Neuromodulation: Technology at the Neural Interface

Received: September 11, 2021 Revised: December 10, 2021 Accepted: January 4, 2022

https://doi.org/10.1016/j.neurom.2022.01.015

# Additive Effect of Dopaminergic Medication on Gait Under Single and Dual-Tasking Is Greater Than of Deep Brain Stimulation in Advanced Parkinson Disease With Long-duration Deep Brain Stimulation

**Agnes Langer, MD[1]; Lara Lucke-Paulig, MD[2,3]; Lucia Gassner, Msc[4,5,6]; Rejko Krüger, MD[2,7,8,9]; Daniel Weiss, MD[2]; Alireza Gharabaghi, MD[10]; Heidemarie Zach, MD[1]; Walter Maetzler, MD[2,11]; Markus A. Hobert, MD[2,11]**

## ABSTRACT

**Introduction:** Patients with advanced Parkinson disease (PD) often experience problems with mobility, including walking under single- (ST) and dual-tasking (DT) conditions. The effects of deep brain stimulation in the subthalamic nucleus (DBS) versus dopaminergic medication (Med) on these conditions are not well investigated.

**Materials and Methods:** We used two ST and two DT-gait paradigms to evaluate the effect of DBS and dopaminergic medication on gait parameters in 14 PD patients (mean age 66 ± 8 years) under $DBS_{OFF}/Med_{ON}$, $DBS_{ON}/Med_{OFF}$, and $DBS_{ON}/Med_{ON}$ conditions. They performed standardized 20-meter walks with convenient and fast speed. To test DT capabilities, they performed a checking-boxes and a subtraction task during fast-paced walking. Quantitative gait analysis was performed using a tri-axial accelerometer (Dynaport, McRoberts, The Netherlands). Dual-task costs (DTC) of gait parameters and secondary task performance were compared intraindividually between $DBS_{OFF}/Med_{ON}$ vs $DBS_{ON}/Med_{ON}$, and $DBS_{ON}/Med_{OFF}$ vs $DBS_{ON}/Med_{ON}$ to estimate responsiveness.

**Results:** Dopaminergic medication increased gait speed and cadence at convenient speed. It increased cadence and decreased number of steps at fast speed, and improved DTC of cadence during the checking boxes and DTC of cadence and number of steps during the subtraction tasks. DBS only improved DTC of cadence during the checking boxes and DTC of gait speed during the subtraction task.

**Conclusion:** Dopaminergic medication showed larger additional effects on temporal gait parameters under ST and DT conditions in advanced PD than DBS. These results, after confirmation in independent studies, should be considered in the medical management of advanced PD patients with gait and DT deficits.

**Keywords:** Deep brain stimulation, dopaminergic medication, dual task, dual-task costs, Parkinson disease

Address correspondence to: Markus A. Hobert, MD, Department of Neurology, Universitätsklinikum Schleswig-Holstein, Christian-Albrechts-University, Arnold-Heller-Str. 3, 24105 Kiel, Germany. Email: Markus.Hobert@uksh.de

[1] Department of Neurology, Medical University of Vienna, Vienna, Austria;
[2] Center for Neurology, Hertie Institute for Clinical Brain Research, Department of Neurodegenerative Diseases, University of Tuebingen, Tuebingen, Germany;
[3] Department of Endocrinology, Diabetology and Geriatrics, Stuttgart General Hospital, Bad Cannstatt, Germany;
[4] Department of Sport Physiology, Institute of Sports Sciences, University of Vienna, Vienna, Austria;
[5] Royal Melbourne Institute of Technology, Melbourne, Australia;
[6] HTA Austria - Austrian Institute for Health Technology Assessment GmbH, Vienna, Austria;
[7] Luxembourg Institute of Health, Strassen, Luxembourg;
[8] Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg;
[9] Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg;
[10] Institute for Neuromodulation and Neurotechnology, Department of Neurosurgery and Neurotechnology, University Hospital Tuebingen, University of Tuebingen, Tuebingen, Germany; and
[11] Department of Neurology, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Christian-Albrechts-University Kiel, Kiel, Germany

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: The authors reported no funding sources.



  

**Conflict of Interest:** Daniel Weiss reports grants and personal fees from Medtronic, grants and personal fees from Abbott, grants and personal fees from Boston Scientific, personal fees from AbbVie, grants and personal fees from Bial, and personal fees from Stada, outside the submitted work. Walter Maetzler receives or received funding from the European Union, the German Federal Ministry of Education of Research, the Michael J. Fox Foundation, Robert Bosch Foundation, Neuroalliance, Lundbeck, and Janssen. He received speaker honoraria from AbbVie, Bayer, GlaxoSmithKline, Licher MT, Rölke Pharma, and UCB, was invited to the advisory boards of AbbVie, Biogen, Lundbeck, and Market Access & Pricing Strategy GmbH, and is an advisory board member of the Critical Path for Parkinson's Consortium. He serves as the cochair of the MDS Technology Task Force. The remaining authors report no conflict of interest.

## INTRODUCTION

Parkinson disease (PD) is a neurodegenerative disease, causing motoric symptoms such as bradykinesia, rigidity, and tremor. In advanced stages, gait impairment and postural instability are common, as well as cognitive impairment, autonomic dysfunction, and psychiatric symptoms.[1] The combination of mobility limitations and cognitive impairment leads to a deterioration of dual-task (DT) ability, which is the ability to execute two or more activities simultaneously.[2–5] It is thus not surprising that patients with advanced PD show changes in spatial and temporal gait parameters, including deteriorations in stride length, step length variability, cadence, velocity, and phase coordination index (PCI), under DT conditions.[2,6–11]

The ability to perform DT is important for daily life performance. Impaired DT ability leads to an increased risk of falls and freezing of gait,[12,13] and increased functional dependence.[4,14] In contrast, DT abilities respond well to different behavioral training methods that reduce falls and freezing of gait, for example,[14–19] giving hope that the DT capabilities and the associated disadvantages are generally treatable. The thorough assessment of such deficits is thus especially relevant in advanced PD because this can influence how these patients are treated.

Knowledge about the effect of dopaminergic medication and deep brain stimulation in the subthalamic nucleus (DBS) on gait is limited. In earlier studies, dopaminergic therapy reliably improved only spatial gait characteristics such as gait speed (via increase of stride length) and stride length in DT gait, but had no significant effect on temporal gait characteristics such as cadence, turning cadence, peak velocity, and turning step duration.[10,20–25] DBS is known to further improve the clinically observable gait (as assessed with the motor part of the Movement Disorders Society Unified Parkinson Disease Rating Scale [MDS-UPDRS III]),[26] increase gait speed,[27,28] and improve step length as well as double support time (DST)[28] in single-task (ST) walking conditions, even in the presence of dopaminergic medication, that is, in pharmacologic ON-state.

The effects of DBS on gait performance under DT conditions in PD are still not well understood. Although some observations showed that DBS improved gait characteristics under DT conditions,[29,30] one study found that DBS did not change walking patterns.[31]

DT performance can be improved by either dopaminergic medication or DBS, but so far, there seems to be only limited additional benefit on DT when both treatments are applied simultaneously.[30–32] Furthermore, evidence is lacking about objective measurements to quantify gait characteristics of DT costs (DTC) under DBS with wearable sensors.

This work aimed to evaluate as a pilot study the effect of dopaminergic medication and DBS on single quantitative gait parameters under ST and DT conditions, using intraindividual comparisons.

## MATERIALS AND METHODS

We recruited 14 study participants (aged 45–76 years) at the Centre for Neurology, Department of Neurodegenerative Diseases of the University of Tuebingen, Germany (Table 1). They were considered eligible for the study when suffering from idiopathic PD according to the United Kingdom Brain Bank Criteria and DBS in the subthalamic nucleus for ≥6 months on both stable dopaminergic medication and stimulation parameters that were judged to be optimal by their attending movement disorder specialist. Exclusion criteria were substantial changes to their dopaminergic medication and/or stimulation parameters; severe orthopedic, visual, and hearing impairments (as judged by the assessor); diagnosis of dementia according to patients' medical records; inability to walk 25 meters unaided; and >1 fall during the last month. The latter exclusion criterion was added for safety reasons. All patients had the same type of DBS device (Medtronic Activa PC, lead number 3389).

The study was approved by the Ethics Committee of the medical faculty of the University of Tuebingen (number 160/2011BO2) and

**Table 1.** Demographics and Clinical Characteristics.

| Demographic/Clinical Characteristic | | Mean (range) | SEM |
|---|---|---|---|
| Men/women, n | 8/6 | | |
| Age, y | | 66 (49–76) | 2.2 |
| BMI, kg/m$^2$ | | 26 (19–35) | 1.0 |
| MMSE (0–30) | | 28 (24–30) | 0.5 |
| BDI (0–63) | | 10 (0–20) | 1.7 |
| MDS-UPDRS I + II + IV (0–128) | | 25 (10–39) | 2.1 |
| MDS-UPDRS III, $DBS_{ON}/Med_{ON}$ (0–132) | | 31 (20–53) | 2.1 |
| Hoehn and Yahr stage | | 2 (2–3) | 0.1 |
| Disease duration, y | | 18 (10–25) | 1.3 |
| DBS duration, y | | 5 (1–8) | 0.5 |
| LEDD, mg/d | | 694 (75–1687) | 141 |
| LEDD of dopamine agonists, mg/d | | 126 (0–480) | 43 |
| Falls during the last 12 mo | | 1 (0–12) | 1.2 |

BDI, Becks Depressions Inventory; BMI, body mass index; DBS, Deep Brain Stimulation of the subthalamic nucleus; LEDD, Levo-dopa equivalent dosage; MMSE, Mini-Mental State Examination; MDS-UPDRS, Movement Disorder's Unified Parkinson's Disease Rating Scale; SEM, Standard Error of th Mean.

was performed according to the standards of the 1964 Declaration of Helsinki. All participants gave written informed consent before inclusion.

### Clinical Assessment

The MDS-UPDRS III was obtained in each condition.[33] Cognitive performance was assessed in medical ON-state ($Med_{ON}$) and active DBS ($DBS_{ON}$) with the Mini-Mental-Status-Examination (MMSE)[34] and with the Trail Making Test,[35] and depressive symptoms with the Beck Depressions Inventory.[36]

### Single- and DT Assessment of Gait and Secondary Tasks

All walking tasks were conducted in a >1.5 m wide corridor with a 20-meter-long test track. Gait data were measured with the DynaPort Hybrid® (McRoberts, Hague, The Netherlands), a device containing a tri-axial accelerometer and gyroscope, respectively. The device was mounted to a belt on the lower back (~L5). The following quantitative temporal gait parameters, covering three relevant domains of gait, pace, rhythm, and variability, were calculated by using established company-provided and validated algorithms:[37–40] gait speed, cadence (measure of step frequency), number of steps to perform the 20-meter test track (number of steps), double support time (DST, duration of the period when both feet touch the ground), and phase coordination index (PCI, measure of gait irregularity).

To assess the ST performances of the secondary tasks (checking boxes and subtractions), the participants had to check boxes on a preprinted 20-box-grid mounted to a clipboard and to subtract serial 7s from a three-digit number as fast as possible. These tasks were performed while standing. The checking-boxes task is an effective task to create a DT interference during walking with a probably stronger motor-motor interference.[41] The construct validity of this task is unclear, nevertheless, it has been shown that the task requires different resources, such as fine motor,[42] visual, and executive functions.[43] The subtracting task creates a stronger motor-cognitive interference during walking.

To assess ST gait performance, all participants had to walk on the test track at a convenient pace, and as fast as possible. To assess DT gait performance, participants either checked boxes on a clipboard while walking, or subtracted serial 7s during the walk. These simultaneously performed tasks had to be done as fast and as correctly as possible, and no instruction about prioritization was given.[43,44]

All participants were asked to perform the ST gait assessments and both DT gait assessments with three different DBS and dopaminergic medication conditions: $DBS_{OFF}/Med_{ON}$ (inactive DBS for about 30 minutes, on dopaminergic medication), $DBS_{ON}/Med_{OFF}$ (active DBS for at least 30 minutes, no dopaminergic medication), and $DBS_{ON}/Med_{ON}$ (active DBS and on dopaminergic medication). We defined the $Med_{ON}$ state as the best subjective motor state 30 minutes to two hours after intake of dopaminergic medication. Formal randomization of the test sequences was not performed because of medication regimes; the order of the tests was varied as much as possible among the participants to avoid order effects. All assessments in OFF medication were performed under fully controlled conditions in the morning, in a practically defined OFF state after withdrawal of dopaminergic medication overnight. ON medication assessments were performed during the day, to make sure that best ON conditions were reached. All participants performed $DBS_{ON}/Med_{ON}$; 11 patients were able to perform $DBS_{ON}/Med_{OFF}$, and ten patients were able to perform $DBS_{OFF}/Med_{ON}$. Reasons were mainly scheduling issues and unwillingness to perform another task with suboptimal treatment. We did not perform any tests entirely without therapy (ie, $DBS_{OFF}/Med_{OFF}$). For better readability, the comparisons $DBS_{ON}/Med_{ON}$ vs $DBS_{OFF}/Med_{ON}$ and $DBS_{ON}/Med_{ON}$ vs $DBS_{ON}/Med_{OFF}$ will be referred to as $DBS_{ON}$ vs $DBS_{OFF}$ and $Med_{ON}$ vs $Med_{OFF}$, respectively.

### Data Handling and Statistical Analysis

Statistical analyses were performed with JMP®, Version 10 (SAS Institute Inc, Cary, NC). Demographic data are displayed with mean and SEM. Standardized response mean (SRM) values were calculated to assess responsiveness of experimental parameters between the different conditions ($DBS_{ON}/Med_{ON}$ vs $DBS_{OFF}/Med_{ON}$, $DBS_{ON}/Med_{ON}$ vs $DBS_{ON}/Med_{OFF}$). SRM values were calculated as mean differences of the different conditions as described above divided by the standard deviation of the differences. SRM values of 0.20 indicate a small response, 0.50 a moderate response, and 0.80 a large response to dopaminergic medication and DBS. Negative values indicate worsening under the respective treatment. Additionally, paired *t*-tests were used to assess *p* values of the comparisons of clinical with experimental parameters intraindividually between the different conditions. In the description of results, we considered the combination of $p < 0.05$ and SRM with moderate or large response as clinically relevant. The number of participants included in each of the comparisons differed because some patients were not able to perform all conditions ($DBS_{ON}/Med_{ON}$ vs $DBS_{OFF}/Med_{ON}$: $n = 10$, $DBS_{ON}/Med_{ON}$ vs $DBS_{ON}/Med_{OFF}$: $n = 11$). False discovery rates were calculated for each condition using the Benjamini-Hochberg procedure.

The comparison of ST versus DT performance was achieved via the calculation of DTC.[41,45] DTC were calculated using the following formula[41,43]:

$$\text{DTC} = \frac{\text{Dual-Task} - \textit{Single} - \textit{Task}}{\textit{Single} - \textit{Task}} \times 100\%$$

for the parameters: number of steps, DST, and PCI. For the parameters, gait speed, cadence, checking-boxes speed, and subtracting speed, the formula was multiplied by −1. Positive DTC describe worse performance under DT than under ST; negative DTC describe better performance under DT than under ST.

## RESULTS

Demographic and clinical parameters of the study participants are shown in Table 1. Mean disease duration was 18 (±4.7) years, and mean MMSE was 28 (±1.9). These results argue for a cognitively fit patient group with relatively long disease duration.

### Gait Parameter at Convenient Gait Speed

Dopaminergic medication had a large effect on cadence ($Med_{OFF}$: 1.78 ± 0.05 steps/s; $Med_{ON}$: 1.87 ± 0.06 steps/s; SRM = 0.95, $p = 0.0048$) and moderate effect on gait speed ($Med_{OFF}$: 0.97 ± 0.09 m/s; $Med_{ON}$: 1.12 ± 0.06 m/s; SRM = 0.77, $p = 0.019$). The effects on number of steps, DST, and PCI as well as the effects of DBS were smaller (SRM < 0.5 and/or $p > 0.05$).



  

### Gait Parameter at Fast Gait Speed (ST)

Dopaminergic medication had a moderate effect on cadence ($Med_{OFF}$: 1.98 ± 0.07 steps/s; $Med_{ON}$: 2.12 ± 0.09 steps/s; SRM = 0.61, $p = 0.006$) and number of steps ($Med_{OFF}$: 23.3 ± 1.6; $Med_{ON}$: 21.1 ± 1.0; SRM = 0.54, $p = 0.03$). The effects on gait speed, DST, and PCI as well as the effects of DBS were smaller (SRM < 0.5 and/or $p > 0.05$).

### Secondary Task Parameters at Fast Gait Speed (ST)

Dopaminergic medication had a moderate effect on checking-boxes speed in ST by a mean of 0.1 boxes/second (±0.4; SRM = 0.73, $p = 0.023$). The effect on subtracting speed and the effects of DBS were smaller (SRM < 0.5 and/or $p > 0.05$).

### DTC of Gait Parameters Under Checking Boxes DT Conditions

Dopaminergic medication had a large effect on DTC of cadence ($Med_{OFF}$: 17.2%±3.1%; $Med_{ON}$: 9.9%±2.6%; SRM = 1.35, $p = 0.006$). The effects on the DTC of gait speed, number of steps, DST, PCI, and checking-boxes speed were smaller (SRM < 0.5 and/or $p > 0.05$). DBS had a moderate effect on DTC of cadence ($DBS_{OFF}$: 12.3%±2.3%; $DBS_{ON}$: 7.4%±2.6%; SRM = 0.78, $p = 0.03$). The effect on the DTC of speed, number of steps, DST, and PCI was smaller (SRM < 0.5 and/or $p > 0.05$).

### DTC of Gait Parameters Under Subtracting DT Conditions

Dopaminergic medication had a moderate effect on DTC of cadence ($Med_{OFF}$: 18.7%±3.8%; $Med_{ON}$: 10.1%±2.2%; SRM = 0.78, $p = 0.04$). The effects on DTC of the remaining parameters were smaller (SRM < 0.5 and/or $p > 0.05$). The effect of DBS on DTC of the remaining parameters was smaller (SRM < 0.5 and/or $p > 0.05$).

### Clinical Assessment of Treatment Effects

Dopaminergic medication led to a six-point (14.8%; SRM = 0.43, $p = 0.045$) and DBS to a 13-point improvement of MDS-UPDRS III (31.6%; SRM = 1.0, $p = 0.006$).

Table 2 shows the effects of dopaminergic medication; Table 3 shows the effects of DBS. SRM values of the effects of dopaminergic medication are displayed in Figure 1, and SRM values of the effect of DBS are displayed in Figure 2. Figures S1 and S2 display the effects of dopaminergic medication and DBS on speed and cadence and DTC of speed and cadence in detail.

## DISCUSSION

The main finding of this study with participants with advanced PD, treated with both dopaminergic medication and DBS in the STN, is that the effect of dopaminergic medication (assessed by comparing $DBS_{ON}/Med_{ON}$ with $DBS_{ON}/Med_{OFF}$) on multiple parameters of gait under ST and DT walking conditions is larger than the effect of DBS (assessed by comparing $DBS_{ON}/Med_{ON}$ with $DBS_{OFF}/Med_{ON}$).

### Medication Effects

Under ST conditions, dopaminergic medication significantly improved gait speed, cadence, DST, and number of steps at

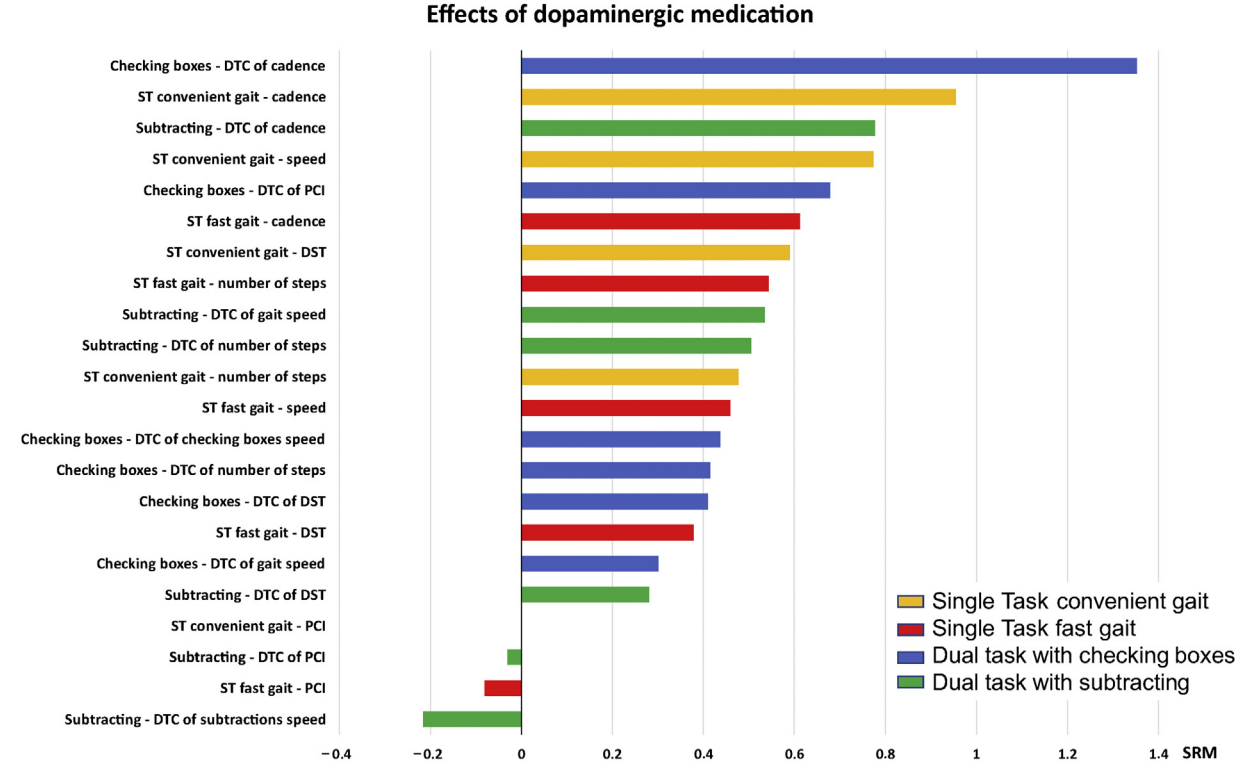


**Figure 1.** Responsiveness of the assessed quantitative gait parameters to dopaminergic medication ($DBS_{ON}/Med_{ON}$ vs $DBS_{ON}/Med_{OFF}$). Parameters are arranged according to the SRM starting from the strongest effect to the lowest effect. SRM values >0.20 indicate small, >0.50 moderate, and >0.80 large responsiveness. [Color figure can be viewed at www.neuromodulationjournal.org]

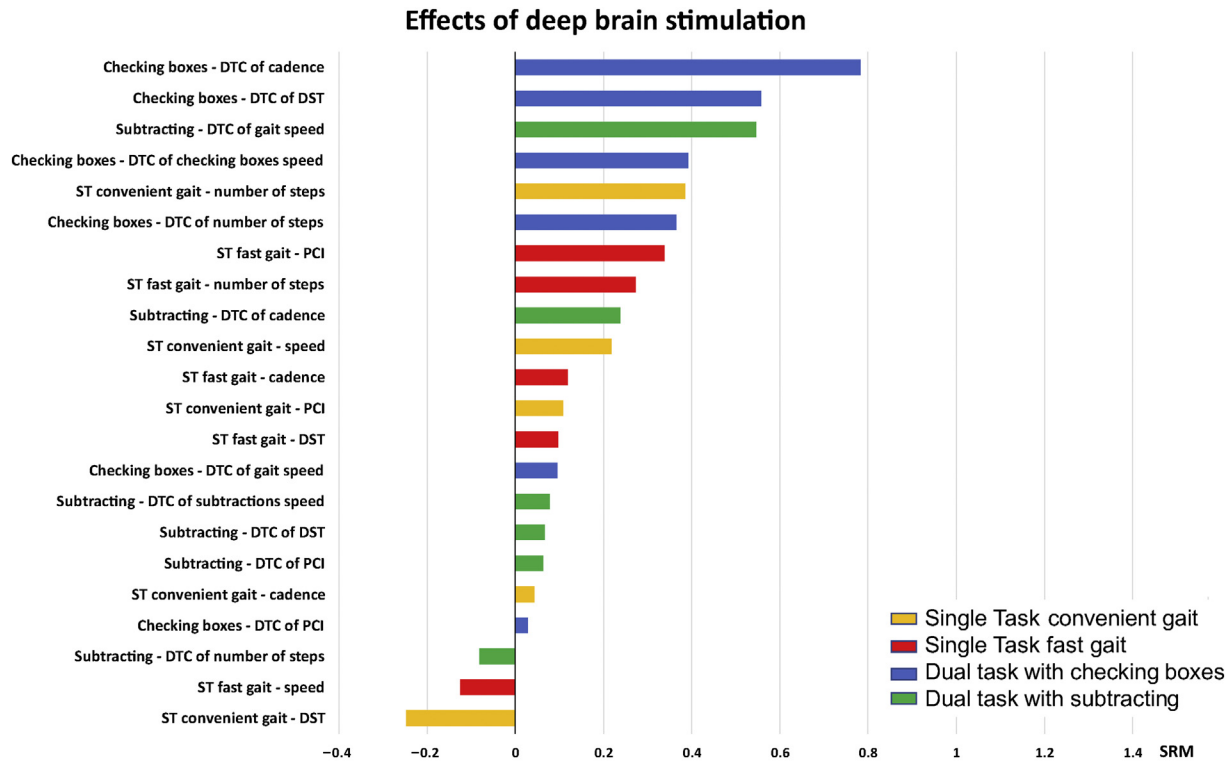


**Figure 2.** Responsiveness of the assessed quantitative gait parameters to deep brain stimulation of the subthalamic nucleus ($DBS_{ON}/Med_{ON}$ vs $DBS_{OFF}/Med_{ON}$). Parameters are arranged according to the SRM starting from the strongest effect to the lowest effect. SRM values >0.20 indicate small, >0.50 moderate, and >0.80 large responsiveness. [Color figure can be viewed at www.neuromodulationjournal.org]

normal gait speed during DBS. Under ST conditions with fast gait speed, dopaminergic medication significantly improved cadence. Our results confirm previous findings, with the addition of finding an improvement in cadence at both comfortable and fast speeds reported in only two of four previous studies.[20,46–48] However, these studies used a substantially shorter walking distance and comfortable, but not fast, walking speed. The different outcomes could also be related to considerably longer disease durations in our participants. The long mean disease duration and concomitant relatively low Hoehn and Yahr (H&Y) stages of our participants suggests that many of our participants had a "benign" course of PD according to a recent definition (H&Y stage ≤3 after a disease duration of >10 years and disease onset at >60 years of age, or 20 years and disease onset at <60 years of age).[49] A preserved plasticity of cortico-striatal pathways, which was shown to be associated with benign PD, could have had an impact on the improvement of cadence by dopaminergic medication.[49–51]

Dopaminergic medication decreased the DTC of cadence in the checking-boxes DT condition and in the subtracting DT condition. This means that the deteriorating effect of the DT situation (compared with ST) on cadence was mitigated by dopaminergic medication. In PD patients, dopaminergic medication has been shown to increase activation of the prefrontal cortex, which plays a role in the cognitive control of gait.[52] Dopaminergic medication could therefore improve the cognitive aspects of DT gait.

Furthermore, the improvement of the cadence by the dopaminergic medication was not at the expense of secondary tasks because the DTC of the secondary tasks did not increase. This is an interesting observation because it contradicts the "posture second strategy" in which PD patients prioritize cognitive tasks over balance in DT.[3] This could influence therapeutic considerations and patient counseling, because according to this rationale, the L-dopa dose after DBS should rather not be reduced to the absolute minimum necessary, even if pure motor control would allow it. The smaller effects of dopaminergic medication on DTC of gait speed, step count, and PCI contradict two previous studies in which DT gait speed and step length improved with dopaminergic medication, but the cadence was unaffected.[20,21] There were, however, no patients treated with DBS in the two studies, meaning that the apparent lack of effect of medication in our study could be explained by the "carry-over effect" of DBS.[53,54] Furthermore, in one of these studies, the PD patients, whose disease duration of 7±4.2 years was much shorter than the 18 years mean duration of our participants, showed similar cadence to the control group.[21] It might therefore be assumed that if the cadence of the PD patients was already normal, no further improvement through dopaminergic medication can be expected.

The limited effect that dopaminergic medication had on the DTC in our setting might be explained by the fact that dopaminergic therapy does not have an impact on set-shifting, which is a relevant prerequisite for DT performance.[55–59] Our observation is similar to results reported earlier that found dopaminergic therapy reliably improved only gait speed and stride length in DT gait, but had no significant effect on cadence, turning cadence, peak velocity, and turning step duration.[20,21] Another possible explanation is the relatively subtherapeutic doses of the dopaminergic medication, because we used the patients' usual doses, which were reduced after starting DBS therapy, rather than a formal L-dopa challenge.

**Table 2.** Effect of Dopaminergic Medication on MDS-UPDRS III and Gait Parameters in ST and DT Conditions.

| Parameter | $DBS_{ON}/Med_{ON}$, mean (±SEM) | $DBS_{ON}/Med_{OFF}$, mean (±SEM) | *p* Value | SRM | FDR |
|---|---|---|---|---|---|
| MDS-UPDRS III | 29 (±1) | 34 (±3) | 0.045 | 0.43 | 0.045 |
| ST walking | | | | | |
| convenient gait speed | | | | | |
| Speed, m/s | 1.12 (±0.06) | 0.97 (±0.09) | 0.019 | 0.77 | 0.048 |
| Cadence, steps/s | 1.87 (±0.06) | 1.78 (±0.05) | 0.0048 | 0.95 | 0.02 |
| Number of steps | 22.56 (±1.12) | 26.87 (±2.29) | 0.02 | 0.48 | 0.03 |
| DST, s | 0.33 (±0.02) | 0.35 (±0.02) | 0.07 | 0.59 | 0.09 |
| PCI, % | 14.57 (± 2.60) | 12.61 (±2.09) | 0.29 | 0.00 | 0.29 |
| Fast gait speed | | | | | |
| Speed, m/s | 1.28 (±0.10) | 1.16 (±0.11) | 0.08 | 0.46 | 0.12 |
| Cadence, steps/s | 2.12 (±0.09) | 1.98 (±0.07) | 0.007 | 0.61 | 0.04 |
| Number of steps | 21.06 (±0.96) | 23.28 (±1.58) | 0.03 | 0.54 | 0.08 |
| DST, s | 0.32 (±0.02) | 0.33 (±0.02) | 0.13 | 0.38 | 0.13 |
| PCI, % | 25.80 (±3.21) | 16.56 (±4.03) | 0.06 | −0.08 | 0.10 |
| DT walking | | | | | |
| Checking boxes | | | | | |
| DTC of speed, % | 23.33 (±4.43) | 28.43 (±3.39) | 0.20 | 0.30 | 0.20 |
| DTC of cadence, % | 9.91 (±2.55) | 17.17 (±3.13) | 0.006 | 1.35 | 0.04 |
| DTC of number of steps, % | 20.18 (±5.24) | 25.23 (± 5.79) | 0.16 | 0.41 | 0.24 |
| DTC of DST, % | 10.43 (±12.56) | 16.89 (±8.41) | 0.16 | 0.41 | 0.24 |
| DTC of PCI, % | −24.51 (±19.08) | 19.53 (± 39.29) | 0.06 | 0.68 | 0.18 |
| DTC of checking boxes speed, boxes/s, % | 6.38 (±6.13) | 18.55 (±9.15) | 0.11 | 0.44 | 0.22 |
| Subtractions | | | | | |
| DTC of speed, % | 23.33 (±4.43) | 32.77 (±4.29) | 0.08 | 0.54 | 0.24 |
| DTC of cadence, % | 10.21 (±2.22) | 18.66 (±3.81) | 0.04 | 0.78 | 0.24 |
| DTC of number of steps, % | 17.86 (±4.62) | 26.95 (±5.96) | 0.12 | 0.51 | 0.18 |
| DTC of DST, % | 12.89 (±7.76) | 21.63 (±9.62) | 0.24 | 0.28 | 0.29 |
| DTC of PCI, % | 37.50 (±61.56) | 32.58 (±28.99) | 0.47 | −0.03 | 0.47 |
| DTC of subtractions speed, subtraction/s, % | −6.78 (±15.13) | 10.07 (±18.58) | 0.10 | −0.22 | 0.20 |

DST, double support time; DTC, Dual task costs; FDR, false discovery rate; Med, dopaminergic medication; OFF, without dopaminergic medication/inactive stimulator; ON, with dopaminergic medication/active stimulation; PCI, phase coordination index.

### DBS Effects

DBS did not have a relevant additional influence on temporal gait parameters in ST walking at convenient and fast gait speed. This was surprising, especially when considering the strong effect DBS showed on the MDS-UPRDS III score (Table 2). This finding argues in favor of the presence of a complex central network that is necessary for human walking and has already been postulated and confirmed previously.[60–64] Compared with DBS, dopaminergic medication had relatively little effect on the MDS-UPDRS III (as a general measure of motor deficits) but substantially "more" effect on gait under both ST and DT conditions.

In addition to the basal ganglia, dopaminergic networks can be found in extrastriatal sites, including the thalamus, cingulate, insula, and prefrontal cortex. The latter two are especially crucial to executive functions needed for gait, which explains the broad, "brain-wide" effect of dopaminergic medication.[65–68] DBS, on the other hand, affects presumably a very circumscribed brain region directly, the main effects of which, in contrast to dopaminergic medication, seem to be reflected mainly in the simple motor tasks of the MDS-UPDRS-III.

Our results can also be explained by the long mean DBS treatment duration of our participants, given that in long-term follow-up after DBS implantation, gait, in contrast to the cardinal symptoms of PD, continues to deteriorate faster after an initial improvement and eventually becomes barely responsive to DBS.[69,70]

DBS had moderate effects only on the DTC of cadence and DST in the checking boxes DT and on gait speed in the subtracting DT, mitigating the deteriorating effect of this DT situation. A possible explanation is that DBS might impair some cognitive functions, leading to an increase in the cognitive effort during dual-tasking and thus diminishing overall performance.[71,72] Moreover, although DBS, unlike dopaminergic medication, can at least improve set-shifting abilities, it still does not seem to be able to significantly improve dual-tasking abilities.[73]

Our findings were also similar to those of previous studies showing no improvement in DT motor skills and gait with $DBS_{ON}$ compared with $DBS_{OFF}$.[31,74] Other studies, however, found significant improvements in step length and DST of DT walking with bilateral DBS in the STN compared with unilateral DBS.[29] Partially, this may be due to the use of different protocols because they compared DBS settings in a $Med_{OFF}$-state. Another study found effects of DBS on gait speed and stride velocity during DT gait when comparing $DBS_{ON}$ with $DBS_{OFF}$ in $Med_{OFF}$, but not when comparing $DBS_{ON}$ with $DBS_{OFF}$ in $Med_{ON}$ as we did.[30] These results argue for an interactive effect of the combination of medication and DBS, which might disguise subtle effects. Alternatively, our result could also suggest that dopaminergic drugs contribute more to the additive effect than DBS. This must be investigated specifically using a more specific study design. We feel that our protocol mirrors real-life experience better than the other study protocols



  

**Table 3.** Effect of DBS on MDS-UPDRS III and Gait Parameters in single-tasking and dual-tasking.

| Parameter | $DBS_{ON}/Med_{ON}$, mean (±SEM) | $DBS_{OFF}/Med_{ON}$, mean (±SEM) | *p* Value | SRM | FDR |
|---|---|---|---|---|---|
| MDS-UPDRS III | 32 (±2.9) | 47 (±2.9) | 0.006 | 1.00 | 0.006 |
| ST walking | | | | | |
| convenient gait speed | | | | | |
| Speed, m/s | 0.99 (±0.08) | 0.95 (±0.06) | 0.26 | 0.22 | 0.43 |
| Cadence, steps/s | 1.79 (±0.05) | 1.79 (±0.05) | 0.45 | 0.04 | 0.56 |
| Number of steps | 22.72 (±0.99) | 23.39 (±0.76) | 0.09 | 0.38 | 0.45 |
| DST, s | 0.35 (±0.19) | 0.34 (±0.02) | 0.24 | −0.25 | 0.60 |
| PCI, % | 13.19 (±2.35) | 13.13 (±2.65) | 0.47 | 0.11 | 0.47 |
| Fast gait speed | | | | | |
| Speed, m/s | 1.18 (±0.10) | 1.21 (±0.09) | 0.35 | −0.12 | 0.44 |
| Cadence, steps/s | 2.04 (±0.08) | 1.99 (±0.06) | 0.16 | 0.12 | 0.80 |
| Number of steps | 21.74 (±0.95) | 22.00 (±0.82) | 0.34 | 0.27 | 0.57 |
| DST, s | 0.32 (±0.18) | 0.33 (±0.23) | 0.39 | 0.10 | 0.39 |
| PCI, % | 23.39 (±3.34) | 26.91 (±5.33) | 0.31 | 0.34 | 0.78 |
| DT walking | | | | | |
| Checking boxes | | | | | |
| DTC ofspeed, % | 25.71 (±4.38) | 27.05 (±2.95) | 0.39 | 0.10 | 0.47 |
| DTC ofcadence, % | 7.38 (±2.60) | 12.30 (±2.31) | 0.03 | 0.78 | 0.18 |
| DTC ofnumber of steps, % | 11.61(±3.67) | 17.58 (±5.07) | 0.17 | 0.36 | 0.26 |
| DTC ofDST, % | 6.36 (±5.80) | 14.94 (±6.07) | 0.08 | 0.56 | 0.24 |
| DTC ofPCI, % | −14.55 (±24.01) | −11.73 (±24.21) | 0.47 | 0.03 | 0.47 |
| DTC ofchecking boxes speed, % | 6.48 (±7.56) | 16.94 (±4.67) | 0.14 | 0.39 | 0.28 |
| Subtractions | | | | | |
| DTC ofspeed, % | 24.83 (±4.02) | 31.38 (±3.10) | 0.06 | 0.55 | 0.36 |
| DTC ofcadence, % | 12.94 (±2.44) | 15.25 (±2.79) | 0.25 | 0.24 | 0.75 |
| DTC ofnumber of steps, % | 18.05 (± 4.77) | 16.19 (±6.74) | 0.41 | −0.08 | 0.82 |
| DTC ofDST, % | 15.14 (±6.83) | 17.19 (±6.49) | 0.43 | 0.07 | 0.52 |
| DTC ofPCI, % | 17.53 (± 2.60) | 30.00 (±6.54) | 0.43 | 0.06 | 0.52 |
| DTC ofsubtraction speed, % | 2.42 (±10.75) | 1.47 (±9.75) | 0.41 | 0.08 | 0.82 |

DST, double support time; DTC, Dual task costs; FDR, false discovery rate; Med, dopaminergic medication; OFF, without dopaminergic medication/inactive stimulator; ON, with dopaminergic medication/active stimulation; PCI, phase coordination index.

because PD patients generally have at least one form of treatment (dopaminergic medication or DBS). They rarely, if ever, experience a complete OFF-state unless there is an inadvertent medication pause and a DBS dysfunction.

### Effect of DT Paradigm

The secondary task of the DT assessment had an influence on the DT interference and on therapy effects. Stronger effects of both DBS and dopaminergic medication were found in the DT walks with checking boxes than in the DT walks when subtracting. A simplistic model using the bottleneck theory argues for a stronger effect of a motor bottleneck in our study cohort than of a cognitive bottleneck. This is consistent with the results of previous studies. One study found in a cohort of PD patients, that the DT performance when checking boxes during walking predicted falls, but not the DT performance when subtracting.[13] Another study found that the subtracting task was more effective to elucidate deficits in gait in older adults with impaired cognitive flexibility than the checking-boxes task.[43,44] This argues in this cohort for a predominantly cognitive bottleneck. This is relevant for the planning of future studies and suggests using a paradigm that meets the deficits of the specific cohort (ie, using a secondary task that includes motor aspects for patients with PD) to create a very challenging assessment situation.

This study faces limitations. In our results, large standard deviations are present. They may point to different subpopulations of PD that are influenced differently by DT. It would, therefore, be desirable to find ways to better differentiate more or less "DT-capable" subpopulations in further studies. Additionally, the effect of DBS on gait and balance changes over time. A wide distribution of the time with DBS might also have an effect on results.[75] Another limitation of our study is that we were not able to provide data on the paradigm in a condition without both medication and DBS. This might disguise the effects of one treatment method alone, because there might be interaction effects between the treatment options and compensation mechanisms that might work better in ("single therapy") ON- than ("dual therapy") OFF-state. The participants did not receive a formal L-dopa-challenge but rather their usual dose of levodopa during the testing, so some effects may be underestimated or affected by a changing effect of dopaminergic medication during the assessment. However, the subjects consistently showed a satisfactory clinical response in the MDS-UPDRS III, so a sufficient dopaminergic dose can be assumed. Some patients also took dopamine agonists, which might have a different effect on cognitive processes than L-dopa.[76] This also allows for better applicability of our results to daily life. For the $DBS_{OFF\ assessment}$, DBS was switched off for only approximately 30 minutes. It is therefore possible that there is still a carry-over effect, which can disguise the effect of DBS.[53,54] Furthermore, given the number of cases and the number of participants that did not perform all conditions, the results should be interpreted cautiously but should motivate the conducting of further studies, not least because of the enormous relevance of DT abilities in daily life.



  

## CONCLUSION

This study describes a larger positive additional influence of dopaminergic medication than of DBS on temporal gait parameters, especially cadence in advanced PD patients treated with these two regimens. Moreover, DTC of cadence during walking when performing checking boxes simultaneously improved the most among the studied parameters by dopaminergic medication, without deterioration of the secondary task performance. Our results might have implications for treating PD patients with dopaminergic medication and DBS. If these, mostly advanced, PD patients suffer from gait impairments and problems performing DT, the optimization of the dopaminergic medication regimen is a very important component of therapy.

### Acknowledgements

The authors would like to thank all the participants in the study.

### Authorship Statements

Agnes Langer was responsible for the execution, interpretation, review, and critique of the statistical analysis as well as the writing and review of the manuscript. Lucia Gassner, Alireza Gharabaghi, and Heidemarie Zach were responsible for the interpretation, review, and critique of the statistical analysis, as well as the writing and review of the manuscript. Lara Lucke-Paulig was responsible for the organization and execution of the research project, the interpretation, review, and critique of the statistical analysis, and the review and critique of the manuscript preparation. Rejko Krüger and Daniel Weiss were responsible for the organization of the research project, the interpretation, review, and critique of the statistical analysis, and the review and critique of the manuscript preparation. Walter Maetzler was responsible for the conception and organization of the research project, the design, interpretation, review and critique, and the review and critique of the manuscript. Markus A. Hobert was responsible for the conception and organization of the research project, the design, execution, interpretation, review and critique, and the writing, review, and critique of the manuscript. All authors approved the final version of the manuscript.

### How to Cite This Article

Langer A., Lucke-Paulig L., Gassner L., Krüger R., Weiss D., Gharabaghi A., Zach H., Maetzler W., Hobert M.A. 2022. Additive Effect of Dopaminergic Medication on Gait Under Single and Dual-Tasking Is Greater Than of Deep Brain Stimulation in Advanced Parkinson Disease With Long-duration Deep Brain Stimulation. Neuromodulation 2022; ■: 1–10.

## SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.01.015.

## REFERENCES

1. Pal G, O'Keefe J, Robertson-Dick E, Bernard B, Anderson S, Hall D. Global cognitive function and processing speed are associated with gait and balance dysfunction in Parkinson's disease. *J Neuroeng Rehabil*. 2016;13:94. https://doi.org/10.1186/s12984-016-0205-y.
2. 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. https://doi.org/10.1155/2012/918719.
3. 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. https://doi.org/10.1016/j.jns.2006.05.010.
4. Fuller RL, Van Winkle EP, Anderson KE, et al. Dual task performance in Parkinson's disease: a sensitive predictor of impairment and disability. *Parkinsonism Relat Disord*. 2013;19:325–328. https://doi.org/10.1016/j.parkreldis.2012.11.011.
5. Wu T, Hallett M, Chan P. Motor automaticity in Parkinson's disease. *Neurobiol Dis*. 2015;82:226–234. https://doi.org/10.1016/j.nbd.2015.06.014.
6. Plotnik M, Dagan Y, Gurevich T, Giladi N, Hausdorff JM. Effects of cognitive function on gait and dual tasking abilities in patients with Parkinson's disease suffering from motor response fluctuations. *Exp Brain Res*. 2011;208:169–179. https://doi.org/10.1007/s00221-010-2469-y.
7. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's disease. *Gait Posture*. 2010;31:169–174. https://doi.org/10.1016/j.gaitpost.2009.09.019.
8. Penko AL, Streicher MC, Koop MM, et al. Dual-task interference disrupts Parkinson's gait across multiple cognitive domains. *Neuroscience*. 2018;379:375–382. https://doi.org/10.1016/j.neuroscience.2018.03.021.
9. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of gait and Parkinson's disease: the effects of dual tasking. *J Neurol Neurosurg Psychiatry*. 2009;80:347–350. https://doi.org/10.1136/jnnp.2008.157362.
10. Cebi I, Scholten M, Gharabaghi A, Weiss D. Clinical and kinematic correlates of favorable gait outcomes from subthalamic stimulation. *Front Neurol*. 2020;11:212. https://doi.org/10.3389/fneur.2020.00212.
11. Scholten M, Klemt J, Heilbronn M, et al. Effects of subthalamic and nigral stimulation on gait kinematics in Parkinson's disease. *Front Neurol*. 2017;8:543. https://doi.org/10.3389/fneur.2017.00543.
12. Yogev-Seligmann G, Giladi N, Gruendlinger L, Hausdorff JM. The contribution of postural control and bilateral coordination to the impact of dual tasking on gait. *Exp Brain Res*. 2013;226:81–93. https://doi.org/10.1007/s00221-013-3412-9.
13. Heinzel S, Maechtel M, Hasmann SE, et al. Motor dual-tasking deficits predict falls in Parkinson's disease: a prospective study. *Parkinsonism Relat Disord*. 2016;26:73–77. https://doi.org/10.1016/j.parkreldis.2016.03.007.
14. Strouwen C, Molenaar EALM, Münks L, et al. Determinants of dual-task training effect size in Parkinson disease: who will benefit most? *J Neurol Phys Ther*. 2019;43:3–11. https://doi.org/10.1097/npt.0000000000000247.
15. Fritz NE, Cheek FM, Nichols-Larsen DS. Motor-cognitive dual-task training in persons with neurologic disorders: a systematic review. *J Neurol Phys Ther*. 2015;39:142–153. https://doi.org/10.1097/npt.0000000000000090.
16. Wong-Yu IS, Mak MK. Multi-dimensional balance training programme improves balance and gait performance in people with Parkinson's disease: a pragmatic randomized controlled trial with 12-month follow-up. *Parkinsonism Relat Disord*. 2015;21:615–621. https://doi.org/10.1016/j.parkreldis.2015.03.022.
17. Wong-Yu ISK, Mak MKY. Multisystem balance training reduces injurious fall risk in Parkinson disease: a randomized trial. *Am J Phys Med Rehabil*. 2019;98:239–244. https://doi.org/10.1097/phm.0000000000001035.
18. Shen X, Mak MK. Technology-assisted balance and gait training reduces falls in patients with Parkinson's disease: a randomized controlled trial with 12-month follow-up. *Neurorehabil Neural Repair*. 2015;29:103–111. https://doi.org/10.1177/1545968314537559.
19. Killane I, Fearon C, Newman L, et al. Dual motor-cognitive virtual reality training impacts dual-task performance in freezing of gait. *IEEE J Biomed Health Inform*. 2015;19:1855–1861. https://doi.org/10.1109/jbhi.2015.2479625.
20. Workman CD, Thrasher TA. The influence of dopaminergic medication on gait automaticity in Parkinson's disease. *J Clin Neurosci*. 2019;65:71–76. https://doi.org/10.1016/j.jocn.2019.03.007.
21. McNeely ME, Duncan RP, Earhart GM. Medication improves balance and complex gait performance in Parkinson disease. *Gait Posture*. 2012;36:144–148. https://doi.org/10.1016/j.gaitpost.2012.02.009.
22. Lord S, Baker K, Nieuwboer A, Burn D, Rochester L. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *J Neurol*. 2011;258:566–572.
23. Elshehabi M, Maier KS, Hasmann SE, et al. Limited effect of dopaminergic medication on straight walking and turning in early-to-moderate Parkinson's disease during single and dual tasking. *Front Aging Neurosci*. 2016;8:4. https://doi.org/10.3389/fnagi.2016.00004.

24. Ferrarin M, Rizzone M, Bergamasco B, et al. Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease. *Exp Brain Res*. 2005;160:517–527. https://doi.org/10.1007/s00221-004-2036-5.
25. Faist M, Xie J, Kurz D, et al. Effect of bilateral subthalamic nucleus stimulation on gait in Parkinson's disease. *Brain*. 2001;124:1590–1600. https://doi.org/10.1093/brain/124.8.1590.
26. Schlenstedt C, Shalash A, Muthuraman M, Falk D, Witt K, Deuschl G. Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2017;24:18–26. https://doi.org/10.1111/ene.13167.
27. Roper JA, Kang N, Ben J, Cauraugh JH, Okun MS, Hass CJ. Deep brain stimulation improves gait velocity in Parkinson's disease: a systematic review and meta-analysis. *J Neurol*. 2016;263:1195–1203. https://doi.org/10.1007/s00415-016-8129-9.
28. Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review. *Neurophysiol Clin*. 2015;45:371–388. https://doi.org/10.1016/j.neucli.2015.07.001.
29. Chenji G, Wright ML, Chou KL, Seidler RD, Patil PG. Parkinsonian gait improves with bilateral subthalamic nucleus deep brain stimulation during cognitive multi-tasking. *Parkinsonism Relat Disord*. 2017;38:72–79. https://doi.org/10.1016/j.parkreldis.2017.02.028.
30. McNeely ME, Earhart GM. Medication and subthalamic nucleus deep brain stimulation similarly improve balance and complex gait in Parkinson disease. *Parkinsonism Relat Disord*. 2013;19:86–91. https://doi.org/10.1016/j.parkreldis.2012.07.013.
31. Seri-Fainshtat E, Israel Z, Weiss A, Hausdorff JM. Impact of sub-thalamic nucleus deep brain stimulation on dual tasking gait in Parkinson's disease. *J Neuroeng Rehabil*. 2013;10:38. https://doi.org/10.1186/1743-0003-10-38.
32. Wegrzyk J, Armand S, Chiuvé SC, Burkhard PR, Allali G. Education level affects dual-task gait after deep brain stimulation in Parkinson's disease. *Parkinsonism Relat Disord*. 2019;68:65–68. https://doi.org/10.1016/j.parkreldis.2019.10.005.
33. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23:2129–2170. https://doi.org/10.1002/mds.22340.
34. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
35. Lezak M. *Orientation and Attention*. 3rd ed. Oxford University Press; 1995:335–384.
36. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67:588–597. https://doi.org/10.1207/s15327752jpa6703_13.
37. Zijlstra W, Hof AL. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. *Gait Posture*. 2003;18:1–10. https://doi.org/10.1016/s0966-6362(02)00190-x.
38. Brandes M, Zijlstra W, Heikens S, van Lummel R, Rosenbaum D. Accelerometry based assessment of gait parameters in children. *Gait Posture*. 2006;24:482–486. https://doi.org/10.1016/j.gaitpost.2005.12.006.
39. Dijkstra B, Zijlstra W, Scherder E, Kamsma Y. Detection of walking periods and number of steps in older adults and patients with Parkinson's disease: accuracy of a pedometer and an accelerometry-based method. *Age Ageing*. 2008;37:436–441. https://doi.org/10.1093/ageing/afn097.
40. Houdijk H, Appelman FM, Van Velzen JM, Van der Woude LH, Van Bennekom CA. Validity of DynaPort GaitMonitor for assessment of spatiotemporal parameters in amputee gait. *J Rehabil Res Dev*. 2008;45:1335–1342.
41. Bock O. Dual-task costs while walking increase in old age for some, but not for other tasks: an experimental study of healthy young and elderly persons. *J Neuroeng Rehabil*. 2008;527–27 https://doi.org/10.1186/1743-0003-5-27.
42. Lerche S, Hobert M, Brockmann K, et al. Mild parkinsonian signs in the elderly–is there an association with PD? Crossectional findings in 992 individuals. *PLoS One*. 2014;9:e92878. https://doi.org/10.1371/journal.pone.0092878.
43. Hobert MA, Niebler R, Meyer SI, et al. Poor trail making test performance is directly associated with altered dual task prioritization in the elderly–baseline results from the TREND study. *PLoS One*. 2011;6:e27831. https://doi.org/10.1371/journal.pone.0027831.
44. Hobert MA, Meyer SI, Hasmann SE, et al. Gait is associated with cognitive flexibility: a dual-tasking study in healthy older people. *Front Aging Neurosci*. 2017;9:154. https://doi.org/10.3389/fnagi.2017.00154.
45. Doumas M, Smolders C, Krampe RT. Task prioritization in aging: effects of sensory information on concurrent posture and memory performance. *Exp Brain Res*. 2008;187:275–281. https://doi.org/10.1007/s00221-008-1302-3.
46. Bryant MS, Rintala DH, Hou JG, Lai EC, Protas EJ. Effects of levodopa on forward and backward gait patterns in persons with Parkinson's disease. *NeuroRehabilitation*. 2011;29:247–252. https://doi.org/10.3233/nre-2011-0700.
47. Kwon KY, Lee HM, Kang SH, Pyo SJ, Kim HJ, Koh SB. Recuperation of slow walking in de novo Parkinson's disease is more closely associated with increased cadence, rather than with expanded stride length. *Gait Posture*. 2017;58:1–6. https://doi.org/10.1016/j.gaitpost.2017.06.266.
48. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a double-edged sword for balance and gait in people With Parkinson's disease. *Mov Disord*. 2015;30:1361–1370. https://doi.org/10.1002/mds.26269.
49. Merola A, Romagnolo A, Dwivedi AK, et al. Benign versus malignant Parkinson disease: the unexpected silver lining of motor complications. *J Neurol*. 2020;267:2949–2960. https://doi.org/10.1007/s00415-020-09954-6.
50. Borgkvist A, Lieberman OJ, Sulzer D. Synaptic plasticity may underlie L-dopa induced dyskinesia. *Curr Opin Neurobiol*. 2018;48:71–78. https://doi.org/10.1016/j.conb.2017.10.021.
51. Kishore A, James P, Krishnan S, Yahia-Cherif L, Meunier S, Popa T. Motor cortex plasticity can indicate vulnerability to motor fluctuation and high L-DOPA need in drug-naïve Parkinson's disease. *Parkinsonism Relat Disord*. 2017;35:55–62. https://doi.org/10.1016/j.parkreldis.2016.12.005.
52. Orcioli-Silva D, Vitório R, Nóbrega-Sousa P, et al. Levodopa facilitates prefrontal cortex activation during dual task walking in Parkinson disease. *Neurorehabil Neural Repair*. 2020;34:589–599. https://doi.org/10.1177/1545968320924430.
53. Schlenstedt C, Gavriliuc O, Boße K, et al. The effect of medication and deep brain stimulation on posture in Parkinson's disease. *Front Neurol*. 2019;10:1254. https://doi.org/10.3389/fneur.2019.01254.
54. Gavriliuc O, Paschen S, Andrusca A, Helmers AK, Schlenstedt C, Deuschl G. Clinical patterns of gait freezing in Parkinson's disease and their response to interventions: an observer-blinded study. *Parkinsonism Relat Disord*. 2020;80:175–180. https://doi.org/10.1016/j.parkreldis.2020.09.043.
55. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. *Neurosci Biobehav Rev*. 2006;30:1–23. https://doi.org/10.1016/j.neubiorev.2005.03.024.
56. Huang YT, Georgiev D, Foltynie T, Limousin P, Speekenbrink M, Jahanshahi M. Different effects of dopaminergic medication on perceptual decision-making in Parkinson's disease as a function of task difficulty and speed-accuracy instructions. *Neuropsychologia*. 2015;75:577–587. https://doi.org/10.1016/j.neuropsychologia.2015.07.012.
57. Moustafa AA, Sherman SJ, Frank MJ. A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. *Neuropsychologia*. 2008;46:3144–3156. https://doi.org/10.1016/j.neuropsychologia.2008.07.011.
58. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*. 2003;41:1431–1441. https://doi.org/10.1016/s0028-3932(03)00117-9.
59. Lewis SJ, Slabosz A, Robbins TW, Barker RA, Owen AM. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. *Neuropsychologia*. 2005;43:823–832. https://doi.org/10.1016/j.neuropsychologia.2004.10.001.
60. Jahn K, Deutschländer A, Stephan T, et al. Supraspinal locomotor control in quadrupeds and humans. *Prog Brain Res*. 2008;171:353–362. https://doi.org/10.1016/s0079-6123(08)00652-3.
61. Mirelman A, Shema S, Maidan I, Hausdorff JM. *Gait*. Handb Clin Neurol. 2018;159:119–134. https://doi.org/10.1016/b978-0-444-63916-5.00007-0.
62. Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. 2005;164:541–548. https://doi.org/10.1007/s00221-005-2280-3.
63. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord*. 2013;28:1520–1533. https://doi.org/10.1002/mds.25674.
64. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23:329–342; quiz 472. https://doi.org/10.1002/mds.21720
65. Christopher L, Marras C, Duff-Canning S, et al. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain*. 2014;137:565–575. https://doi.org/10.1093/brain/awt337.
66. Mihaescu AS, Kim J, Masellis M, et al. Graph theory analysis of the dopamine D2 receptor network in Parkinson's disease patients with cognitive decline. *J Neurosci Res*. 2021;99:947–965. https://doi.org/10.1002/jnr.24760.
67. Pilotto A, Schiano di Cola F, Premi E, et al. Extrastriatal dopaminergic and serotonergic pathways in Parkinson's disease and in dementia with Lewy bodies: a 123 I-FP-CIT SPECT study. *Eur J Nucl Med Mol Imaging*. 2019;46:1642–1651. https://doi.org/10.1007/s00259-019-04324-5.
68. Salami A, Garrett DD, Wåhlin A, et al. Dopamine D 2/3 binding potential modulates neural signatures of working memory in a load-dependent fashion. *J Neurosci*. 2019;39:537–547. https://doi.org/10.1523/jneurosci.1493-18.2018.
69. St George RJ, Nutt JG, Burchiel KJ, Horak FB. A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD. *Neurology*. 2010;75:1292–1299. https://doi.org/10.1212/WNL.0b013e3181f61329.
70. Kim R, Kim HJ, Shin C, et al. Long-term effect of subthalamic nucleus deep brain stimulation on freezing of gait in Parkinson's disease. *J Neurosurg*. 2019;131:1797–1804. https://doi.org/10.3171/2018.8.jns18350.
71. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol*. 2008;7:605–614. https://doi.org/10.1016/s1474-4422(08)70114-5.
72. David FJ, Munoz MJ, Corcos DM. The effect of STN DBS on modulating brain oscillations: consequences for motor and cognitive behavior. *Exp Brain Res*. 2020;238:1659–1676. https://doi.org/10.1007/s00221-020-05834-7.
73. 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. https://doi.org/10.1109/tnsre.2007.897074.



  

74. 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. https://doi.org/10.1093/brain/awn238.
75. Szlufik S, Kloda M, Friedman A, et al. The neuromodulatory impact of subthalamic nucleus deep brain stimulation on gait and postural instability in Parkinson's disease patients: a prospective case controlled study. *Front Neurol*. 2018;9:906. https://doi.org/10.3389/fneur.2018.00906.
76. Brusa L, Pavino V, Massimetti MC, Bove R, Iani C, Stanzione P. The effect of dopamine agonists on cognitive functions in non-demented early-mild Parkinson's disease patients. *Funct Neurol*. 2013;28:13–17.

## COMMENT

The authors present results of a pilot study of a small series of patients with PD who underwent analysis of the effects of DBS and medication therapy on temporal characteristics of gait including gait speed, cadence, DST, and phase coordination index (gait irregularity) in ST and DT conditions. Subjects were tested in the on- and off-medication conditions and in the on- and off-DBS conditions. The effect of dopaminergic medication (tested in the off- and on-medication/on-DBS conditions) on cadence, gait speed, and number of steps was large or moderate in single- and DT test situations, whereas the effects of DBS were generally small (with the exception of moderate effect on DT cadence). Notably, the beneficial effects of medications were achieved without any degradation of performance on the secondary tasks (checking boxes and serial subtraction) compared with baseline performance on checking boxes and serial subtraction when performed as single tasks. As a pilot study, major limitations are related to the small sample size as well as the inability of some subjects to complete all testing paradigms, which resulted in large standard deviations in data analyses. Whether the reported results would be achieved in a larger scale study remains to be determined. DBS was deactivated for approximately 30 minutes, which might have been insufficient time to allow complete washout of the DBS effect, which could have reduced the apparent magnitude of on/off-DBS differences. Testing in the "on-medication" state was accomplished by administering the subjects' typical doses of medications, which might have been reduced following implementation of DBS therapy to a level that, by itself, would be subtherapeutic (administration of medication produced, on average, only six point improvement of Unified Parkinson Disease Rating Scale III vs 13 point improvement with DBS); had subjects been treated with larger (challenge) doses, the impact of medications on gait might have been greater than was observed. The subthalamic nucleus was the only DBS target studied. Whether the results apply to DBS of the globus pallidus, which has become a common DBS target in the United States and which might have different effects on gait, is unknown. As the authors note, the observation that dopaminergic medication has a more beneficial impact on gait in single- and DT conditions compared with DBS has potentially important clinical implications. Commonly, the success of DBS therapy is measured by the extent of reduction of dopaminergic medications after implementation of DBS therapy; however, as the authors explain, it might not be advisable to reduce medications post-DBS to the minimum amount possible because medications might provide beneficial effects on gait that DBS does not provide. This is consistent with previous suggestions that aggressive reduction of medications post-DBS might not be desirable for all PD patients (Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010;362:2077–2091. Mei S, Eisinger RS, Hu W, et al. Three-year gait and axial outcomes of bilateral STN and GPi Parkinson's disease deep brain stimulation. *FrontHum Neurosci*. 2020;14:1). In the setting of PD, gait deteriorates over time despite otherwise stable improvement of motoric function provided by successful deep brain stimulation (DBS) therapy. For this reason, further larger scale investigation of the observations reported by the authors are warranted in an effort to develop treatment strategies that optimize gait, especially in DT situations, to provide patients with PD the greatest improvement of quality of life.

Kenneth Follett, MD
*Omaha, NE, USA*