. *Parkinsonism Relat Disord* 2005, **11**:95–99.

21. Devos D, Defebvre L, Bordet R: Dopaminergic and non-dopaminergic pharmacological hypotheses for gait disorders in Parkinson's disease. *Fundam Clin Pharmacol* 2010, **24**:407–421.

22. Hausdorff JM, Gruendlinger L, Scollins L, O'Herron S, Tarsy D: Deep brain stimulation effects on gait variability in Parkinson's disease. *Mov Disord* 2009, **24**:1688–1692.

23. Kelly VE, Israel SM, Samii A, Slimp JC, Goodkin R, Shumway-Cook A: Assessing the effects of subthalamic nucleus stimulation on gait and mobility in people with Parkinson disease. *Disabil Rehabil* 2010, **32**:929–936.

24. Davis JT, Lyons KE, Pahwa R: Freezing of gait after bilateral subthalamic nucleus stimulation for Parkinson's disease. *Clin Neurol Neurosurg* 2006, **108**:461–464.

25. Liu W, McIntire K, Kim SH, Zhang J, Dascalos S, Lyons KE, Pahwa R: Bilateral subthalamic stimulation improves gait initiation in patients with Parkinson's disease. *Gait Posture* 2006, **23**:492–498.

26. Moreau C, Defebvre L, Destee A, Bleuse S, Clement F, Blatt JL, Krystkowiak P, Devos D: STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology* 2008, **71**:80–84.

27. Witt K, Daniels C, Reiff J, Krack P, Volkmann J, Pinsker MO, Krause M, Tronnier V, Kloss M, Schnitzler A, et al: Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol* 2008, **7**:605–614.

28. Marconi R, Landi A, Valzania F: Subthalamic nucleus stimulation in Parkinson's disease. *Neurol Sci* 2008, **29**(Suppl 5):S389–S391.

29. Yogev-Seligmann G, Hausdorff JM, Giladi N: The role of executive function and attention in gait. *Mov Disord* 2008, **23**:329–342.

30. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, et al: Gait speed and survival in older adults. *JAMA* 2011, **305**:50–58.

31. Morris ME, Huxham F, McGinley J, Dodd K, Iansek R: The biomechanics and motor control of gait in Parkinson disease. *Clin Biomech (Bristol, Avon)* 2001, **16**:459–470.

32. Morris ME, Iansek R, Matyas TA, Summers JJ: The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain* 1994, **117**(Pt 5):1169–1181.

33. Blin O, Ferrandez AM, Serratrice G: Quantitative analysis of gait in Parkinson patients: increased variability of stride length. *J Neurol Sci* 1990, **98**:91–97.

34. Frenkel-Toledo S, Giladi N, Peretz C, Herman T, Gruendlinger L, Hausdorff JM: Effect of gait speed on gait rhythmicity in Parkinson's disease: variability of stride time and swing time respond differently. *J Neuroeng Rehabil* 2005, **2**. doi:10.1186/1743-0003-2-23.

35. Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL: Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov Disord* 1998, **13**:428–437.

36. Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM: Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci* 2003, **212**:47–53.

37. Stolze H, Kuhtz-Buschbeck JP, Drucke H, Johnk K, Illert M, Deuschl G: Comparative analysis of the gait disorder of normal pressure hydrocephalus and Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2001, **70**:289–297.

38. Gelb DJ, Oliver E, Gilman S: Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999, **56**:33–39.

39. Nilsson MH, Tornqvist AL, Rehncrona S: Deep-brain stimulation in the subthalamic nuclei improves balance performance in patients with Parkinson's disease, when tested without anti-parkinsonian medication. *Acta Neurol Scand* 2005, **111**:301–308.

40. Piper M, Abrams GM, Marks WJ Jr: Deep brain stimulation for the treatment of Parkinson's disease: overview and impact on gait and mobility. *Neuro Rehabilitation* 2005, **20**:223–232.

41. Kave G: Standardization and norms for a Hebrew naming test. *Brain Lang* 2005, **92**:204–211.

42. Yogev-Seligmann G, Rotem-Galili Y, Dickstein R, Giladi N, Hausdorff JM: Effects of explicit prioritization on dual task walking in patients with Parkinson's disease. *Gait Posture* 2012, **35**:641–646.

43. Fahn S, Elton R: Members of the UPDRS development committee: Unified Parkinson's disease rating scale. In *Recent developments in Parkinson's disease*. Edited by Goldstein M, Fahn S, Marsden CD, Calne D. Florham Park: NJ: Macmillan Health Care Information; 1987:153–163.

44. Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z: Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain* 2010, **133**:2007–2021.

45. AGS Guidelines: Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc* 2001, **49**:664–672.

46. Podsiadlo D, Richardson S: The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991, **39**:142–148.

47. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N: Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol* 2006, **29**:15–17.

48. Dwolatzky T, Whitehead V, Doniger GM, Simon ES, Schweiger A, Jaffe D, Chertkow H: Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatr* 2003, **3**:4.

49. Schweiger A, Doniger GM, Dwolatzky T, Jaffe D, Simon ES: Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. *Acta Neuropsychologica* 2003, **1**:407–413.

50. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM: Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord* 2006, **21**:950–957.

51. Kelly VE, Eusterbrock AJ, Shumway-Cook A: A review of dual-task walking deficits in people with Parkinson's disease: motor and cognitive contributions, mechanisms, and clinical implications. *Parkinsons Dis* 2012, **2012**:918719.

52. Page D, Jahanshahi M: Deep brain stimulation of the subthalamic nucleus improves set shifting but does not affect dual task performance in Parkinson's disease. *IEEE Trans Neural Syst Rehabil Eng* 2007, **15**:198–206.

53. Alberts JL, Voelcker-Rehage C, Hallahan K, Vitek M, Bamzai R, Vitek JL: Bilateral subthalamic stimulation impairs cognitive-motor performance in Parkinson's disease patients. *Brain* 2008, **131**:3348–3360.

54. Nieoullon A: Dopamine and the regulation of cognition and attention. *Prog Neurobiol* 2002, **67**:53–83.

55. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P: A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. *Cogn Behav Neurol* 2003, **16**:193–210.

56. Caliandro P, Insola A, Scarnati E, Padua L, Russo G, Granieri E, Mazzone P: Effects of unilateral pedunculopontine stimulation on electromyographic activation patterns during gait in individual patients with Parkinson's disease. *J Neural Transm* 2011, **118**:1477–1486.

57. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ Jr, Rothlind J, Sagher O, Moy C, et al: Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010, **362**:2077–2091.
58. Follett KA, Torres-Russotto D: Deep brain stimulation of globus pallidus interna, subthalamic nucleus, and pedunculopontine nucleus for Parkinson's disease: which target? *Parkinsonism Relat Disord* 2012, **18**(Suppl 1):S165–S167.
59. Zibetti M, Torre E, Cinquepalmi A, Rosso M, Ducati A, Bergamasco B, Lanotte M, Lopiano L: Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *Eur Neurol* 2007, **58**:218–223.
60. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, Rothlind J, Sagher O, Reda D, Moy CS, et al: Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009, **301**:63–73.
61. Camicioli R, Majumdar SR: Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study. *Gait Posture* 2010, **32**:87–91.
62. Lapointe LL, Stierwalt JA, Maitland CG: Talking while walking: cognitive loading and injurious falls in Parkinson's disease. *Int J Speech Lang Pathol* 2010, **12**:455–459.
63. Plotnik M, Giladi N, Dagan Y, Hausdorff JM: Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the "ON" medication state. *Exp Brain Res* 2011, **210**:529–538.
64. Hausdorff JM: Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. *Hum Mov Sci* 2007, **26**:555–589.
65. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM: Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci* 2010, **65**:1086–1092.
66. Bloem BR, Hausdorff JM, Visser JE, Giladi N: Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord* 2004, **19**:871–884.
67. Duncan RP, Leddy AL, Cavanaugh JT, Dibble LE, Ellis TD, Ford MP, Foreman KB, Earhart GM: Accuracy of fall prediction in Parkinson disease: six-month and 12-month prospective analyses. *Parkinsons Dis* 2012, **2012**:237673.
68. Foreman KB, Addison O, Kim HS, Dibble LE: Testing balance and fall risk in persons with Parkinson disease, an argument for ecologically valid testing. *Parkinsonism Relat Disord* 2011, **17**:166–171.
69. Allcock LM, Rowan EN, Steen IN, Wesnes K, Kenny RA, Burn DJ: Impaired attention predicts falling in Parkinson's disease. *Parkinsonism Relat Disord* 2009, **15**:110–115.