

Current Biology

A causal role for the human subthalamic nucleus in non-selective cortico-motor inhibition

Highlights

- During rapid action stopping, CSE is broadly suppressed
- This is ostensibly due to the non-selective influence of the STN
- We measured CSE via TMS while influencing STN via DBS
- DBS removed the non-selective effect of stopping on CSE, causally linking STN and CSE

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In brief

Wessel et al. causally link the human subthalamic nucleus (STN) to non-selective motor inhibition. Combining transcranial magnetic stimulation and deep-brain stimulation (DBS), they show that the broad effects of rapid action stopping on cortico-spinal excitability (which are present OFF-DBS and in healthy controls) are absent when STN is disrupted via DBS.

Report

A causal role for the human subthalamic nucleus in non-selective cortico-motor inhibition

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<https://doi.org/10.1016/j.cub.2022.06.067>

SUMMARY

Common cortico-basal ganglia models of motor control suggest a key role for the subthalamic nucleus (STN) in motor inhibition.^{1–3} In particular, when already-initiated actions have to be suddenly stopped, the STN is purportedly recruited via a hyperdirect pathway to net inhibit the cortico-motor system in a broad, non-selective fashion.⁴ Indeed, the suppression of cortico-spinal excitability (CSE) during rapid action stopping extends beyond the stopped muscle and affects even task-irrelevant motor representations.^{5,6} Although such non-selective CSE suppression has long been attributed to the broad inhibitory influence of STN on the motor system, causal evidence for this association is hitherto lacking. Here, 20 Parkinson's disease patients treated with STN deep-brain stimulation (DBS) and 20 matched healthy controls performed a verbal stop-signal task while CSE was measured from a task-unrelated hand muscle. DBS allowed a causal manipulation of STN, while CSE was measured using transcranial magnetic stimulation (TMS) over primary motor cortex and concurrent electromyography. In patients OFF-DBS and controls, the CSE of the hand was non-selectively suppressed when the verbal response was successfully stopped. Crucially, this effect disappeared when STN was disrupted via DBS in the patient group. Using this unique combination of DBS and TMS during human behavior, the current study provides first causal evidence that STN is likely involved in non-selectively suppressing the physiological excitability of the cortico-motor system during action stopping. This confirms a core prediction of long-held cortico-basal ganglia circuit models of movement. The absence of cortico-motor inhibition during STN-DBS may also provide potential insights into the common side effects of STN-DBS, such as increased impulsivity.^{7–11}

RESULTS

Twenty patients with idiopathic Parkinson's disease (PD) treated via chronic bilateral subthalamic nucleus (STN) deep-brain stimulation (DBS) implantation participated in the study (cf. Table 1 for sample details and STAR Methods for inclusion and exclusion criteria). Patients completed two research sessions spaced 6–8 days apart (except in N = 2, where the spacing was 14 days). One session was performed ON-DBS and one with the stimulator in the OFF state, in a pseudo-randomized order. Patients performed both sessions on their typical dopaminergic medication. Furthermore, twenty elderly healthy control participants performed a single session of the experiment for comparison. Patients and controls were well matched with respect to age (mean 66.2 versus 65.4 years, range: 43–77 versus 47–79), gender (19 male versus 16 male), and handedness (18 right-handed versus 19 right-handed). In all sessions, participants performed a verbal version of the stop-signal task¹² with an adaptively tracked stop-signal delay (a protocol overview for

each session can be found in Figure 1). The stop-signal task was used to invoke inhibitory control processes and produce the expected typical pattern of non-selective suppression of cortico-spinal excitability (CSE) during action stopping.¹² This non-selective suppression was to be compared between patients and controls, and—crucially—within patients ON- versus OFF-DBS.

DBS was delivered at the typical clinical settings for each patient. This was done to maximize the causal effect across the experiment and to mimic realistic treatment conditions that provide a straightforward positive control (i.e., the clinical effect of DBS on Parkinsonian motor symptoms). Indeed, DBS was effective in eliciting a positive therapeutic effect between sessions (mean unified PD rating scale scores, motor subscale: 25 ON stimulation, range 10–48 versus 33 OFF stimulation, range 18–57, $t(19) = 4.38$, $p = 0.0003$, $d = 0.78$).

Behavioral results in the stop-signal task conformed to the expected patterns (cf. Table 2). Specifically, GO-RT was slower than failed STOP-RT in all sessions, and the probability of

Table 1. Patient sample characteristics

1st	Since Op (months)	Age (years)	Delay (days)	UPDRS score	
				OFF	ON
OFF	20	63	7	35	19
ON	15	42	7	57	35
ON	19	67	7	32	23
OFF	46	71	8	40	47
ON	49	73	7	40	48
OFF	100	60	14	41	22
OFF	71	70	7	28	14
OFF	36	57	8	22	18
OFF	48	65	8	31	30
OFF	43	68	7	18	16
ON	17	53	7	47	40
OFF	27	65	7	42	21
OFF	21	59	7	25	10
ON	40	55	7	33	19
ON	26	60	7	25	24
OFF	6	70	6	28	16
OFF	11	63	7	22	17
OFF	28	75	7	29	25
OFF	6	69	7	47	41
ON	13	65	14	21	13

1st, first session DBS settings; since Op, months between DBS implantation surgery and first session date; age, age at time of implantation in years; delay, delay between first and second session in days; UPDRS, unified Parkinson's disease rating scale motor subscale scores OFF- and ON-DBS while ON usual PD medications.

successful stopping converged around 0.5 (reflecting the success of the stop-signal delay tracking algorithm). GO-RT was slower in patients compared with controls, both ON-DBS ($t(19) = 3.71$, $p = .002$, $d = 0.93$) and OFF-DBS ($t(19) = 4.2$, $p < 0.0001$, $d = 1.39$). Furthermore, GO-RT was significantly faster ON-DBS compared with OFF-DBS ($t(19) = 2.17$, $p = 0.043$, $d = 0.48$). Similarly, failed STOP-RT was slower in patients compared with controls, both ON-DBS ($t(19) = 3.28$, $p = 0.004$, $d = 0.82$) and OFF-DBS ($t(19) = 4.36$, $p = 0.0003$, $d = 1.45$), although there was no significant difference between DBS sessions ($t(19) = 2.07$, $p = 0.053$, $d = 0.5$). Finally, stop-signal reaction time (SSRT, measured using the integration method) was slower in DBS patients compared with healthy comparisons, both ON-DBS ($t(19) = 2.96$, $p = 0.008$, $d = 0.99$) and OFF-DBS ($t(19) = 2.37$, $p = 0.03$, $d = 0.76$). There was no difference between patient sessions ($t(19) = 0.23$, $p = 0.82$, $d = 0.05$). Neither STOP nor GO trial accuracy showed any group differences.

Of primary interest to the current study, prior work in healthy adults¹³ and in PD patients OFF-DBS¹² has shown that the successful stopping of verbal responses leads to a suppression of CSE at a task-unrelated hand muscle (a pattern that has also been shown for other effector/muscle combinations^{5,6}). In accordance with these studies, we measured CSE from the first dorsal interosseus (FDI) muscle of the hand during STOP and GO trials across both sessions. The hand was resting on the table

and not involved in the task. In the DBS-OFF session and in healthy controls, we hypothesized to find CSE suppression of FDI when the verbal response was successfully stopped. Indeed, OFF-DBS, a repeated-measures ANOVA showed a significant main effect of trial type ($F(1/18) = 6.5$, $p = 0.02$, $\eta^2 = 0.015$) as well as a significant main effect of timing ($F(5/90) = 3.03$, $p = 0.014$, $\eta^2 = 0.084$), with no interaction ($F(5/90) = 1.79$, $p = 0.12$, $\eta^2 = 0.009$). False discovery rate-corrected follow-up t tests at $p = 0.05$ revealed significant STOP versus GO trial differences at 170, 200, 230, and 260 ms after the stop signal (Figure 2, left panel; cf. Table S2 for CSE values). The same pattern was found for healthy controls, which again showed a significant main effect of trial type ($F(1/19) = 27.8$, $p < 0.001$, $\eta^2 = 0.022$) and a significant main effect of timing ($F(5/95) = 3.16$, $p = 0.011$, $\eta^2 = 0.015$) as well as a significant interaction ($F(5/95) = 2.62$, $p = 0.029$, $\eta^2 = 0.01$), with individual comparisons ($p = 0.05$, FDR-corrected) revealing significance STOP versus GO differences at the same time points as the OFF-DBS group (Figure 2, right panel).

Crucially, we hypothesized that disruption of the STN via DBS would abolish the CSE suppression effect in patients ON-DBS. Indeed, this was the case (Figure 2, middle panel). No significant effects of trial type ($F(1/18) = 2.00$, $p = 0.17$, $\eta^2 = 0.005$) or timing ($F(5/90) = 0.75$, $p = 0.59$, $\eta^2 = 0.005$) or any significant interaction ($F(5/90) = 0.88$, $p = 0.5$, $\eta^2 = 0.007$) were found in the ON-DBS session. Follow-up t tests revealed that there were no significant differences between STOP and GO trials at any time point in the ON-DBS condition. Moreover, direct comparisons between the STOP trials of patients ON-DBS and OFF-DBS revealed significantly lower CSE in the OFF compared with the ON condition at the 230 ms time point ($t(18) = 1.78$, $p = 0.047$, $d = 0.49$), as well as a marginally significant difference at the 200 ms time point ($t(18) = 1.53$, $p = 0.071$, $d = 0.35$).

An unexpected outcome was that unlike in either patient session, healthy controls' CSE values appeared to be below the baseline throughout the trials for both STOP and GO trials (although this was only significant for GO trials at the 230 ms time point). Although this could indicate that healthy individuals more dynamically adjust the excitability of their cortico-motor system between baseline periods and task-relevant periods, this pattern would need independent replication to confirm its reliability (especially since the same pattern was not observed in another published study of non-selective CSE suppression during vocal stopping in healthy participants¹³).

DISCUSSION

The STN is a key basal ganglia region involved in the inhibitory control of movement.¹ According to dominant models of motor control, the STN is part of two cortico-basal ganglia-thalamo-cortical loops, which implement different types of motor inhibition—the selective, specific, and comparatively slow indirect pathway, and the non-selective, broad, and comparatively fast hyperdirect pathway.^{2,3} In line with the purported role of these cortico-subcortical circuits in motor inhibition, movement disorders like PD are characterized by abnormal neural signaling along these pathways.^{14,15} Accordingly, PD and other movement disorders are often successfully treated using

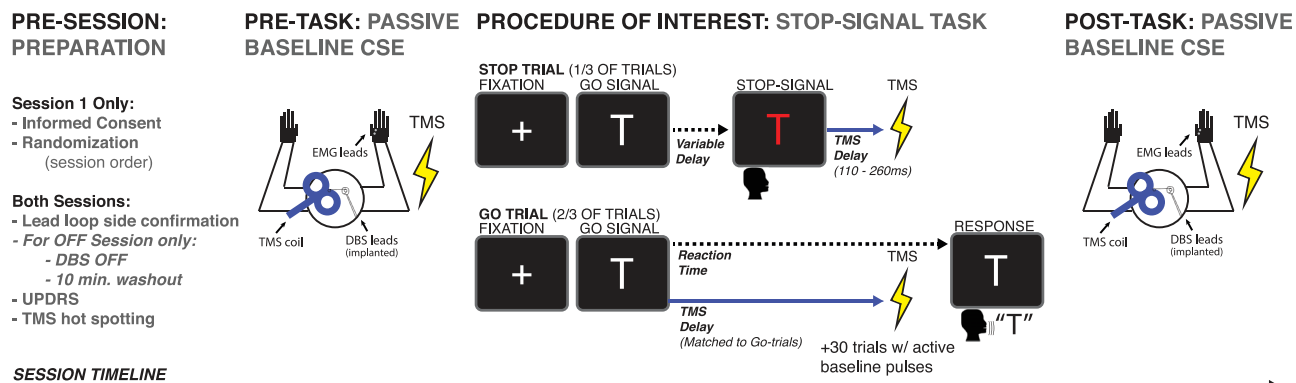


Figure 1. Timeline of an example patient session

All patients took part in two sessions on separate days, one performing all stages with their DBS stimulator ON and another in the OFF setting. Healthy controls took part in a single session only.

DBS targeting the subcortical nodes of these circuits—in the case of PD, most commonly the STN.^{16,17}

Functionally, a long-standing proposal regarding the role of the STN in motor inhibition is that it broadly and non-selectively net-inhibits motor representations in the primary motor cortex (M1^{2,3,18}), especially when recruited via the hyperdirect pathway.^{19,20} Indeed, a hyperdirect connection between the (pre)frontal cortical regions that are activated by stop-signals and the STN has recently been demonstrated.²⁰ The purportedly non-selective physiological effects of this hyperdirect inhibitory pathway from STN onward can be observed via changes to CSE in different cortico-motor tracts, which can be measured using transcranial magnetic stimulation (TMS)-elicited motor-evoked potentials. This technique has been used extensively in human work on motor inhibition (see Duque et al.²¹ for a review). Notably, CSE is reduced even in task-unrelated motor effectors when a specific action is rapidly stopped.⁵ For example, stopping an action performed with the feet, or even the stopping of a verbal response, is accompanied by suppression of CSE of task-unrelated hand muscles.^{6,13} This was also found in the OFF-DBS session in our current study (Figure 2, left panel), as well as in healthy, age-matched controls (Figure 2, right panel). Such non-selective CSE suppression is in line with the neuroanatomical proposal that individual STN neurons broadly project to neurons in the output nuclei of the basal ganglia,^{2,3} thus causing broad suppression of the motor system during situations in which inhibitory control is rapidly implemented. Although the non-selective suppression of CSE during action stopping has long been purported as the key physiological demonstration of the ostensibly broad effects of STN during motor inhibition, the current study is the first to provide causal evidence for this association.

Testing this hypothesis required a combination of TMS and DBS during behavior. This is a substantial methodological challenge, as it involves applying a magnetic pulse to a brain that is concurrently being stimulated electrically through an implanted wire loop. Indeed, CSE investigations with DBS patients are exceedingly rare, even without behavior.^{22,23} In the current study, we used the sustained clinical stimulation protocol to disrupt STN while measuring CSE during the stop-signal task.

Notably, there is one report of an alternative, experimental protocol that uses intermittent, temporally specific electrical pulses applied through the DBS device, which has been used concurrently with CSE measurements.²⁴ Compared with that protocol, the sustained clinical protocol used here has several advantages and disadvantages. The advantage of intermittent stimulation is that it allows tighter control over the timing of the effects of STN and reduces potential network-level effects that can be brought about by sustained, clinical DBS. However, in the current study design, this was outweighed by several considerations that favored the clinical protocol. First, although the effects of DBS are highly complex and result from multiple factors,²⁵ the clinical protocol is by far the most well-studied one and is well-tolerated by the patients. Second, the clinical protocol has an innate positive control (improvement in PD motor symptoms, captured by unified PD rating scale [UPDRS]), which is important to validate the efficacy of the intervention (i.e., as a manipulation check). Third, there is substantial cross-subject variability in the timing of the CSE suppression that takes place after stop-signals, even in healthy subjects. The superior temporal precision of an intermittent stimulation protocol would have increased the chances of missing the critical window, whereas the clinical protocol ensures that the effects on STN were present throughout the critical time period on each trial. Finally, the usage of the clinical protocol allows more direct extrapolations from the results of the current experiment to the real-world clinical treatment scenario, where there are important implications (see next paragraph). Hence, although future work could potentially use a more precise, intermittent stimulation protocol—ideally in a larger sample—to identify the specific timing at which STN exerts its influence on CSE changes during action stopping, the current study provides first clear-cut causal evidence for this association.

As mentioned above, the current finding, alongside the theoretical models it lends confirmative evidence to, is in line with a body of existing research on the effects of STN-DBS on behavior and cognition. STN-DBS, although beneficial to the motor symptoms of PD, has been known to result in behavioral disinhibition symptoms, such as impulsive decision-making under conflict^{7–10} and pathological gambling.^{11,26} The observations

Table 2. Behavioral comparison of patients ON- versus OFF-DBS

Subject	GO-RT		Failed STOP-RT		SSRT		Go accuracy		Stop Acc.	
	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
1	663	858	601	786	344	246	0.96	0.96	0.55	0.61
2	556	646	513	546	326	317	0.96	0.96	0.59	0.60
3	731	779	640	743	474	543	0.93	0.90	0.50	0.55
4	1,045	909	959	778	422	409	0.93	0.89	0.56	0.55
5	673	680	565	601	416	391	0.92	0.92	0.48	0.58
6	648	639	609	587	391	416	0.96	0.92	0.52	0.55
7	821	824	725	725	341	383	0.96	0.96	0.56	0.54
8	756	968	659	764	336	377	0.95	0.85	0.71	0.63
9	857	873	772	769	353	364	0.96	0.96	0.53	0.54
10	547	522	438	479	273	358	0.96	0.96	0.44	0.86
11	816	786	638	671	281	296	0.92	1.00	0.51	0.51
12	833	898	654	689	350	340	0.92	0.90	0.51	0.50
13	689	794	625	715	305	318	0.92	0.92	0.50	0.53
14	637	893	530	751	301	284	0.92	0.92	0.50	0.51
15	795	907	670	766	470	609	0.85	0.82	0.50	0.46
16	663	625	564	533	264	401	0.96	0.92	0.48	0.75
17	618	836	424	690	355	108	0.92	0.90	0.33	0.52
18	699	909	519	766	421	286	0.96	0.96	0.41	0.56
19	714	666	586	548	324	372	1.00	0.92	0.46	0.44
20	937	810	798	657	284	301	0.92	0.96	0.51	0.46
Mean	735	791	624	678	351	356	0.94	0.93	0.51	0.56
Significance	*		n.s.		n.s.		n.s.		n.s.	

RT, reaction time in milliseconds; SSRT, stop-signal reaction time (integration method). Accuracy is reported in proportion correct. Below the sample means, the significance of t tests between ON- and OFF-DBS is reported for each metric. n.s. indicates a non-significant p value; *p < 0.05.

made in the current study could provide a potential physiological mechanism by which these disinhibitory effects of STN-DBS could manifest. Indeed, previous work has shown that the resolution of conflict between an appropriate and a competing inappropriate response tendency is accompanied by both the non-selective suppression of CSE and by increased neural drive from STN to motor cortex.²⁷ The disruption of STN via DBS and the associated inability of the inhibitory control system to exert broad motor inhibition (demonstrated in the current study) could indeed result in the premature expression of suboptimal behaviors in many real-world scenarios, although this hypothesis will require future explicit testing.

At face value, however, it may then seem surprising that DBS had no significant effect on SSRT. Notably, the literature on the effects of STN-DBS on SSRT is highly variable—and, indeed, contains outright contradictory findings. Although several studies have indeed found a significant increase in SSRT ON-DBS^{28–30} (which would superficially align with the current finding of reduced stop-related CSE suppression ON-DBS, as well as with findings of impaired motor inhibition ON-DBS in other inhibitory control paradigms^{31,32}), there are also multiple studies that have found the opposite effect: faster SSRT ON- compared with OFF-DBS.^{33–35} Some of this discord could be explained through the usage of different quantification methods for SSRT. The most recent consensus recommendations for SSRT calculations suggest the integration method with replacement of GO-omission trials³⁶ (which is what was used in the

current study). However, when the original mean method¹² was used to quantify SSRT in the current data, the results were substantially different (instead of virtually unchanged SSRT values between ON- and OFF-DBS under the integration method, the mean method indicated a statistically significant speeding ON-DBS). However, deviations in method alone cannot explain the discrepancy in past findings, as some papers come to opposite conclusions using the same (or highly similar) methods for SSRT calculation. Instead, there is likely a larger issue with SSRT as a variable itself. Indeed, the assumptions that underpin the SSRT calculation have been subject to recent criticism on empirical,³⁷ neurophysiological,³⁸ and theoretical³⁹ grounds. Moreover, current models of action stopping in the stop-signal task in particular have suggested that actions in that task are stopped in several stages,^{39,40} rather than by a single, unitary process (as is assumed by SSRT). These neurophysiologically informed models have explicitly proposed that non-selective, broad suppression of CSE (and the underlying hyperdirect activation of STN) is only the first step in a cascade of inhibitory processing that enables action stopping after stop-signals. Hence, the usage of SSRT as a unitary, catch-all measure of the inhibition process underlying action stopping is becoming increasingly controversial. However, it is important to distinguish between the stop-signal task itself (as a method to evoke and study the processes involved in inhibitory control) and the latent variable of SSRT (as a method to measure the speed of these processes). The notion that the stop-signal

CORTICO-SPINAL EXCITABILITY OF FDI TRACT

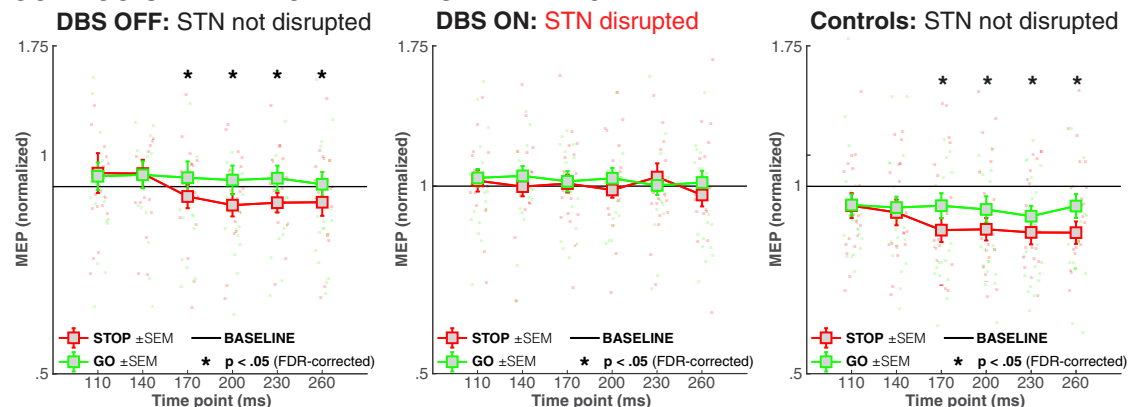


Figure 2. CSE results at the task-unrelated FDI muscle during the stopping of the verbal response

Patients OFF-DBS (left) show the expected pattern of non-selective CSE suppression during stopping, which is also observed in healthy controls (right). With STN disrupted in patients ON-DBS (middle), this suppression disappears. Time points on the bottom refer to the time relative to the stop signal (in case of stop trials) or a matched time point (in case of go trials). Dots show individual subject condition means (see also Table S2). Error bars denote the SEM.

task can be used to study inhibitory control is uncontroversial, and the paradigm is still viewed as the gold-standard method for this purpose.³⁶ However, in regards to measuring the inhibitory control processes in that task, we (and others, e.g., Huster et al.⁴¹) have advocated that investigators focus on overtly observable, physiological markers of inhibition at the level of the motor system,⁴² rather than on a latent behavioral variable like SSRT, which is derived from an indirect calculation (one that is subject to frequent revisions³⁶). As such, the current study causally demonstrates a direct relationship between STN and overtly measurable, physiological changes in cortico-motor excitability—moreover, a relationship that is in line with long-held theoretical, neuroanatomical, and clinical frameworks of inhibition in the human brain.

Notably, in the current study (as well as Wessel et al.¹²), patients performed both DBS sessions on their typical medication. PD is characterized by damage to the dopamine neurons of the nigrostriatal pathway, with pharmaceutical dopamine-replacement therapy being the first-line treatment. The effects of dopamine medication on motor symptoms of PD are similar to those of DBS⁴³ and dopamine is key to prominent computational models of basal ganglia functioning.⁷ Indeed, allelic variation in polymorphisms of dopamine transporter genes⁴⁴ as well as dopamine receptor availability both correlate with SSRT.⁴⁵ However, the effects of dopaminergic medication on stop-signal behavior are more mixed^{46,47} (which again may be a reflection of the limitations of SSRT). Importantly, neither acute dosages⁴⁸ nor chronic treatment⁴⁹ with dopaminergic medication seem to have an effect on baseline CSE (although there are some effects on the cortical silent period, see Nitsche et al.⁵⁰). Hence, although dopamine is likely to have complex effects on the dynamics of action selection, response execution, and motor inhibition (due to its broad involvement in both the pro- and anti-kinetic pathways of the basal ganglia), the dynamics of task-/stop-related suppression of CSE under dopamine require further explicit study.

In summary, we here provide first probable causal evidence for the involvement of the STN in effecting non-selective motor

inhibition in the human brain, confirming a key prediction of many long-held theoretical models of movement control and offering potential mechanistic insights into well-known side effects of STN-DBS treatment.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.cub.2022.06.067>.

ACKNOWLEDGMENTS

We would like to thank the patients for their participation and three anonymous reviewers for helpful feedback on an earlier version of this manuscript. This research was funded by grants from the National Institutes of Health (R01 NS102201) and National Science Foundation (NSF CAREER 1752355) to J.R.W. and training grant funding from the National Institutes of Health (T32 GM108540) to D.A.D.

AUTHOR CONTRIBUTIONS

Conceptualization, J.R.W.; methodology, J.R.W. and J.D.W.G.; formal analysis, J.R.W., D.A.D., and N.H.C.; investigation, N.H.C.; writing – original draft, J.R.W.; writing – review & editing, D.A.D., N.H.C., and J.D.W.G.; visualization, J.R.W. and J.D.W.G.; supervision, J.R.W.; funding acquisition, J.R.W.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: January 7, 2022

Revised: June 7, 2022

Accepted: June 22, 2022

Published: July 15, 2022

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Behavioral data	Open Science Framework	https://osf.io/ut83e/
MEP data	Open Science Framework	https://osf.io/ut83e/
Software and algorithms		
Task code	N/A	https://osf.io/ut83e/
Analysis code	N/A	https://osf.io/ut83e/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Jan R. Wessel, jan-wessel@uiowa.edu.

Materials availability

This study did not generate new unique reagents.

Data and code availability

All original code has been deposited at the OSF and is publicly available as of the date of publication. De-identified data have been deposited at the OSF and are publicly available as of the date of publication. DOIs are listed in the key resources table.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Sample size

The only previous investigation of non-selective CSE suppression in STN-DBS patients (which was performed OFF-DBS¹²) showed an effect size of $\eta^2 = 0.4$ for the main effect of TRIAL TYPE. Assuming an alpha level of 0.05 and a correlation across the dependent measures of $r \geq 0.6$ (which is typical for normalized motor evoked potential amplitudes), a sample size of twenty participants is necessary to detect an effect with an a priori power of 0.9.

Participants

Twenty patients with idiopathic PD treated via chronic bilateral STN-DBS implantation, as well as twenty elderly healthy control participants, provided written informed consent and participated in the study. Details of the patient sample can be found in Table 1, inclusion and exclusion criteria are listed below. Electrode implantation was performed using standard clinical protocols and stimulation sites were identified and verified using clinical microelectrode recordings. Experimentation was performed in accordance with the Declaration of Helsinki and the University of Iowa Institutional Review Board (IRB #201712739). All patients participated in both sessions and were paid \$200 for their participation. Healthy controls were paid at an hourly rate of \$15.

Inclusion and exclusion criteria

Inclusion criteria:

- 1) Idiopathic Parkinson's Disease patients with implanted STN DBS stimulators
- 2) able to walk independently, or with assistance
- 3) able to make their own decisions
- 4) age range = 18 - 80 years old
- 5) Fluent in the English language
- 6) Self-reported normal or corrected-to-normal vision and hearing
- 7) Implanted with a Medtronic Activa model DBS stimulator

Exclusion criteria:

- 1) Other neurological or psychiatric disorders that were not treated using DBS
- 2) Self-reported preexisting neurological and/or psychiatric condition

- 3) Inability to provide consent
- 4) Implanted with a non-Activa model DBS stimulator
- 5) Seizure disorder or taking medication to lower seizure risk
- 6) Family history of seizure disorder

METHOD DETAILS

Procedure

Patients completed two research sessions spaced 6–8 days apart (14 days apart in N=2 due to scheduling conflicts); one with their DBS ON and one with their DBS OFF. The order of the sessions was counterbalanced and randomly assigned (via coinflip) during the first session. Patients were instructed to take their usual PD medications per normal routine and timing of experimental testing was scheduled such that time from last dose was similar between each participant's research session (see [Table S1](#) for medication information). Before the first session, patients completed the informed consent process and co-signed a DBS lead safety form completed by the implanting neurosurgeon (JDWG), indicating the side of their head on which the extra loops of DBS leads were coiled. Then, in case the session was determined to be in the OFF state, their DBS was turned OFF, followed by a washout period of 10 minutes, after which the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) was administered to assess motor symptom severity. In the ON session, the UPDRS was administered without a washout period. Following UPDRS, motor hotspotting using the transcranial magnetic stimulator was performed (see below). To prevent any discharge near the coiled leads or battery pack, visible padding was placed over the location of the battery pack and clear markings were placed on a disposable head cap to indicate the side of the extra loops of implanted lead wires. Healthy control participants performed a single session only. After motor hotspotting, all participants performed a practice block of the task (described in the next section), followed by the main task.

Behavioral task

The task was adapted from Wessel et al.¹² Exact details can be found therein. In short, participants were instructed to fixate on a central fixation cross for 1,000ms after which a letter (either T or D) appeared ([Figure 1](#)). Responses to the letter were made by speaking it into a desktop USB-microphone as fast and accurately as possible (with a response deadline of 1,500ms), unless a stop-signal occurred. The stop-signal consisted of the letter color changing to red, at an initial delay of 200ms after the go-signal, which was then adaptively manipulated to achieve a stopping success rate ($p(\text{stop})$) of 0.5 cf.,³⁶ Stop-signals occurred on 1/3 of all trials and subjects were instructed that responding quickly and stopping successfully were equally important. In each session, participants performed 720 trials of 3,500ms duration each, split into 6 blocks. The practice block included 12 trials.

QUANTIFICATION AND STATISTICAL ANALYSIS

Voice data preprocessing

Voice data were preprocessed as in Wessel et al.¹² Each participant's voice responses in the stop-signal task were screened for incorrect responses (wrong letter) or incorrect voice onset classification by the automated algorithm. Incorrect responses were retained in the data and counted against GO trial accuracy. Trials in which the automated algorithm did not correctly detect the voice onset (2.78% of trials per session on average) were removed from further analyses.

EMG recording and TMS stimulation

EMG recordings and TMS stimulation were performed as in Tatz et al.,⁶ details regarding hardware settings and equipment can be found therein. The TMS site was determined to be opposite of the implanted DBS lead loops (see [Figure 1](#) schematics; resulting in right M1 as the TMS site in 9 subjects and left M1 in 11 subjects). EMG was recorded from the contralateral FDI muscle. After hotspotting of the precise location over M1 that corresponded to that muscle, single monophasic TMS pulses were applied to that hotspot during the task, at an intensity of 115% of resting motor threshold (mean output: 57% of maximum stimulator capacity). TMS was applied at four relevant time points ([Figure 1](#)): during passive rest before and after the task (10 pulses each), at active baseline during the task (in a subset of 30 go trials), and after stop/go-signals during task performance. The latter were the conditions of primary interest. Each stop-signal was followed by a TMS pulse delivered at one of six time points, covering the time range during which the non-selective CSE suppression is typically expected after a stop-signal (110 – 260ms in steps of 30ms). Matching time periods on go-trials were chosen for stimulation as well (i.e., TMS was time-locked to the matching stop-signal delay staircase on a given go-trial). On 30 trials, an active baseline pulse was delivered in the inter-trial interval instead (at 500, 700, or 900ms after the end of the response window while the fixation cross was on the screen). To allow for a recharging of the TMS stimulator, no pulse was delivered on trials immediately following such baseline trials.

Motor-evoked potentials

Motor-evoked potentials (MEPs) from the FDI-EMG trace were preprocessed as in Tatz et al.⁶ and averaged for each condition (passive baseline, active baseline, STOP+110[ms], STOP+140, STOP+170, STOP+200, STOP+230, STOP+260, GO+Stop-Signal-Delay

[SSD]+110, GO+SSD+140, GO+SSD+170, GO+SSD+200, GO+SSD+230, GO+SSD+260). Trials in which TMS stimulation occurred before the response were removed from analysis. Mean STOP/GO-condition MEP amplitudes for each subject were normalized by the mean active baseline MEP. The task-related STOP/GO-trial condition-MEPs of interest were compared using two-way repeated-measures ANOVAs with the factors TRIAL TYPE (STOP, GO) and TIMING (110:30:260). Follow-up directed t tests were performed to compare STOP vs. GO at each time point and corrected for multiple comparisons using the false-discovery rate procedure.⁵¹ Only successful STOP-trials were included in the analysis (failed STOP-trials represent the faster part of the GO-RT distribution and hence included many responses prior to TMS, which were excluded from the analysis). Per convention, successful STOP-trials were compared to the slower half of GO-trials – i.e., those in which reaction times (RTs) exceeded the subject median (since successful stop-trials represent the slower half of the GO-RT distribution, Verbruggen et al.³⁶). However, the results of the ANOVAs were qualitatively unchanged (i.e., significances were identical) even when STOP trials were compared to all GO trials. One observation in one patient (STOP-230 in the ON DBS session) represented an extreme outlier (MEP 323% of active baseline, $z = 3.62$); that observation was removed from the analysis. Effect sizes were reported in Cohen's d for t tests and planned comparisons, and in generalized η^2 for all ANOVAs.