Deep-brain stimulation of the subthalamic nucleus improves overriding motor actions in Parkinson’s disease

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Abstract

Findings from previous research using the classic stop-signal task indicate that the subthalamic nucleus (STN) plays an important role in the ability to inhibit motor actions. Here we extend these findings using a stop-change task that requires voluntary action override to stop an ongoing motor response and change to an alternative response. Sixteen patients diagnosed with Parkinson’s disease (PD) and 16 healthy control participants (HC) performed the stop-change task. PD patients completed the task when deep-brain stimulation (DBS) of the STN was turned on and when it was turned off. Behavioral results indicated that going, stopping, and changing latencies were shortened significantly among PD patients during STN DBS, the former two reductions replicating findings from previous DBS studies using the classic stop-signal task. The shortened go latencies observed among PD patients fell within the control range. In contrast, stopping latencies among PD patients, although reduced significantly, continued to be significantly longer than those of the HC. Like go latencies, stop-change latencies were reduced sufficiently among PD patients for them to fall within the control range, a novel finding. In conclusion, STN DBS produced a general, but differential, improvement in the ability of PD patients to override motor actions. Going, stopping, and stop-change latencies were all shortened, but only going and stop-change latencies were normalized.

1. Introduction

The ability to flexibly alter one’s behavior to sudden changes in the environment is a hallmark of voluntary action control [1]. A neural network that includes frontal brain areas and the basal ganglia is considered vital for the selection and inhibition of voluntary actions [2]; for a review, see [3]. Consequently, various neuropsychiatric conditions (e.g., schizophrenia, Attention Deficit Hyperactivity Disorder, obsessive-compulsive disorder) and neurological syndromes related to frontal–basal ganglia dysfunction, such as Huntington’s disease, Tourette’s syndrome, and Parkinson’s disease (PD) have been associated with suboptimal inhibitory action control [4–8]. This study replicates and extends previous work on the ability to stop and change voluntary motor actions in individuals diagnosed with Parkinson’s disease by altering basal ganglia-cortical interactions through electrical stimulation of the subthalamic nucleus (STN). In the following, we present a comprehensive review of relevant literature, including studies on the impact of therapeutic interventions such as dopaminergic medication and deep-brain stimulation (DBS), on inhibition of voluntary motor actions and PD.

1.1. Action inhibition deficit in PD

Studies of inhibitory control in PD have relied on powerful experimental tasks. For example, using the anti-saccade task, Chan et al. [9] and Praamstra and Plat [10] reported that medicated PD patients are...
less proficient than healthy controls at looking away from a peripheral stimulus after it appears, suggesting the presence of an inhibitory deficit in volitional saccade control. Studies also show that STN DBS modulates performance on the anti-saccade task in PD by inducing more errors on anti-saccade trials but also speeding up pro- and anti-saccade reaction latencies [11,12]. One of the most influential tasks used to measure inhibitory action control is the stop-signal task [13]. Typically, participants are instructed to quickly press a response button to go signals, but to try to inhibit their go response upon the unpredictable presentation of an infrequent stop signal [14]. Behavior on the stop-signal task has been conceptualized as the outcome of an independent race between the go process and the stop process [13,15,16]. If the go process finishes before the stop process, then inhibition fails, and an overt response is issued (failed stop trials). On the other hand, if the stop process beats the go process, then inhibition is successful, and the overt response is withheld (successful stop trials). A set of assumptions that underlie the formal race model allows estimation of an individual’s stop-signal latency (or stop-signal reaction time; SSRT) as an index of inhibitory control. Gauggel and colleagues [4] were the first to compare stop-task performance of a group of 32 medicated PD patients to that of 31 age-matched controls. Their results indicated that reaction time (RT) of manual button-press responses to go signals was comparable between the two groups. The PD patients however, showed notably prolonged stopping latencies to auditory stop signals compared to the controls, pointing to a specific deficit in response inhibition.

Mirabella and colleagues [17] studied inhibitory control over arm movements in patients with moderately advanced PD and report no differences either in reactive or proactive inhibition between patients presenting predominantly left-sided symptoms versus those with predominantly right-sided motor symptoms. However, PD patients were significantly more impaired in both forms of inhibitory control than healthy subjects. Recently, Di Caprio et al. [18] replicated this finding with patients in earlier disease stages. Importantly they showed that the reactive stopping deficit associated with earlier stages of the disease was relatively smaller than that occurring in patients in advanced stages. Furthermore, proactive inhibition was not affected in early-stage PD patients.

A recent meta-analysis confirmed that patients diagnosed with PD show a behavioral inhibition deficit when compared to matched controls on go/no-go, Stroop, anti-saccade, and stop-signal paradigms [19]. In general, the inhibition deficit was apparent in patient groups taking their regular dopaminergic medication as well as in clinical samples performing the stop task while off their regular medication. Interestingly, disease duration modulated the effect of dopaminergic replacement therapy on the inhibitory deficit. More specifically, impaired inhibitory control was found in patients with moderate-to-advanced PD (irrespective of medication) and with early-stage PD while off medication. Interestingly, inhibition performance of patients in the early stages of the disease who were taking dopaminergic medication generally approximated the healthy control range.

The studies reviewed above compared action control between patients and healthy controls. Extending these between-group findings, a rigorous test of dopaminergic effects on response inhibition involves a within-subject design, directly comparing stop-task performance of patients when on and off their medication. Obeso and colleagues were the first to directly study the effect of levodopa on going and stopping in PD patients using a so-called conditional stop task [20]. Patients were instructed to make one of two “critical” responses only, but not other “non-critical” responses (e.g., “only stop responses with the index finger, but do not stop responses with the middle finger of the dominant hand”). In their sample of moderate to advanced PD patients, levodopa intake did not speed up go responses and did not ameliorate the stopping deficit [20], see also [21]. The progressive loss of dopamine-producing cells in the midbrain might explain the absence of beneficial effects of dopamine-replacement therapy on stopping control in more advanced stages of the disease [19]. In contrast to the null-findings associated with advanced stages of PD, within-patient comparisons of on vs. off medication conditions confirmed that levodopa intake significantly improved stopping (but not going) in early-stage PD; that is, around three years since diagnosis [22].

Beyond dopamine-replacement therapy, a complementary or alternative treatment for the clinical motor symptoms associated with PD involves electrical stimulation of the STN. This procedure involves the surgical implantation (often bilaterally) of an electrode in the STN that emits high-frequency electrical stimulation, which ameliorates the cardinal PD motor symptoms such as bradykinesia, rigidity, and tremor [23]. Functional neuroimaging studies involving healthy participants linked the STN with stopping control [24-28]. Extending these correlational findings, clinical studies including PD patients who have been treated with DBS provided behavioral evidence that the STN is causally involved in reactive stopping ([29–32]; see also Mirabella et al., 2013, for STN DBS effects on proactive stopping). Patients typically performed the stop task under two stimulation conditions. During STN-DBS, their ability to stop motor actions upon the presentation of a stop signal significantly improved, as indicated by shorter SSRT, compared to the (within-subject) condition during which DBS was turned off. This shows that functional modulation of the STN-region ameliorates the deficit in the ability to inhibit motor actions associated with PD (for a review, see [33]). Notably, the amelioration of stopping latency appears to require bilateral stimulation [34].

1.2. Overriding actions: stopping and changing

The stop task requires inhibiting a motor action to an external stop signal to quantify the latency of the stopping process (SSRT). However, in everyday life, response inhibition rarely occurs in isolation. When changes in the environment require one to change the ongoing course of action, inhibition of the initial unwanted response is just one necessary step that is often followed by the execution of an alternative goal-directed response. The stop-change task [35,36] captures both the stopping and the changing components that are necessary to override ongoing motor actions. The stop-change task, like the stop task, requires participants to (i) quickly press a response button to go signals that constitute the majority of trials (e.g., “press the left button to a green arrow pointing left and press the right button to a green arrow pointing right”). However, on a limited trial set, a stop-change signal suddenly occurs (e.g., the green arrow turns red). Upon a stop-change signal, participants should (ii) inhibit their initial response to the go signal; and (iii) press the alternative response button. Because the stop-change signal occurs shortly after presentation of the go signal, the underlying cognitive processes potentially overlap. Analyzing both behavioral and simulation data, Verbruggen and colleagues (2008) investigated the timing of differential activation of task goals related to going, stopping, and changing on stop-change trials and addressed the question whether these task goals are serially active or in parallel [37]. They concluded that both a non-deterministic serial activation of cognitive processes (i.e., go is replaced by stop, is replaced by change), and a limited-capacity parallel activation of these processes (stop and change occur simultaneously) explained behavior on the stop-change task [38]. Importantly, activating the change response requires inhibiting the initial go response.

In healthy young adults, stopping latencies in the stop-change task are generally longer than in the standard stop task [36,39-42]. In a previous study, we compared stop-change performance of a group of medicated PD patients to that of healthy age-matched controls [43]. The results indicate that RT to the initial go signal is comparable between the two groups, but PD patients exhibited notably prolonged stopping latencies. This is a replication of the pattern characterized by preserved going coupled with impaired stopping in medicated PD patients as reported by Gauggel and colleagues (2004) who used the standard version of the stop task. Application of the stop-change task extended these findings, namely, PD was associated with significant slowing of the
Recent studies have highlighted the importance of both going and stopping in PD patients, suggesting that dopamine facilitation in PD shifts performance control toward slower responding to the benefit of inhibitory control. This apparent trade-off between going and stopping in PD patients indicates difficulties in stopping and changing voluntary motor actions. Sixteen patients diagnosed with PD performed the stop-change task once during STN-DBS (i.e., DBS on) and once while DBS was turned off (i.e., DBS off). The go task consisted of pressing a left or right response button with the left or right index finger to, respectively, left or right pointing green arrows. Unpredictably, on 30% of the trials, the green arrow turned red, indicating that the ongoing go response had to be stopped and changed (e.g., a right button press had to be stopped and a left button press had to be given instead). This constituted, respectively, the stop and change instructions. Our dependent behavioral measures included going, reflecting the ability to both stop and generate an alternative overt action to an external signal. Given that action override contributes to stop-change response, indicating difficulties in flexibly changing to alternative motor actions upon external cues [43].

### 1.3. The present study

Previous research with the standard stop-signal task suggests a causal role of the STN in inhibitory action control. Here, we extend these findings using the stop-change paradigm to delineate the causal involvement of the STN in manual action override that constitutes stopping and changing voluntary motor actions. Sixteen patients diagnosed with PD performed the stop-change task once during STN-DBS (i.e., DBS on) and once while DBS was turned off (i.e., DBS off). The go task consisted of pressing a left or right response button with the left or right index finger to, respectively, left or right pointing green arrows. Unpredictably, on 30% of the trials, the green arrow turned red, indicating that the ongoing go response had to be stopped and changed (e.g., a right button press had to be stopped and a left button press had to be given instead). This constituted, respectively, the stop and change instructions. Our dependent behavioral measures included going, reflecting the latency of initiating an overt change response to the go signal (i.e., go RT). Second, we calculated stopping latency (SSRT) upon presentation of a stop-change signal as index of inhibitory action control. Based on previous DBS studies [29–31], we expected STN-DBS to shorten both go RT and SSRT. The third dependent variable was stop-change RT; the latency between stop-change signal onset and overt change response, reflecting the ability to both stop and generate an alternative overt action to an external signal. Given that action override benefits from shorter stopping latencies (see [43]), we expected STN-DBS to shorten stop-change RT.

### 2. Method

#### 2.1. Participants

This study included 16 PD patients treated with STN DBS (see Table 1 for participant information). Participants with PD were recruited from the Movement Disorders and the Neurosurgery clinics at the University of Virginia and were diagnosed with PD by a neurologist specialized in movement disorders. Sixteen healthy controls (HC) were recruited from community advertisement or as qualifying family members of PD participants. All participants were screened for dementia using the mini-mental status examination (MMSE; [45]). All PD patients self-reported the absence of depressive symptoms during interview, which was corroborated by medical record chart review. Five of the 16 patients were taking anti-depressant medication, and all reported stable and efficacious control of depression. Exclusion criteria for all participants included past diagnosis of bipolar disorder or schizophrenia (based on patient report and corroborated by medical record review), untreated diabetes, history of head injury or comorbid neurological condition, history of stroke or cardiac arrest, or major pulmonary disease as reported by participant and corroborated by medical record review. All participants self-reported right-handedness and normal or corrected-to-normal vision. They all provided informed consent prior to participating in this study that was carried out in accordance with the Declaration of Helsinki and in compliance with standards of ethical conduct in human research as regulated by the University of Virginia human investigation committee. All DBS patients were tested at least three months post-DBS surgery and exhibited an effective and stable response to DBS treatment. At the time of DBS surgery, all patients expressed mild to moderate motor symptoms but ameliorated independently, rating either stage II or III on the Hoehn and Yahr scale [46]. Of the 16 PD patients, 9 showed predominantly right-sided symptoms, 6 had predominantly left-sided symptoms, and 1 patient was classified as having bilateral motor symptoms. Notably, inhibitory control does not appear to differ between PD patients with left-dominant versus right-dominant symptoms [17, 18]. None of the patients presented with impulse control disorder (ICD; exhibiting maladaptive reward-driven behaviors) or freezing of gait (FOG; or sudden arrests in amelioration) symptoms based on medical record review. Testing was completed during the “on” state of the medication cycle. All but one of the PD patients were taking medications to improve dopaminergic function. Seven of the patients were taking a dopamine agonist in addition to a dopamine precursor. Thirteen DBS patients had bilateral STN electrode placements, whereas 3 patients had unilateral left STN electrode placements only (see Table 2 for individual stimulation parameters). The surgical placement of DBS macroelectrodes followed standard procedures described previously [47].

| Table 1 | Participant characteristics. |
|---------|-----------------------------|
|         | PD (n = 16) | HC (n = 16) |
| Age (years) | 61.9 (7.6) | 63.6 (4.9) |
| Gender (male:female) | 11:5 | 11:5 |
| Education (years) | 15.4 (3.1) | 14.4 (3.3) |
| MMSE (raw score) | 29.2 (1.5) | 29.3 (1.2) |
| Disease duration (years) | 13.5 (5.9) | – |
| Time since diagnosis (years) | 11.9 (5.7) | – |
| Time since surgery (months) | 12.1 (6.9) | – |
| Total LEDD (mg) | 631.3 (224.3) | – |

MMSE = Mini-Mental State Examination; LEDD = Levodopa Equivalent Daily Dosage; Standard deviation in parentheses.

| Table 2 | Individual DBS parameters. |
|---------|-----------------------------|
|         | Left STN | Right STN |
| ID | DBS | Amp (V) | Rate (Hz) | PW (µs) | Amp (V) | Rate (Hz) | PW (µs) |
| 1 | Bilateral | 3.1 | 130 | 90 | 1.1 | 130 | 90 |
| 2 | Bilateral | 4.0 | 130 | 60 | 4.0 | 130 | 60 |
| 3 | Bilateral | 4.5 | 160 | 90 | 2.0 | 160 | 90 |
| 4 | Bilateral | 1.8 | 160 | 90 | 3.3 | 160 | 90 |
| 5 | Bilateral | 2.4 | 130 | 60 | 2.8 | 130 | 60 |
| 6 | Bilateral | 1.5 | 130 | 60 | 1.5 | 130 | 60 |
| 7 | Bilateral | 1.5 | 160 | 60 | 4.0 | 160 | 90 |
| 8 | Bilateral | 3.5 | 130 | 60 | 3.0 | 130 | 60 |
| 9 | Bilateral | 3.5 | 130 | 60 | 2.5 | 130 | 60 |
| 10 | Bilateral | 3.8 | 130 | 60 | 3.8 | 130 | 60 |
| 11 | Bilateral | 4.0 | 160 | 90 | 4.5 | 160 | 90 |
| 12 | Bilateral | 3.0 | 130 | 90 | 0.7 | 130 | 90 |
| 13 | Bilateral | 3.3 | 185 | 90 | 3.0 | 185 | 90 |
| 14 | Left | 3.5 | 160 | 60 | – | – | – |
| 15 | Left | 3.5 | 130 | 60 | – | – | – |
| 16 | Left | 3.6 | 160 | 90 | – | – | – |

Mean (sd) = (0.9) (18.2) (15.4) (1.2) (18.9) (15.6)

Amp = Amplitude; PW = Pulse width.
placement were based on direct visualization of the STN on T2-weighted magnetic resonance images. Final electrode position was based on microelectrode recordings and confirmed intraoperatively with macrostimulation after implantation of the DBS electrode. To optimize control over clinically manifest motor symptoms, selection of final bipolar contacts and stimulation settings was determined on an individual basis.

2.2. Tasks and procedures

The stop-change task was presented on a 17-inch digital display monitor (see Fig. 1). The computer screen, placed at a distance of about 90 cm, was positioned such that stimuli appeared at eye level. Stimuli consisted of green and red arrows that were presented centrally against a white background. Each trial began with the presentation of a fixation square (0.8 cm height \times width, subtending a visual angle of 0.46°) in the center of the computer screen. A green arrow (go signal) was presented after a variable duration that was randomly selected from the range 1750–2250 ms in intervals of 50 ms. The arrow stimulus consisted of a rectangular stem (2.1 \times 2.1 cm) attached to a triangular arrowhead (1.5 cm height \times 2 cm base). Arrows were presented pseudo randomly, with the constraint that they signaled left- and right-hand responses equally often within a block of trials. Arrow presentation was response-terminated by a button press with the right or left thumb, registered by comfortable handheld grips or if a time limit of 1,500 ms had passed.

For each trial, a right- or a left-pointing green arrow appeared first. Participants were instructed to quickly and accurately press a response button with the corresponding thumb to the direction of the green arrow (go trials). However, on 30 % of trials, the green arrow turned red (stop-change signal). This stop-change signal instructed participants to stop their initial go response to the direction of the green arrow and to respond with the opposite hand instead (stop-change trials). For example, if a green arrow pointing to the right changed to red, the participant should press the left button with the left thumb. Participants were instructed not to delay their go responses in an effort to increase their override chances.

Two independent staircase-tracking algorithms dynamically adjusted the delay between the onset of the go signal and the onset of the stop-change signal for each hand separately to control inhibition probability [46]. After successful inhibition of the initial go response, the stop-change signal delay on the next stop-change trial increased by 50 ms, making it harder to stop and change on the next stop-change trial. After a failed stop-change trial, the delay decreased by 50 ms making it easier to stop and change. The tracking algorithms ensured that motor actions were successfully stopped and changed on about half of the stop-change trials, which increases the accuracy of SSRT estimation using the integration method ([14,15]; see Fig. 2). This procedure compensates for differences in go RT between participants, between DBS conditions, and between the left and right hands.

The task consisted of five blocks of 104 trials, the first of which served as a practice block to obtain stable performance. Participants completed the stop-change task twice on the same day; once with DBS turned off (DBS off) and once with the device turned on (DBS on). After DBS was turned on or off, patients waited 30 min before starting the task to ensure that tremors had subsided after inducing stimulation and that there was no rebound-exaggerated impairment after terminating stimulation [31,49,50]. The testing order of stimulation conditions was counterbalanced and randomly determined among patients. To measure fine motor control with and without STN DBS, each participant completed two additional tests. The Purdue pegboard test [51] quantified manual dexterity in each hand as the total time to place and remove grooved pegs on a pegboard. The tapping task quantified repetitive fine motor speed in each hand as the average number of index finger taps across three trials of a 10-second tapping interval.

2.3. Data analyses

SSRT was calculated individually for each stimulation condition and for each hand separately using the integration method ([1,13], see Fig. 2). For the reported analyses, data were collapsed across hands because none of the critical dependent RT patterns differed significantly between left and right hands (all \( p \)-values > 0.10). Data patterns were also comparable for patients with predominantly left-sided symptoms and predominantly right-side motor symptoms (see also [17,18]). Data obtained from unilateral and bilateral STN DBS patients were combined in the analyses because data patterns were similar after excluding the three unilateral DBS patients (see [31], for a similar strategy and discussion).

First, we used paired t-tests to compare the effects of STN stimulation (DBS on vs. DBS off) on go RT, SSRT, stop-change RT, and on square root error percentages within the PD group. Next, we used repeated measures analyses of variance (ANOVAs) and t-tests as appropriate to compare the key dependent measures across PD patients on DBS with HC. One-sided \( p \)-values were reported for testing specific hypothesis. We did not apply Bonferroni correction for performing t-tests on different dependent variables. A final set of Pearson correlation analyses tested the relationship between go RT, SSRT, and stop-change RT (since performing multiple correlation tests increases the probability of type I errors, alpha was lowered from 0.05 to 0.01).

3. Results

3.1. DBS on versus DBS off

Analyses of pegboard and finger tapping performance confirmed the expectation that STN stimulation improved fine motor dexterity (time to complete pegboard test: DBS on = 30, DBS off = 37 s, \( t(15) = 2.08, p = 0.03 \), one-sided; number of finger taps: DBS on = 41, DBS off = 37, \( t(15) = 2.52, p = 0.01 \), one-sided).

![Fig. 1. Stop-Change Task.](image-url) Participants press the left or right button indicated by the green arrow (go trials). On 30 % of the trials, the green arrow turned red (stop-change trials) upon which participants should inhibit the go response and execute the alternative response. Upon presentation of the stop-change signal in this example, participants should inhibit their left-hand response and execute a right-hand response instead.
As predicted, responses to go signals (see Fig. 3) were faster when DBS was turned on compared to when DBS was off (DBS on = 594, DBS off = 681 ms, \(t(15) = 3.68, p = 0.001\), one-sided). The simulation-induced speeding of responses was accompanied by an increase in choice errors (DBS on = 14%, DBS off = 11%, \(t(15) = 3.7, p = 0.002\)) and a reduction in response omissions on go trials (DBS on = 3%, DBS off = 5%, \(t(15) = 2.9, p = 0.01\)).

3.1.2. Stopping
The tracking algorithm worked well. Patients were able to stop and change their initial go response on about half of the stop-change trials in both stimulation conditions (DBS on = 53%, DBS off = 56%, \(t(15) = 1.73, p = 0.11\)). Mean stop-change signal delay did not differ significantly between stimulation conditions (DBS on = 275, DBS off = 297 ms, \(t(15) = 0.75, p = 0.47\)). In line with the predictions of the race model, RT on failed change trials (i.e., responses that escaped inhibition) were shorter than overall mean go RT (respectively 597 vs. 638 ms; Trial Type: \(F(1, 15) = 6.04, p = 0.03\)). The magnitude of this difference was comparable for the two conditions (Trial Type x DBS: \(F(1, 15) = 3.9, p = 0.07\)). As predicted, SSRT (see Fig. 4) was significantly shorter during stimulation as compared to when stimulation was turned off (DBS on = 271, DBS off = 324 ms, \(t(15) = 2.08, p = 0.03\), one-sided).

3.1.3. Changing
Deep-brain stimulation improved stop-change RT (see Fig. 5) by about 60 ms (DBS on = 592, DBS off = 652 ms, \(t(15) = 1.96, p = 0.03\), one-sided).

3.2. DBS on versus HC
The clinical group and the HC group were comparable in terms of age, education, MMSE score, and gender distribution (\(t\)-values < 1, see Table 1).

3.2.1. Going
Table 3 shows that PD patients on DBS were as fast to respond to go
signals as the HC group (DBS on = 594, HC = 597 ms; Group: t(30) = 0.52, p = 0.96). Compared to controls, the clinical group committed more choice errors and omission errors on go trials (choice errors: DBS on = 14 %, HC = 2 %; Group: t(30) = 4.1, p = 0.0003; omission errors: DBS on = 3 %, HC = 0.5 %; Group: t(30) = 3.03, p = 0.005).

3.2.2. Stopping

The tracking algorithm timed the onset of the stop-change signal such that both groups were able to stop and change their responses on about half of the trials (DBS on = 53 %, HC = 54 %; Group: t(30) = 0.50, p = 0.62). Stop-change signal delay values did not differ significantly between groups (DBS on = 275, HC = 341 ms; Group: t(30) = 1.34, p = 0.19). In line with the predictions and assumptions of the race model, RT on stop-change trials that escaped inhibition was shorter than mean RT on go trials (respectively 541 vs. 596 ms; Trial Type: F(1, 31) = 24.50, p = 0.00003). Both groups showed this pattern, although the RT difference was larger among HC than for PD (Trial Type x Group: F(1, 30) = 6.85, p = 0.01). SSRT was significantly prolonged among PD with DBS on compared to the HC group (DBS on = 271, HC = 213 ms; Group: t(30) = 2.11, p = 0.02, one-sided) and DBS off compared to HC (DBS off = 324, HC = 213; Group: t(30) = 2.75, p = 0.007, one-sided).

3.2.3. Changing

Stop-change latencies were comparable for PD with DBS on and HC (respectively 592 vs. 590 ms; Group: t(30) = 0.03, p = 0.98).

3.3. Correlations between going, stopping, and changing

Off DBS, there was a positive correlation between SSRT and stop-change RT, indicating that patients with relatively shorter stopping latencies were also faster to execute the stop-change response (r = 0.65, p = 0.006). With DBS turned on, stopping and stop-change RT no longer correlated significantly. On DBS, go RT, and stop-change RT correlated positively; patients responding relatively fast to go signals were also faster to issue the stop-change response (r = 0.68, p = 0.004). Looking at DBS-related changes in SSRT and stop-change RT, those patients whose SSRT greatly improved with stimulation also showed the largest benefits of stimulation on stop-change RT (r = 0.64, p = 0.008). In HC, the critical dependent variables did not correlate significantly.

4. Discussion

We used the stop-change task to study the effects of DBS of the STN on the ability to override motor actions. This task required participants diagnosed with PD to stop an ongoing action and to execute an alternative response instead. To delineate the causal involvement of the STN in manual action override, PD patients performed the stop-change task twice - once while DBS was turned on and once when DBS was off.

The present findings confirmed the prediction that STN DBS improves going, defined as the ability to initiate and execute motor actions in response to an external cue. Stimulation improved going to such an extent that go latencies were very close to HC values. In addition, we confirmed that stimulation significantly improved fine motor control as measured by performance improvements on the pegboard and finger tapping tests (see also [52]). While this DBS effect on response speed is in line with the well-documented therapeutic effects of STN DBS on clinical motor systems associated with PD [23], it does conflict with a few studies reporting no beneficial effects of STN DBS on go reaction latencies and error rates in inhibition tasks. Swann et al. [30] reported numerically faster go RT on STN DBS, but the difference was not statistically significant. In fact, PD patients’ go RT off and on DBS did not differ from controls. Notably, their go task was a spatial correspondence task. Similarly, patients in the study by Mirabella et al. [29] were instructed to make a simple spatially corresponding movement to a stimulus location. Perhaps the strong linkage between spatial mapping of stimulus presentation and responses across the two studies aided PD patients to go RT.

Differently, in the current study, the speeding up of going induced by STN DBS was accompanied by reduced response accuracy compared to the DBS off condition. The shift in the balance towards speed at the expense of accuracy might be explained in terms of the DBS-related modulation of basal ganglia functioning, resulting in lower response thresholds [32,53]. This tradeoff between speed and accuracy is in line with previous DBS findings in PD and may help to explain some of the discrepant results [31,32,54-56]. We have argued previously that PD patients show specific tradeoffs between going and stopping that are influenced by dopaminergic treatments [44]. Our understanding of why sometimes PD patients are slower or no different than controls in terms of DBS effects on go speed is incomplete. It is interesting that in the current task there was a clear two-choice discrimination that did not benefit from spatial correspondence, albeit this is speculative.

The inhibitory deficit associated with PD was confirmed by showing that PD without DBS present longer stopping latencies compared to a matched HC group (see also [4,19,43]). As predicted, STN DBS significantly reduced the inhibitory deficit. The observation that stimulation shortened stopping latencies by about 44 ms replicates previous DBS studies that employed the standard stop task [29-31]. Although stimulation significantly improved response inhibition, stopping latencies for PD with DBS on were still significantly longer than HC stopping values. Thus far, the clinical literature on treatment effects, including dopaminergic medication and DBS, has captured the inhibition component per se. However, action override to sudden changes in the environment not only requires inhibition of the ongoing response but also the execution of an alternative goal-directed action. The added value of the current stop-change study is the extension of the standard stop paradigm with the instruction to execute an alternative response. In addition to the observed amelioration of the inhibition deficit, stimulation of the STN also shortened stop-change response latencies. The stimulation-related improvement was such that stop-change response latencies were very similar to HC. These findings are novel and point to the causal involvement of the STN in the ability to override motor actions as signaled by an external cue. Taken together, STN DBS significantly improved stopping and therefore ameliorated the ability to override actions flexibly.

STN DBS significantly improved the selection and generation of motor actions (i.e. going) but at the same time, the speeded responses were more prone to choice errors. This speeding up at the expense of accuracy also has clinical implications, since behavior of DBS patients in everyday life has been labeled as impulsive [57,58]. Previous investigations using the go/no-go paradigm pointed to increased motor impulsivity with stimulation, which was accompanied by an increase in the number of commission errors on no-go trials [54,59,60], especially when responses were prepotent because of a relatively low frequency of no-go trials [61]. The go/no-go paradigm captures the stimulation-related shift in balance between speed and accuracy (i.e., the tradeoff, see also [55]). In the present study, the trade-off between speed and accuracy in going was accompanied by a DBS-related attenuation of the inhibitory deficit. This, together with improved stop-change latencies, provides clear support for the hypothesis that
STN DBS improves action control over behavior. Previous work with the Simon conflict paradigm also supported the notion that STN DBS induces impulsive, premature responding in conflict situations (i.e., a shift in speed-accuracy tradeoff), but at the same time improves the proficiency with which inhibitory control was engaged to suppress these action impulses [32]. The dissociation between these two factors helps resolving past paradoxical findings related to the effects of STN-DBS on behavior. We recently reported that dopaminergic medication also contributes to shifts in tradeoffs between going and stopping latencies [44]. Collectively, these patterns support the view that changes in executive motor control caused by PD and modulated by dopamine and DBS involve complex dynamics and tradeoffs in going and inhibitory processes. A challenge of future research is developing better models of these dynamics and tradeoffs.

A related challenge for future investigations is further specification of the neural mechanisms underlying these dynamic processes and tradeoffs. Roles for frontal-basal ganglia circuitries in both going and stopping control are fundamental to leading theoretical frameworks [62, 63]. Neuroimaging studies of healthy participants performing the stop task have suggested these ideas by showing the involvement of a functional network of cortical brain areas, such as the right inferior frontal gyrus (rIFG) and the pre-supplementary motor area (preSMA), as well as subcortical structures that include the basal ganglia and more specifically the STN [25, 26, 28]. These structures have also been implicated in neural models that adjust speed-accuracy thresholds and tradeoffs [53, 55]. Thus, the STN appears to be a key node in circuits that regulate inhibitory control and adjustments in inhibition to adapt reaction speed thresholds. One of the important questions for future research is whether unique circuitries within STN contribute to distinct forms of control. Initial studies are suggestive that more dorsal STN circuitries may be critical for selective suppression of specific motor reactions [56], whereas more central/ventral circuitries may be involved in broader forms of inhibition related to global stopping or global setting of inhibition thresholds to adjust speed-accuracy tradeoffs [60, 64-66]. The emergence of these kinds of dissociations would help explain variability in executive motor control in individual patient outcomes and potentially guide electrode placement decisions to optimize executive control and avoid DBS-induced deficits in control (see also [67]).

It is important to acknowledge some limitations and extant issues associated with the current study results. First, it should be acknowledged that controls performed the task only once whereas patients completed the task twice. While we counterbalanced DBS conditions to preclude session or learning effects, we did not test session effects formally by having controls test twice. Second, given the relatively small sample size, we did not fully account for several patient factors that may have affected the magnitude of the inhibition deficit associated with PD. For example, a subgroup of patients showing FOG generally experience more difficulties on tasks that draw upon inhibitory control compared to patients without FOG [68-70]. Also, PD patients exhibiting ICD appear to show shorter stopping latencies compared to PD patients without ICD [71]. There is clear need for future studies of DBS effects on inhibitory motor control to investigate how stimulation impacts these vulnerable subgroups and might alter control in clinical phenotypes of PD in dissociable ways.

Third, we included a subsample of 3 patients treated with unilateral DBS of the left STN. Using a clinical sample consisting only of patients with bilateral DBS would have ruled out any differential effects of unilateral stimulation on inhibitory control. Compared to right STN DBS, there is evidence that selective stimulation of the left STN impairs performance on the Wisconsin Card Sorting Test [72], and worsens speech and language [73]. Of particular relevance with respect to the present results is the study by Mancini et al. [34] showing that unilateral (i.e. either left or right-sided) stimulation in advanced PD did not affect stopping latencies in a comparable inhibitory control task.

We were unable to fully obtain active electrode positions on our patients, a factor that could have important implications on performance [60, 64, 65]. As already discussed, van Wouwe et al. [56] investigated action control using a Simon conflict task by directly comparing DBS of dorsal with ventral subregions of the STN. Interestingly, they found that selective stimulation of dorsal, as opposed to ventral, STN circuitries crucially modulated selective suppression of a specific motor impulse.

While active electrodes are generally situated more dorsally in the STN, clinical stimulation settings generally produce relatively large stimulation areas that encompass tissue activation throughout the STN and neighboring structures. The broad range of clinical STN-DBS frequency settings between participants in the present dataset has differential effects on gait, balance, speed [74], and possibly on cognition. Therefore, van Wouwe and colleagues [56] used preset stimulation parameters that were scaled down from clinical settings and were similar for all participants. This restricted the estimated activation field of neural tissue. In contrast, the present investigation, like the vast majority of DBS studies investigating inhibitory control, employed clinically relevant stimulation parameters that yield the patient’s best outcome in terms of the amelioration of clinical motor symptoms. Thus, future investigations of DBS effects on action control will be informed by designs that restrict stimulation parameters to stimulate STN subregions more selectively (see also [66]).

A final limitation is that PD patients in the current study performed both testing sessions while taking their prescribed dopaminergic medications. Thus, while a benefit is that we tested patients in a similar medication state across the testing sessions, we are unable to fully account for interactions between DBS and dopaminergic medications. We recently reported that dopamine medication modulates going and stopping latencies in the stop-change task, proposing that dopamine impacts tradeoffs between these forms of response control [44]. There is certainly need for future investigation involving systematic study of DBS and dopamine interactions on tradeoffs between going and stopping. It is worth pointing out that the current findings on stopping control replicate prior studies testing patients on their dopamine medications, which further argues that the DBS effect on stopping control contributes beyond any benefit afforded by dopamine medication. For example, Fluchère and colleagues [75] used a full factorial design to study the effects of both STN-DBS (on vs. off) and dopaminergic medication (on vs. off) on response impulsivity in the Simon conflict task. They report a higher incidence of subthreshold EMG errors with STN stimulation. This increased impulse expression on the muscular level was attributed to a stimulation-related lowering of the response threshold. By contrast, dopaminergic medication did not affect the incidence of partial EMG errors, but negatively affected the ability to keep EMG errors in check. As such, dopaminergic medication impaired the ability to prevent overt response errors [75].

In sum, STN DBS improved the ability to initiate manual actions as well as the ability to override these actions by shortening both stopping and overall stop-change latencies. Only going and stop-change latencies were in the healthy control range under stimulation. These findings support the notion that dynamic aspects of action and inhibitory control underlying goal-directed behavior rely in part on neural circuitry that includes the STN. The improved ability to override one’s behavior might be an important factor that drives the therapeutic effects of STN DBS that are manifest in everyday life.

Declaration of Competing Interest
None.

CRediT authorship contribution statement
W. P. M. van den Wildenberg: Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. Nelleke C. van Wouwe: Conceptualization, Validation, Investigation, Writing - original draft,
Writing - review & editing, Project administration. K. Richard Ridderinkhof: Conceptualization, Writing - original draft, Writing - review & editing. Joseph S. Neimat: Resources, Writing - original draft, Writing - review & editing. W. Jeffrey Elias: Resources, Writing - original draft, Writing - review & editing. Theodore R. Bashore: Conceptualization, Writing - original draft, Writing - review & editing. Scott A. Wylie: Conceptualization, Methodology, Data curation, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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