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# Deep Brain Stimulation and Levodopa Affect Gait Variability in Parkinson Disease Differently

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## ABSTRACT

**Background:** Both dopaminergic medication and subthalamic nucleus (STN) deep brain stimulation (DBS) can improve the amplitude and speed of gait in Parkinson disease (PD), but relatively little is known about their comparative effects on gait variability. Gait irregularity has been linked to the degeneration of cholinergic neurons in the pedunculopontine nucleus (PPN).

**Objectives:** The STN and PPN have reciprocal connections, and we hypothesized that STN DBS might improve gait variability by modulating PPN function. Dopaminergic medication should not do this, and we therefore sought to compare the effects of medication and STN DBS on gait variability.

**Materials and Methods:** We studied 11 patients with STN DBS systems on and off with no alteration to their medication, and 15 patients with PD without DBS systems on and off medication. Participants walked for two minutes in each state, wearing six inertial measurement units. Variability has previously often been expressed in terms of SD or coefficient of variation over a testing session, but these measures conflate long-term variability (eg, gradual slowing, which is not necessarily pathological) with short-term variability (true irregularity). We used Poincaré analysis to separate the short- and long-term variability.

**Results:** DBS decreased short-term variability in lower limb gait parameters, whereas medication did not have this effect. In contrast, STN DBS had no effect on arm swing and trunk motion variability, whereas medication increased them, without obvious dyskinesia.

**Conclusions:** Our results suggest that STN DBS acts through a nondopaminergic mechanism to reduce gait variability. We believe that the most likely explanation is the retrograde activation of cholinergic PPN projection neurons.

**Keywords:** Deep brain stimulation, gait irregularity, Parkinson disease, wearable sensors

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## INTRODUCTION

Disorders of gait are a common feature of Parkinson disease (PD). They can be classified into two types, which commonly coexist: gait speed and amplitude abnormalities because of bradykinesia and rigidity and gait rhythm disturbances. Elevated gait variability is associated with an increased risks of falls.[1,2]

Overall, straight-line gait speed and the amplitude of parameters including step length, trunk motion, and arm swing are improved by dopaminergic medication.[3] Other parameters, such as cadence, turning in place, and aspects of gait initiation, are less responsive.[4] Published work is suggestive of decreased gait variability with medication,[1,3] but the literature is sparse.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for PD, improving rigidity, bradykinesia, and tremor and reducing motor fluctuations.[5,6] It usually results in a substantial reduction in levodopa requirements, which may in turn reduce levodopa-induced side effects. STN DBS improves many of the same gait parameters as medication, producing greater overall speed and stride amplitude and reducing double-limb support time.[7,8] The benefits are not universal, and a proportion of patients will have worse gait on stimulation. A previous study has suggested that STN DBS may reduce parkinsonian gait variability.[9] In contrast to the other published studies,[1,3] no effect of medication on variability was found in this latter study.

There is evidence that gait irregularity in PD may not be a primarily dopaminergic issue. In addition to dopaminergic neuronal degeneration in the substantia nigra pars compacta, there also is degeneration of cholinergic neurons in the pedunculopontine nucleus (PPN),[10–12] an area which has a major role in coordination of gait and posture. Postural and gait disturbance can be produced in animals by purely cholinergic PPN lesions without any dopaminergic degeneration at all.[13] In humans, the extent of freezing and falling correlates with the degree of cholinergic PPN neuron loss found post mortem.[13] Although the evidence at this point is still fairly preliminary, there are indications that acetylcholinesterase inhibitors may make gait more regular and stable: Rivastigmine reduces the SD of step time,[14] and donepezil reduced fall frequency in PD in one study.[15] There is evidence from leucine-rich repeat kinase 2 (LRKK2) mutation carriers that gait variability can already be abnormal as a very early prodromal feature[16]; this is compatible with a role for the PPN, which is believed to be affected as early in the pathological process (Braak stage 3) as the substantia nigra.[17] In addition, the cholinergic system is implicated in rapid eye movement sleep behavior disorder, which may occur as a prodromal feature of PD.

There are reciprocal connections between the PPN and STN that are likely to be activated by STN DBS. We therefore hypothesized that STN DBS might improve gait variability by modulating PPN function. Because the proposed mechanism is cholinergic, this is something that dopaminergic medication should not do, and therefore, we would expect measures of gait variability to be affected by DBS but not by medication.

In this study, we use a wearable inertial measurement unit (IMU) array to accurately quantify multiple gait parameters in patients with PD both on and off their treatment (levodopa or STN DBS) to compare the effects of dopaminergic medication and STN DBS on gait variability. In addition to lower limb gait parameters, the analysis also includes some upper limb and trunk variables to investigate whether the treatments have consistent effects body-wide. Modern systems can measure dozens of gait features and to restrict the analysis to a reasonable number, we selected those that are prominent in the literature. These included stride length,[18–21] toe-out angle,[22] foot strike angle,[18,23] single-limb support time,[21,24] arm range of motion (ROM),[19,20,25,26] and trunk ROM in sagittal, coronal, and transverse planes.[18–20,27]

Often in previous studies, the variability present within each parameter has been expressed in terms of its SD or coefficient of variation (CV) for multiple gait cycles in a testing session (eg, the SD of stride length during a two-minute walk). However, these measures potentially conflate long-term variability (eg, gradual slowing, which is not necessarily pathological) with short-term variability (true irregularity). Gradual slowing may reflect the progressive decrement in the amplitude and speed of movement over time that is a hallmark of PD, or it may simply reflect fatigue. We are primarily interested in the short-term variability and have used analysis methodology that aims to separate this out. The technique used, Poincaré analysis, is commonly used in quantitative analysis of other physiological phenomena, in particular heart rate variability, and it has been used in the analysis of gait in healthy individuals.[28]

## MATERIALS AND METHODS

### Participants

Participants were recruited through the Oxford Quantification in Parkinsonism (OxQUIP) study at the John Radcliffe Hospital in Oxford. OxQUIP is a large prospective cohort study of neurophysiologic biomarkers in parkinsonian patients and is approved by the ethics committee (Research Ethics Committee reference 16/SW/0262). Informed consent was obtained from all participants after explaining the procedures to them. The study included adult participants of either gender with normal or corrected-to-normal vision in both eyes. Participants with PD had a diagnosis of PD according to the United Kingdom PD Brain Bank criteria[29] and Movement Disorders Society criteria.[30] Age-matched healthy controls had no history of neurologic disease and were often, but not always, the spouse of a patient. Participants were screened with the Mini-Mental State Examination (MMSE), and those with significant cognitive impairment were excluded. All included participants in this study had MMSE scores of at least 25.

Demographic data, clinical characteristics, and rating scores are shown in Table 1. For simplicity within this paper, participants without DBS, who are tested on and off medication, are referred to as the medication group, and those undergoing DBS, who are tested on and off stimulation, are referred to as the DBS group. Patients undergoing DBS were tested in the on-medication condition throughout; STN DBS typically reduces medication requirements by 30% to 50%, and in this case, the DBS group had a mean dose in levodopa equivalent units that was 42% less than the medication group.

Two groups of patients with PD were recruited. A group with bilaterally implanted STN DBS systems were tested first with stimulation on. The system was then switched off, and after 30 minutes, the patients were retested with the system remaining off for the duration of testing. Another group of patients without DBS systems but at a similar disease stage were tested in the medication-off and then medication-on states. The medication-off state is defined as at least 12 hours without dopaminergic

**Table 1.** Demographics, Clinical Characteristics, and Rating Scale Scores in Both the Patients With PD and Healthy Control Groups.

| ID | Age (y) | Gender | PD duration (y) | MDS-UPDRS Part 3 ON | MDS-UPDRS Part 3 OFF | H&Y ON | H&Y OFF | DBS duration (y) | LEU (mg) | Medication |
|---|---|---|---|---|---|---|---|---|---|---|
| DBS01 | 65 | F | 18 | 33 | 40 | 3 | 3 | 4 | 1235 | Amantadine, co-beneldopa, co-careldopa CR, entacapone/levodopa/carbidopa, ropinirole |
| DBS02 | 65 | F | 15 | 29 | 36 | 2 | 2 | 2 | 410 | Co-beneldopa, rasagiline, ropinirole |
| DBS03 | 56 | M | 10 | 34 | 93 | 0 | 3 | 1 | 700 | Amantadine, co-careldopa, entacapone/levodopa/carbidopa |
| DBS04 | 51 | M | 7 | 26 | 38 | 1 | 1 | 3 | 400 | Co-beneldopa |
| DBS05 | 54 | M | 12 | 36 | 50 | 2 | 3 | 2 | 250 | Amantadine, co-careldopa |
| DBS06 | 58 | M | 12 | 60 | 72 | 2 | 2 | 5 | 650 | Co-beneldopa, pramipexole PR |
| DBS07 | 56 | M | 10 | 37 | 58 | 2 | 2 | 3 | 350 | Amantadine, co-careldopa |
| DBS08 | 62 | M | 11 | 34 | 55 | 2 | 2 | 3 | 620 | Co-careldopa, rotigonine |
| DBS09 | 57 | F | 3 | 40 | 68 | 3 | 3 | 2 | 0 | None |
| DBS10 | 60 | F | 11 | 28 | 38 | 2 | 2 | 2 | 200 | Co-careldopa, pramipexole PR |
| DBS11 | 64 | M | 9 | 17 | 48 | 2 | 2 | 1 | 435 | Co-careldopa, pramipexole PR, rasagiline, opicapone |
| Stimulation group | 58.9 ± 4.4 (51–65) | 7M:4F | 10.7 ± 3.7 (3–18) | 34.0 ± 10.2 (17–60) | 54.2 ± 16.9 (36–93) | 1.9 ± 0.8 (0–3) | 2.3 ± 0.6 (1–3) | 2.5 ± 1.1 (1–5) | 477 ± 310 (0–1235) | |
| MED01 | 62 | M | 8 | 18 | 41 | 2 | 2 | | 1564 | Co-beneldopa, co-careldopa, entacapone, rasagiline |
| MED02 | 69 | M | 3 | 17 | 29 | 2 | 2 | | 680 | Co-beneldopa, ropinirole |
| MED03 | 63 | M | 6 | 27 | 49 | 2 | 2 | | 500 | Co-beneldopa, rasagiline |
| MED04 | 62 | F | 9 | 34 | 42 | 2 | 2 | | 315 | Apomorphine, co-careldopa CR, rotigotine |
| MED05 | 59 | M | 3 | 14 | 39 | 2 | 2 | | 948 | Co-careldopa, entacapone |
| MED06 | 74 | M | 7 | 19 | 43 | 2 | 2 | | 940 | Co-beneldopa MR, entacapone/levodopa/carbidopa |
| MED07 | 63 | F | 12 | 28 | 65 | 3 | 3 | | 1200 | Co-beneldopa, entacapone/levodopa/carbidopa |
| MED08 | 70 | M | 20 | 39 | 38 | 2 | 2 | | 300 | Co-beneldopa |
| MED09 | 61 | M | 7 | 11 | 44 | 2 | 2 | | 1140 | Co-beneldopa, co-beneldopa CR, pramipexole, safinamide |
| MED10 | 58 | M | 16 | 24 | 59 | 2 | 2 | | 660 | Apomorphine pen, co-beneldopa, opicapone, rotigotine, safinamide |
| MED11 | 74 | M | 8 | 32 | 41 | 2 | 2 | | 610 | Co-careldopa, rasagiline, ropinirole XL, trihexyphenidyl |
| MED12 | 65 | M | 8 | 27 | 47 | 2 | 2 | | 1340 | Co-careldopa, co-careldopa CR, opicapone, ropinirole |
| MED13 | 70 | M | 7 | 16 | 41 | | 2 | | 325 | Entacapone/levodopa/carbidopa, rasagiline |
| MED14 | 54 | F | 5 | 11 | 42 | 2 | 2 | | 1278 | Co-careldopa CR, entacapone/levodopa/varbidopa, rasagiline, ropinirole XL |
| MED15 | 70 | M | 13 | 22 | 58 | 2 | 2 | | 441 | Co-beneldopa, co-beneldopa CR, entacapone, levodopa/carbidopa |
| Medication group | 64.9 ± 5.8 (54–74) | 12M:3F | 8.8 ± 4.5 (3–20) | 22.6 ± 8.2 (11–39) | 45.2 ± 8.9 (29–65) | 2.1 ± 0.2 (2–3) | 2.1 ± 0.2 (2–3) | | 816 ± 401 (300–1564) | |
| Control group | 57.9 ± 6.5 (51–80) | 19M:23F | | 3.5 ± 4.2 (0–16) | | | | | | |

Figures in parentheses are ranges. For the DBS participants, "ON" and "OFF" refer to the state of the patient's stimulator system, their medication state not being altered.
F, female; H&Y, Hoehn and Yahr score; ID, identification number; LEU, levodopa equivalent unit; M, male.

medication, and the medication-on state is one hour after dose. Age-matched healthy controls were tested once. Dyskinesias were not observed in the patients during testing, but we cannot exclude that subtle dyskinesias were present; this is considered further in the Discussion.

### Experimental Design and Statistical Analyses

Testing consisted of gait analysis and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor assessment). Gait data were collected using a body-worn network of six inertial measurement units (MobilityLab System; APDM, Portland, OR) with synchronized sensors positioned on both wrists and both feet, the trunk, and the lumbar area. Each sensor comprised triaxial accelerometers, gyroscopes, and magnetometers. This system has already been used for gait assessment in PD in several studies.[31–33] Patients performed a two-minute walk in a quiet, uncarpeted 15-meter corridor, making turns when necessary. Periods of straight-line walking and turns were segregated by the software, and only straight-line walking variables were analyzed for this study.

The parameters analyzed are shown in Figure 1 and Table 2 and included a range of lower limb, trunk, and upper limb measures. Values for each participant are the mean of right- and left-sided values.

Step-by-step measures of gait parameters were exported from MobilityLab and processed using GraphPad Prism (GraphPad Software, San Diego, CA). Poincaré analysis was used for quantification of variability during gait. A Poincaré plot, also known as a first return map, is a scatter plot in which each successive value of a given variable (eg, stride length) is plotted against the one before, ie, $x = f(i)$; $y = f(i + 1)$. This is shown schematically at the top left of Figure 2. Deviation of points from the line of identity ($y = x$) occurs because of step-to-step variability in the parameter concerned. This short-term variability is quantified using the SD of the distance from the identity line, known as SD1, where

$$SD1 = \sqrt{\frac{\sum((x-y) - \overline{(x-y)})^2}{2n}}$$

The spread of data points along the identity line represents long-term variability, for example, because of gradual slowing over the testing session. It is quantified by its SD, SD2, where

$$SD2 = \sqrt{\frac{\sum((x+y) - \overline{(x+y)})^2}{2n}}$$

SD1 and SD2 were calculated for each parameter analyzed for each participant in each condition.

The groups were compared using paired *t*-tests where data were normally distributed and the Wilcoxon signed-rank test (WSRT) otherwise. Correction was made for multiple comparisons using the Benjamini-Hochberg method, with a false discovery rate of 5%.

## RESULTS

The effects of medication and DBS on gait parameters are depicted in Figure 1, which shows off and on values of each parameter for the two interventions; each pair of points linked by a line represents a single patient. Gait parameters from the healthy controls were used to generate age-matched normative ranges, defined as the central 95% of the range of control values. These are shown in the figures as gray bands; the horizontal dashed lines are control means. Table 2 gives the mean values per parameter, group, and condition and the details of the statistical comparison of off/on values.

### Lower Limb Gait Parameters

Both medication and DBS improved stride length (Fig. 1a; medication $p = 0.0016$, *t*-test; DBS $p = 0.019$, *t*-test) toward the control mean. Both medication and DBS also increased foot strike angle (Fig. 1c; medication $p = 0.0062$, *t*-test; DBS $p = 0.0051$, *t*-test). After correction for multiple comparisons, the medication-induced change in stride length and the medication- and DBS-induced changes in foot strike angle remained significant (Table 2). There was no significant treatment effect for absolute toe-out angle or single-limb support time.

### Axial and Upper Limb Gait Parameters

Medication significantly increased all axial and upper limb ROM parameters, including the arm ROM (Fig. 1e; $p = 0.0005$, *t*-test) and trunk ROM in the coronal, sagittal, and transverse planes (Fig. 1f–h; $p = 0.0034$, WSRT; $p = 0.025$, WSRT; $p = 0.030$, *t*-test). No such effect was seen with stimulation. After correction for multiple comparisons, the medication-induced changes in arm ROM and trunk ROM in the coronal plane remained significant (Table 2).

### Variability in Gait Parameters

Figure 3 shows examples of the step-by-step values of stride length on and off therapy for the first five participants in the medication and DBS groups. In these examples, some of the medication group patients can be seen to have increased variability on treatment (MED01 and MED03), whereas patients undergoing DBS, DBS02, DBS03, and DBS05, appear to have decreased variability on treatment.

To quantify the degree of variability, Poincaré analysis was carried out for each parameter, patient, and treatment condition. Examples of the analysis for toe-out variability are shown in Figure 2. The plot at the top left shows the principles of Poincaré analysis, with the SD perpendicular to (SD1) and along (SD2) the identity line being calculated separately and representing short- and long-term variability, respectively. Data from a healthy control are shown in the top right plot. The bottom row shows data from medication group (left) and DBS group (right) participants. The administration of medication results in the data points (blue) being more scattered than at baseline (black), ie, an increase in variability, whereas switching on DBS results in the data points (red) being more tightly clustered than at baseline, ie, a decrease in variability.

Figure 4 and Table 3 show the changes in SD1 (short-term variability) and SD2 (long-term variability) produced by medication or DBS. Each point on each plot represents the difference in on- vs off-treatment variability for an individual patient. In the lower limbs, medication increased short- and long-term toe-out angle variability (Fig. 4d; $p = 0.0015$, WSRT; $p = 0.022$, WSRT), while leaving the other parameters unaffected. In contrast, STN DBS decreased both short- and long-term toe-out angle variability (Fig. 4b; $p = 0.021$, *t*-test; $p = 0.0077$, *t*-test). DBS also decreased short-term variability in stride length (Fig. 4a, $p = 0.049$, *t*-test), foot strike angle (Fig. 4c; $p = 0.0029$, WSRT), and single-limb support (Fig. 4b; $p = 0.0020$, WSRT) as well as long-term variability in single-limb support

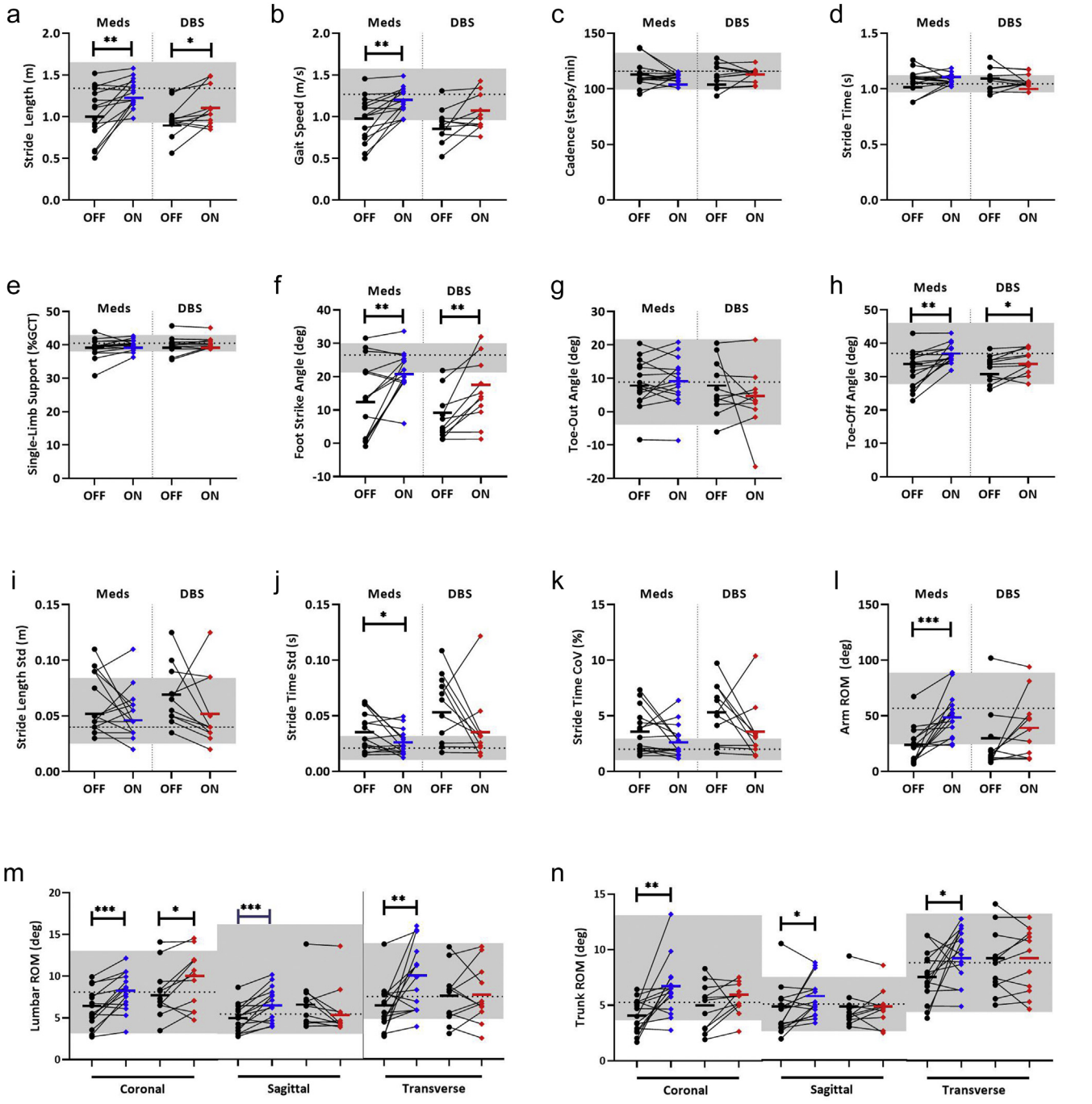


**Figure 1.** Treatment effect of STN DBS and medication on selected gait parameters against the normative range. a. stride length; b. single limb support as a percentage of gait cycle time; c. foot strike angle; d. toe out angle; e. arm range of motion; f-h. trunk range of motion respectively in the coronal, sagittal and transverse planes. Black, off treatment; blue, on medication; red, on DBS; gray, normative range, calculated as the 95% CI of each parameter from the age-matched control group. *Statistical significance after the Benjamini-Hochberg correction. deg, degree; Meds, medications.

(Fig. 4b; $p = 0.042$, WSRT). After correction for multiple comparisons, the medication-induced change in SD1 for toe-out angle and the DBS-induced changes in SD1 for single-limb support and foot strike angle and SD2 for toe-out angle remained significant.

Both SD1 and SD2 for trunk ROM were increased by medication in all planes: coronal (Fig. 4j; $p = 0.0086$, WSRT; $p = 0.0004$, WSRT), sagittal (Fig. 4k; $p = 0.0015$, WSRT; $p = 0.026$, WSRT), and transverse (Fig. 4l; $p = 0.030$, $t$-test; $p = 0.026$, WSRT). After correction for multiple comparisons, the changes in SD1 and SD2 in the coronal plane and SD1 in the sagittal plane remained significant. DBS did not significantly change the variability in any of the measures of trunk ROM (Fig. 4f–h).

Mean arm ROM variability was increased (in both SD1 and SD2) by medication in ten of 15 patients, although the change was not statistically significant. DBS produced no change in arm ROM variability.

**Table 2.** Effect of Medication and DBS on Gait Parameters Quantified as Mean Values per Parameter, Group, and Condition.

| Parameter | HC group | Medication group | | | DBS group | | |
|---|---|---|---|---|---|---|---|
| | Mean | Mean value (Range; % of HC) | | *p* Value | Mean value (Range; % of HC) | | *p* Value |
| | | Off | On | | Off | On | |
| Lower limb | | | | | | | |
| Stride length, m | 1.34 | 1.04 (0.51–1.5; 77) | 1.29 (1.1–1.6; 95) | **0.0016**[*] | 0.964 (0.85–1.5; 72) | 1.11 (0.57–1.3; 83) | 0.019[*] |
| Single-limb support, %GCT | 40.5 | 39.1 (31–44; 97) | 39.9 (36–43; 98) | 0.17[*] | 39.9 (35–46; 98) | 40.5 (39–45; 100) | 0.20[*] |
| Foot strike angle, deg | 26.5 | 13.6 (−0.88 to 32; 51) | 21.5 (18–34; 81) | **0.0062**[*] | 7.72 (1.2–22; 29) | 15.4 (1.3–32; 58) | **0.0051**[*] |
| Toe-out angle, deg | 8.90 | 8.45 (−8.4 to 20; 95) | 9.15 (−8.7 to 21; 103) | 0.53[*] | 7.15 (−6.1 to 21; 80) | 3.70 (−16 to 22; 42) | 0.34[*] |
| Axial | | | | | | | |
| Trunk coronal ROM | 5.27 | 4.03 (1.7–6.4; 76) | 6.52 (3.9–13; 124) | **0.0034**[†] | 4.87 (2.7–7.5; 92) | 5.60 (1.9–8.3; 106) | 0.24[*] |
| Trunk sagittal ROM | 5.05 | 4.40 (1.9–11; 87) | 5.61 (3.3–8.8; 111) | 0.025[†] | 4.62 (2.5–8.5; 91) | 4.75 (3.0–9.4; 94) | 0.70[†] |
| Trunk transverse ROM | 4.38 | 7.57 (3.8–11; 173) | 9.61 (4.9–13; 220) | 0.030[*] | 8.86 (4.6–13; 202) | 9.00 (5.0–14; 205) | 0.78[*] |
| Upper limb | | | | | | | |
| Arm ROM, deg | 56.6 | 23.3 (6.6–67; 41) | 49.8 (23–89; 88) | **0.0005**[*] | 26.3 (11–94; 47) | 39.8 (8.0–102; 70) | 0.41[†] |

Figures in parentheses give the range and percentage of healthy control mean values. The Benjamini-Hochberg method was used to correct for multiple comparisons, and the statistically significant *p* values are shown in bold.
deg, degree; GCT, gait cycle time; HC, healthy control.
[*]Paired *t*-test.
[†]Wilcoxon signed-rank test.

## DISCUSSION

We found that STN DBS reduced step-to-step variability in a range of lower limb gait parameters in PD, whereas dopaminergic medication had no significant effect. The lack of effect of medication is at odds with previous literature,[1,3] whereas the results of DBS back the conclusion of an earlier work.[9] Our findings suggest that STN stimulation, but not dopaminergic medication, modulates the circuits that control gait rhythm and, therefore, that control of amplitude and rhythm may be separate. This idea is reinforced by the observation that in the DBS group, there was a reduction in variability of some gait parameters (such as toe-out angle and single-limb support) in the absence of any significant systematic change in the amplitude of these parameters.

The disagreement with previous work about the effect of medication on variability may be accounted for by the way in which variability is being measured. Bryant et al[3] used the CV of four gait parameters across the whole walking assessment. Slowing owing to bradykinesia/fatigue can contribute to variability on this measure. Medication or DBS would both lessen bradykinesia; therefore, either would reduce the overall CV, even if the short-term variability was not altered at all. Participants DBS05, DBS03, and MED04 in Figure 3 are examples with slowing when off treatment, which disappears when on treatment. It is therefore possible that our SD1 is simply measuring a different thing than the CV measure. Interestingly, our data for stride length do show a nonsignificant trend to reduced variability in SD2 (long-term variability), which would fit with a reduction in bradykinesia.

One previous study looking specifically at single-limb support (swing) time variability showed no change in variability with DBS.[24] We found it to be unaffected by medication but clearly reduced by DBS. The explanation may lie in the specific task used in the earlier study, which was stepping in place. This is likely to be qualitatively different in terms of neural control than normal gait with forward movement.

As described in the Introduction, there is evidence to suggest that the degeneration of cholinergic neurons in the PPN occurs in PD[10–12] and underlies gait rhythm disturbance,[13] and this could explain the lack of response to levodopa. We believe that STN DBS improves parkinsonian gait regularity by modulating PPN activity. Evidence from positron emission tomography imaging provides further support for this idea.[34] How might DBS do this? One obvious possibility is the activation of glutamatergic neurons projecting from the STN to the PPN, which then excite cholinergic PPN neurons. However, STN to PPN projections are sparse, accounting for some 1% of the STN neurons.[35] Alternatively, STN DBS might activate glutamatergic STN efferents to the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNpr), which both project to the PPN and could therefore modulate its activity. However, the GPi and SNpr to PPN connections are both inhibitory. STN stimulation also could directly activate the cholinergic neurons by retrograde stimulation of their PPN-STN projections,[35–37] and we believe this is the more likely explanation for our findings.

Cholinergic PPN neurons project very widely, to targets including the substantia nigra,[36,38–43] STN,[35–37] thalamus,[36,43] pallidum,[36,42–44] striatum,[36] superior colliculus,[42,45] cerebral cortex,[36] and spinal cord. Dual labeling and single-neuron tracer studies show that individual cholinergic PPN neurons project to many of these targets through multiple axon collaterals.[42,46]

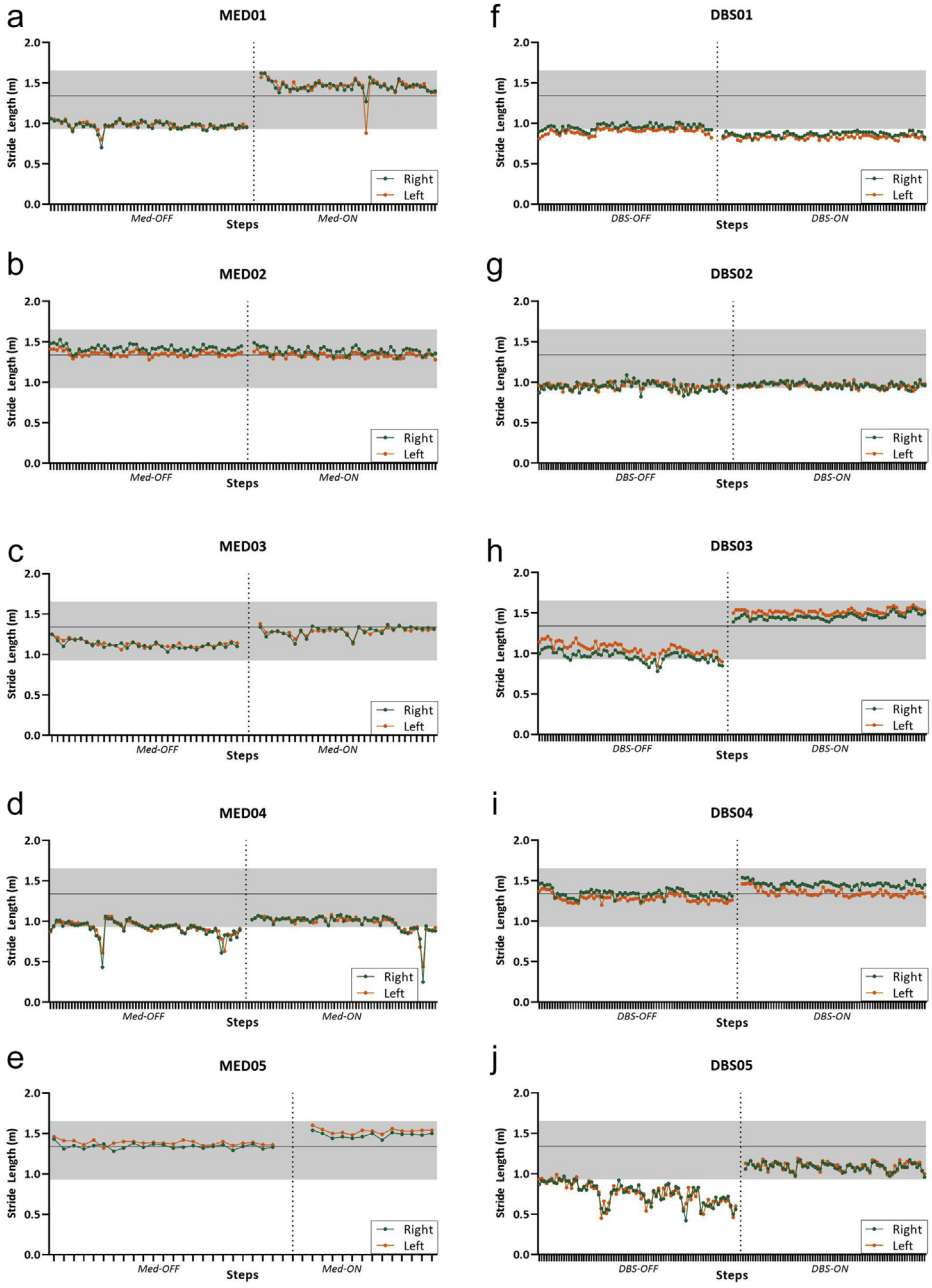


**Figure 2.** Example Poincaré plots of toe-out angle on and off treatment. The top left shows the principles of Poincaré analysis, with the standard deviation perpendicular to (SD1) and along (SD2) the identity line being calculated separately, and representing short- and long-term variability, respectively. The top right graph shows the data from a healthy control (HC) participant. Medication (MED) and DBS group participants are shown in the graphs on the bottom row, on the left and right respectively. OFF, off treatment; ONMED, on medication; ONDBS, on DBS.

Antidromic activation of branches in the STN by DBS will lead to orthodromic activation of all the collaterals, causing a widespread activation of PPN targets as if the signals were coming from the PPN itself. Thus, STN DBS could act to boost cholinergic PPN activity in a wide range of locations, including other parts of the basal ganglia, the midbrain locomotor region (which comprises the PPN itself and the adjacent cuneiform nucleus), and spinal locomotor centers. This is illustrated in Figure 5.

This hypothesis leads to testable predictions. First, we would expect STN DBS to have cholinergic effects on other nuclei to which the PPN also projects. One such location is the superior colliculus (SC),[45] which receives projections from both the SNpc and the PPN. The SC is a critical structure in the generation of saccadic eye movements, which have been studied extensively in patients with PD,[47–50] including patients undergoing DBS.[51–53] In the visually guided prosaccade task, the participants move their eyes as quickly as possible toward a novel visual target. The pro-saccadic latency (PSL), ie, the time between stimulus presentation and the onset of the saccade, is mildly (7%) prolonged by levo-dopa.[47] In contrast, the injection of the cholinergic agonist nicotine into monkey SC reduced the PSL by 40%,[54] whereas the strong central anticholinergic drug promethazine increased it.[55] STN DBS

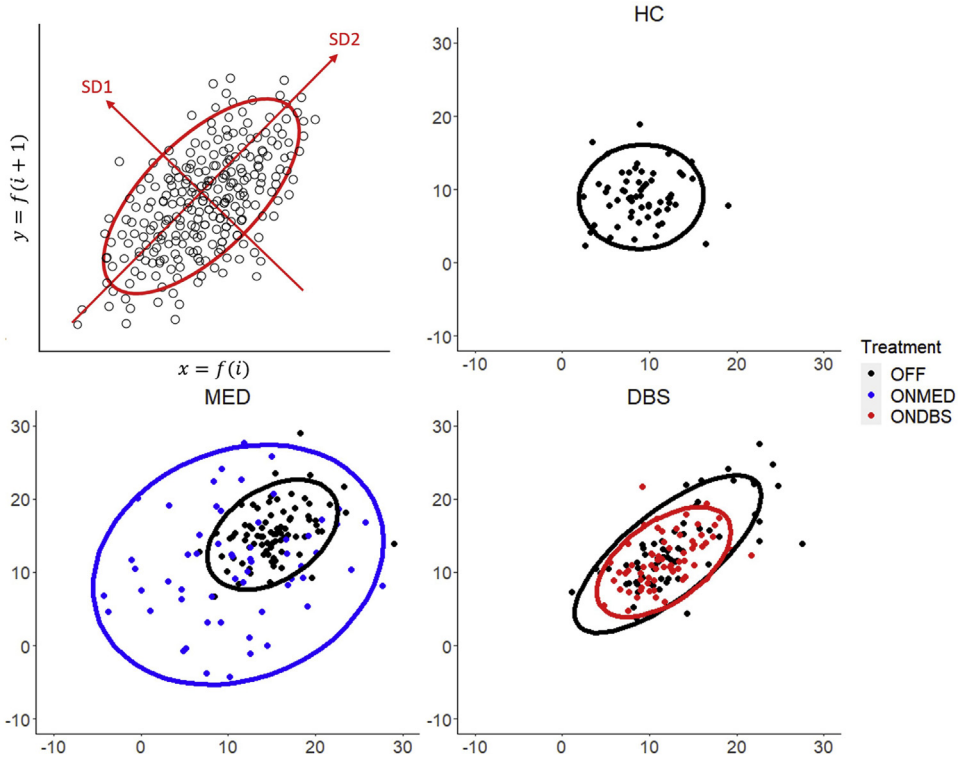


**Figure 3.** Step-by-step analysis of patient stride length under STN DBS vs medication treatment (example individual participant data shown for five medication challenges (panels a-e) and five DBS participants (panels f-j)). Green, right leg; orange, left leg; gray, normative range, calculated as the 95% CI of each parameter from the age-matched control group.

shortens the PSL,[51,52,56,57] in keeping with a cholinergic, but not a dopaminergic, effect. Furthermore, DBS of the GPi, which also receives cholinergic PPN afferents,[44] also shortens the PSL to a similar degree.[52] In the case of the STN, the DBS effect could be mediated by driving the excitatory projection to the SNpr, which itself sends an inhibitory projection to the SC. However, the route from the GPi is less obvious. The retrograde activation of the PPN arborization from either location would provide a unifying explanation for the similar effect on saccades.

Second, activating the same cholinergic PPN arborizations from a different location should have a comparable effect on gait regularity. In keeping with this, DBS of the GPi, which is carried out for similar symptoms to STN DBS, appears to have a similar beneficial effect on gait.[58] To our knowledge, there is no literature examining gait variability for patients undergoing DBS of the GPi in depth, and we intend to investigate this in future work.

Direct stimulation of the PPN itself might be expected to have a more potent effect, and the PPN has been explored by several groups as a target for DBS,[59–66] specifically in the setting of freezing of gait (FoG), which could be viewed as an extreme form of rhythm disturbance. FoG is linked to severe PPN degeneration.[13] PPN DBS, however, will not treat dopaminergic deficits, and the group of patients to whom it is theoretically best suited—those with freezing but little upper body parkinsonism—is small. This has led some to experiment with dual STN/PPN stimulation.[60] Importantly, it should be noted that according to our hypothesis, STN stimulation is exciting a select group of PPN neurons in a specific way, and the effects of DBS directly to the PPN will be qualitatively as well as quantitatively different than the effects of retrograde activation from STN stimulation. Direct stimulation could activate all cell types in the PPN as well as the PPN afferents; there could therefore be effects on multiple other upstream and downstream nuclei that could not be seen with activation from the STN.

### Effects on the Trunk and Upper Limbs

The effects of medication and DBS on the trunk and upper limbs were strikingly different than those seen in the lower limbs. Arm swing ROM was significantly increased by medication, whereas DBS produced a smaller and nonsignificant change. This may be accounted for by the fact that patients undergoing DBS were in the on-medication state, in that much of the possible improvement in arm ROM had already been made by medication. Moreover, lower limb variability was unaffected by medication and reduced by DBS, whereas upper limb and trunk variability was unaffected by DBS but increased by medication.

The extent to which arm swing is passive, with the arm viewed as a mass damper in the form of a pendulum driven by movement at the shoulder,[67–69] or active, produced by muscle activity under control of a central pattern generator,[70,71] has long been debated. It is probably a combination of the two,[72] with passive motion complemented by some added muscle activity, possibly to provide small movement corrections that keep arm swing coordinated with the rest of the body. In PD, arm swing is typically asymmetrically reduced, even in an early phase of the disease, and exhibits an altered phase relationship with lower limb movement. Lower limb bradykinesia in PD may lessen shoulder movement and thus pendulum drive, and increased damping because of parkinsonian rigidity will reduce arm swing amplitude and alter its phase

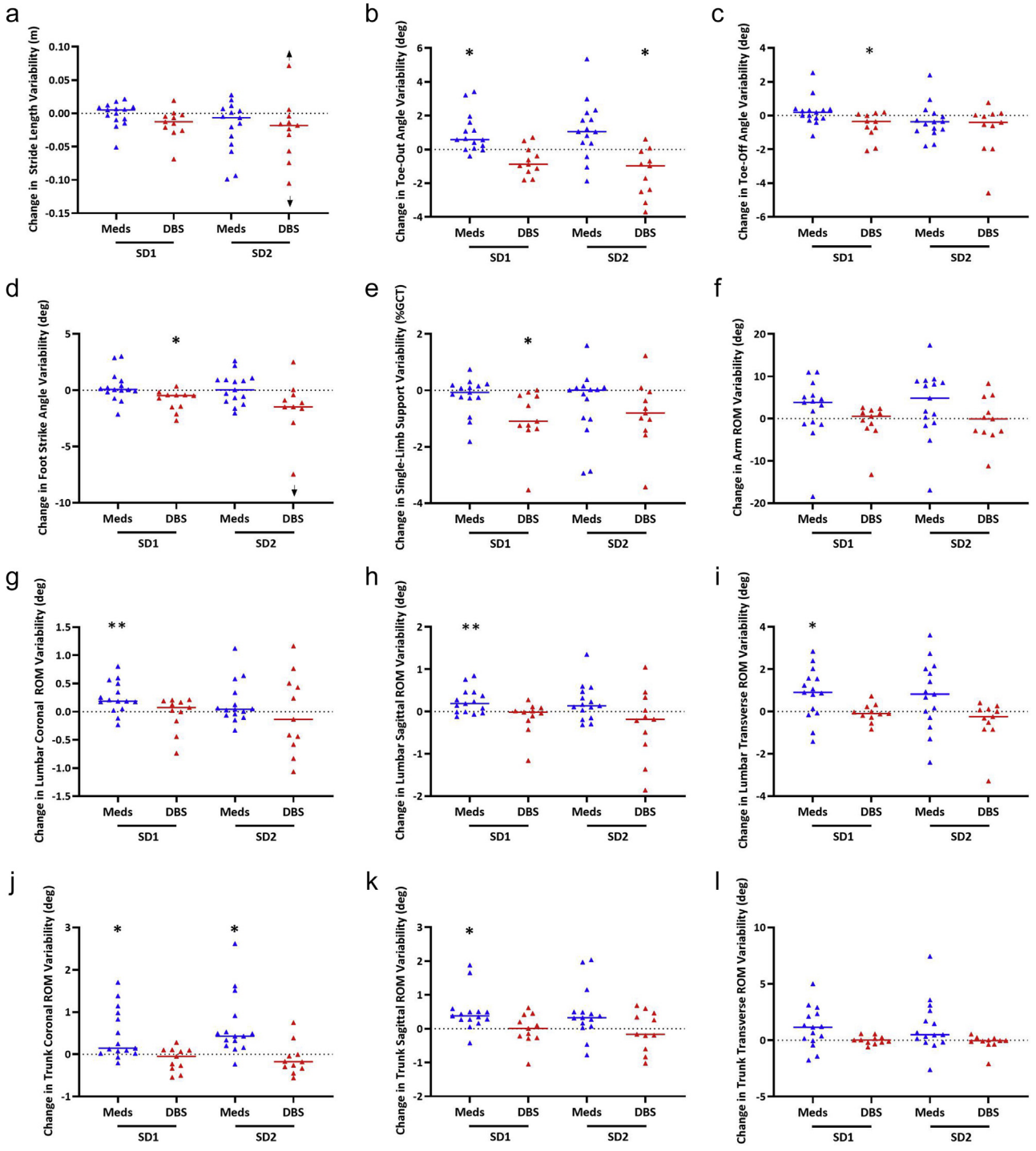


**Figure 4.** Short-term (SD1) and long-term (SD2) variability changes resulting from STN DBS or medication. a. stride length; b. single limb support as a percentage of gait cycle time; c. foot strike angle; d. toe out angle; e. arm range of motion; f-h. trunk range of motion respectively in the coronal, sagittal and transverse planes. Statistical analysis is presented in Table 3. Arrowhead denotes data point out of scale. Meds, medications.

relationship with lower limb movements. The changes in arm swing also might be viewed as evidence for dysfunction in a putative pattern generator for upper limb motion. The fact that medication produces a greater increase in arm ROM than DBS, despite DBS being highly effective in alleviating rigidity, might further suggest that, unlike lower limb gait rhythm, arm swing is under the control of a pattern generator that is dopamine dependent. There is an interesting parallel with swimming in PD, which is affected both by bradykinesia and impaired interlimb coordination: Levodopa appears to improve the former, but not the latter.[73]

The trend to increased arm swing variability we observed with medication seems at odds with this because it would suggest that the

**Table 3.** Changes in SD1 and SD2 Variabilities On and Off Treatment.

| Parameter | Medication group | | | | DBS group | | | |
|---|---|---|---|---|---|---|---|---|
| | SD1 | | SD2 | | SD1 | | SD2 | |
| | Change | *p* Value | Change | *p* Value | Change | *p* Value | Change | *p* Value |
| Lower limb | | | | | | | | |
| Stride length (m) | −0.00127 | 0.423† | −0.0204 | 0.233† | −0.0151 | 0.0487* | −0.0242 | 0.0537† |
| Single-limb support (%GCT) | −0.206 | 0.588† | −0.484 | 0.340† | −0.987 | **0.002**† | −0.818 | 0.042† |
| Foot strike angle (deg) | 0.316 | 0.588† | 0.130 | 0.875* | −0.913 | **0.0029**† | −2.71 | 0.087† |
| Toe-out angle (deg) | 0.966 | **0.0024**† | 1.19 | 0.0171† | −0.696 | 0.0205* | −1.40 | **0.0077*** |
| Axial | | | | | | | | |
| Trunk coronal ROM | 0.467 | **0.0086*** | 0.662 | **0.0004**† | −0.115 | 0.193* | −0.104 | 0.384* |
| Trunk sagittal ROM | 0.494 | **0.0015**† | 0.46 | 0.0256† | −0.0149 | 0.917† | −0.0604 | 0.738† |
| Trunk transverse ROM | 1.12 | 0.0297* | 1.24 | 0.0256† | 0.0167 | 0.879† | −0.190 | 0.376* |
| Upper limb | | | | | | | | |
| Arm ROM (deg) | 2.22 | 0.0681† | 3.49 | 0.0942† | −0.888 | 0.527* | −0.304 | 0.857* |

The Benjamini-Hochberg method was used to correct for multiple comparisons, and the statistically significant *p* values are shown in bold.
deg, degree; GCT, gait cycle time.
*Paired *t*-test.
†Wilcoxon signed-rank test.

function of such a pattern generator was more, rather than less, impaired with the addition of exogenous levodopa. A possible explanation for the increase in variability with medication would be the induction of dyskinesias. Overt dyskinesias were not observed in the patients during testing; nevertheless, we cannot be certain that subtle dyskinesias were not present, and if present, these would likely appear in the sensor data as increased movement variability.

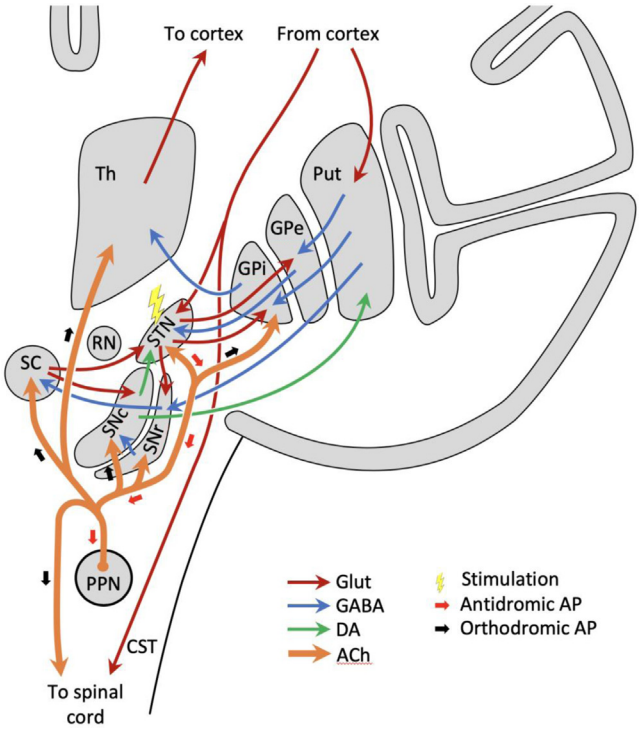


**Figure 5.** The proposed explanation for the effects shown in the study. Stimulation of the STN (lightning bolt symbol) results in antidromic APs in afferent cholinergic fibers from the PPN (small red arrows). When these reach branch points, they generate orthodromic APs in all the other collateral branches (small black arrows), activating multiple other PPN projection targets. ACh, acetyl choline; APs, action potentials; CST, corticospinal tract; DA, dopamine; GABA, γ-aminobutyric acid; Glut, glutamate; GPe, globus pallidus externus; GPi, globus pallidus internus; Put, putamen; RN, red nucleus; SC, superior colliculus; SNc, substantia nigra pars compacts; SNr, substantia nigra pars reticulata; Th, thalamus.

Another interpretation also is possible: The increased range and variability of arm movements with medication is simply the result of a reduction in damping of arm movement together with higher amplitude and more irregular pendulum drive at the shoulder because of higher levels of gait variability and consequently higher range and irregularity of trunk movements. This would produce the concomitant increases in the amplitude and irregularity of arm swing. The absence of a significant change in most of the measures of range and irregularity of arm and trunk movement resulting from DBS may then simply be a consequence of the reduction it produces in lower limb parameter variability.

Measuring gait variability has become much easier in recent years with the proliferation of wearable sensors[74] that are replacing motion detection camera systems, video recording analysis, and force sensitive mats in many gait laboratories. Although previous studies often analyzed only a few measures, modern systems can potentially report on >100 items. This presents significant issues regarding multiple comparisons, particularly with small data sets as is typical of DBS studies. Which of these variables are the most clinically relevant is an important and unexplored question. In this study, we restricted our analysis to a small subset, selected based on prevalence in the literature.

It is noteworthy that many of the MDS-UPDRS Part III items include amplitude, speed, and variability in the same question. We believe that with gait, the segregation of amplitude and rhythm is clear; it is an open question as to whether that also applies to other movements, for example, finger tapping. IMU systems should be able to separate these features out and answer this question.

## Study Limitations

Patients undergoing DBS in this study were on their medication throughout. Some of the effects of DBS on absolute values of gait parameters may have been different in magnitude if testing had been in the medication-off state. For example, the relatively small increase

in arm ROM with DBS may have been because much of the possible improvement had already been made by medication; the lack of a significant increase in arm ROM with DBS may therefore be a false negative finding. In addition, because the DBS on and off conditions were tested sequentially, the effect of medication also may have been slightly different in the two states. The sequence of testing within each group was not randomized, and medication on was tested after medication off, whereas DBS off was tested after DBS on, and it is therefore possible that effects such as fatigue may have played a role. Nevertheless, the changes in variability are clear and differ not just quantitatively but also qualitatively between the groups. We therefore feel that it is unlikely that these are confounded by medication state.

Data from the two sides of the body were combined for analysis here, but PD is characteristically asymmetrical. Although the principal qualitative conclusions of this study are unlikely to be affected by this, it would be of interest in the future to compare quantitatively the effects of treatment on variability on the most affected and least affected sides.

The principal use of Poincaré analysis in medical research has been in the analysis of heart rate variability. Significant heart rate variability is normal, and a lack of variability is pathological. In this study, we are making the opposite assumption, ie, that a reduction in variability is a good thing. Increased gait variability is certainly associated with PD and with falls. We must acknowledge, however, that we do not have direct evidence that the variability is causative of falls and that reducing the variability will by itself reduce falls. Lengthy periods of passive monitoring will be needed to investigate this association, complemented by the use of tools such as the Activities-specific Balance Confidence[75] or Falls Efficacy[76] scales. Only then will we know if the difference in the effect of DBS and medication on gait variability is large enough to be clinically important. The type of system we have used here lends itself well to passive monitoring of falls and gait variability, and it is an issue that will be pursued in future work.

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## Authorship Statements

Chrystalina A. Antoniades and James J. FitzGerald designed the study, analyzed the data, and drafted the paper. Marko Bogdanovic, Nagaraja Sarangmat, Bastiaan R. Bloem, and Tim Buchanan helped with the revised versions of the paper. Salil Patel and Bronwyn Gavine collected the data, analyzed the data, and helped with the revised versions of the paper. Zi H. Su collected the data, analyzed the data, and drafted the paper. All authors approved the final version of the manuscript.

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