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Event-related deep brain stimulation of the subthalamic nucleus affects conflict processing

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Abstract

Objectives: Many lines of evidence suggest that response conflict recruits brain regions in the cortical-basal ganglia system. Within the basal ganglia, deep brain recordings from the subthalamic nucleus (STN) have shown that conflict triggers a transient increase in low-frequency oscillations (LFO, 2–8Hz). Here, we deployed a new method of delivering short trains of event-related deep brain stimulation (DBS) to the STN to test the causal role of the STN and its associated circuits in conflict-related processing.

Methods: In a double-blind design, we stimulated the STN in patients with Parkinson's disease by locking brief trains of DBS to specific periods of the trial within a Stroop task.

Results: Stimulation had a specific effect on conflict compared to non-conflict trials by relatively speeding responses on conflict trials (i.e., reducing the Stroop effect, defined as the difference in reaction time between conflict and non-conflict trials) when it was delivered in the pre-response period in the preparation phase. Stimulation also increased errors when it was delivered early in the response window. This corresponded to the timing of conflict-induced increase in LFO

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Notes

The data associated with this manuscript are accessible through this URL: <https://osf.io/574ap/>

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observed in the absence of stimulation but was not directly related to the reduction in Stroop effect.

Interpretation: These results support the theory that the time of LFO increase recorded from the STN corresponds to a conflict-processing function. They also provide one of the first demonstrations of event-related DBS of the STN in humans during a cognitive control paradigm.

Keywords

Response control; Low-frequency oscillations; conflict

Introduction

A cardinal function of the basal ganglia is action selection.^{1,2} This becomes especially important when an individual is faced with multiple possible courses of action – i.e., a situation of response conflict. The subthalamic nucleus (STN) is well situated to play a role in conflict processing. The STN is thought to broadly excite the globus pallidus pars interna (GPi), the basal ganglia output nuclei, which may, in turn, suppress impending movements via the thalamus.¹ In computational models, activation of the STN (putatively via a prefrontal conflict detector) is thought to raise the decision “threshold”, which could correspond to a pause of the motor system, and lead to slower and more accurate responses.³ Consistent with this putative role for the STN in conflict, local field potential (LFP) recordings from the STN have consistently shown increased power of low-frequency oscillations (LFO) during conflict tasks.^{4–8} Activation in the STN region during conflict has also been revealed by functional MRI.⁹ Further, continuous STN deep brain stimulation (DBS) in Parkinson’s disease (PD) patients has been reported to induce impulsive responses in conflict conditions.^{10–12} In addition, improvement in response inhibition with STN DBS has also been reported, suggesting the effect of stimulation is likely dependent on the task and the type of response control.^{13–15} While these studies implicate the STN and the wider basal ganglia in inhibiting responses in conflict processing, the causal role of the STN and associated circuits and the temporal dynamics, especially with regard to LFO, remain unclear.

Here we harnessed a new method of event-related DBS during task performance. We delivered stimulation in a chronometric, double-blind, design through externalized DBS leads and in brief trains locked to specific periods within a given task trial. To pioneer this technique, we chose the classic verbal Stroop task which consists of conflict and non-conflict trials (participants name the color of a word; on conflict trials the color and the written word are different, on non-conflict trials they are the same). Our use of the verbal Stroop was motivated by several considerations: a) an efficient ratio of 1:1 conflict and non-conflict trials, b) the robustness of the behavioral effect even at the individual level, and c) a documented neural signature of conflict – an increase in LFO power.⁸ We applied stimulation in four different conditions in both conflict and non-conflict trials: no stimulation, Ready (before the imperative cue), and Early and Late (in the response phase). Stimulation in the Ready period was to investigate preparatory activities since the STN is active between ready and imperative cues. For example, movement-related potentials have been recorded in the STN between a ready and an imperative cue (go), corresponding to the

well-known contingent negative variation (CNV) potential recorded from scalp EEG electrodes.¹⁶ During this period, although subjects cannot anticipate whether the upcoming cue will entail conflict or not, they are getting ready to make a response and will need to overcome competing responses in the case of conflict. Therefore, the STN might have a function in broadly suppressing alternatives in preparing for movement, as originally proposed in the Mink model of the basal ganglia.¹ We also applied Early and Late stimulation in the response period with several possible outcomes in mind. First, if event-related DBS in the presence of conflict *augments* an STN-mediated pause function, then Early or Late stimulation might decrease the error rate and slow responses in conflict trials (i.e. boost a ‘brake’). Alternatively, if event-related DBS *disrupts* the STN and related circuitry, it might lead to more errors and perhaps faster RT in conflict trials. Finally, we recorded the STN LFP to a) test the presence of an early LFO in the response phase as reported in several studies,^{6–8} and b) to test whether stimulation effects at early or late times might correspond to the LFO power increase.

Methods

Subjects.

Thirteen PD patients (nine men, mean age 60.4 years, range 44–73 years) undergoing DBS surgeries were recruited. STN targeting was guided by MRI stereotaxy and intraoperative microelectrode recordings as previously described¹⁷. Quadripolar electrodes with four platinum-iridium contacts (Model 3387; Medtronic, Inc., Minneapolis, Minnesota, USA) were implanted unilaterally or bilaterally in the STN, with the most ventral contact (contact 0) placed at the base of the STN. In the first surgery, DBS leads were externalized through the scalp that enabled recordings for the current study before the subcutaneous pulse generator was implanted in the second surgery. One day to seven days after the first surgery, patients on their regular medications participated in a Stroop task with event-related DBS. They provided written consent form, and the protocol was approved by the University Health Network (Toronto) Research Ethics Board. The clinical details of the patients are shown in the Table.

Stimulation during the task was applied unilaterally in the right STN, and LFP data were recorded from both sides, but we only analyzed LFP data from the contralateral (left side) on no stimulation trials, as this was free of stimulation-induced artifacts. Stimulation caused saturation of the amplifier that contaminated recordings for both the stimulated and the contralateral electrode. Therefore, we could not analyze LFP during the stimulation trials. Connection to the stimulator also caused signal saturation in the electrode for stimulation even in no stimulation trials. As a result, we only analyzed LFP from the non-stimulated side in no stimulation trials. We excluded some patients from LFP analysis: two patients with unilateral implants did not have LFP data, and one patient had excessive dyskinesia that affected the recordings. For the behavioral effect of stimulation, two patients (Patients 1 and 2, Table 1), for whom only LFP was reported were not stimulated using the event-related DBS paradigm. Additionally, one patient (Patient 4) was excluded because of a low threshold of side effects from stimulation and because the stimulation intensity used fell two standard deviations below the group mean. In total, the data from 10 patients are reported for

the LFP analysis and 10 patients for the behavioral effect of stimulation, with 8 patients in both datasets. Although left and right STN are expected to show similar LFP activity based on the previous Stroop study,⁸ previous studies showed that the right hemisphere is more involved than the left hemisphere in response inhibition¹⁸ (but for a different view see¹⁹). Therefore, we choose to stimulate the right STN and record from the left STN.

Stimulation.

This was applied to contact #1 as cathode since this contact was most likely located in the STN and an external electrode on the patients' chest wall was the anode. The level of stimulation was adjusted for each patient individually. At the beginning of the experiment, high-frequency continuous DBS (130Hz) stimulation with pulsewidth of 100 μ s was gradually increased until the patient reported side effects such as paresthesia. The intensity was then decreased in steps of 1mA until no side effects were reported. The stimulation was applied in the form of trains that consisted of 11 pulses (~ 80ms, 130Hz, monophasic, squarewaves, pulse width 100 μ s). Stimulation intensity for the event-related DBS was 1.92 ± 0.76 (SD) mA. The trigger pulses for stimulation were prepared using Spike2 software (Cambridge Electronic Design, Cambridge, UK) and delivered through Power 1401 (Cambridge Electronic Design, Cambridge, UK) to a constant current stimulator (Digitimer, Welwyn Garden City, Hertfordshire, UK). The experiment was run in MATLAB (MathWorks, Inc., Natick, MA) and Psychtoolbox 3,²⁰ and on an Apple MacBook (Apple, Cupertino, CA).

Contact localization.

We used neurophysiological mapping to verify the location of the stimulated contact. During intraoperative recordings, the ventral border of the STN was identified when the pattern of cell firing changed crossing this border and was used to define the final target for the implantation of the DBS electrode.²¹ Based on the operative reports, the top and bottom margins of the STN in reference to the final position of the DBS 3387 electrode (Medtronic, Minneapolis) were determined. The locations of each contact relative to the STN were then estimated using the known dimensions of the electrode, i.e., four 1.5mm contacts separated by 1.5mm each. We performed post-operative MRI in every patient to confirm the final location of the DBS electrodes and contacts. This information was used in conjunction the intraoperative recordings to confirm the position of the electrodes relative to the STN. In most cases, however, the exact borders of the STN were not clearly distinguishable on the preoperative MRI and even less so on the postoperative MRI, hence the intraoperative recordings served as the primary method for determining the electrode position with the postoperative imaging serving as an adjunct confirmation. All patients had at least one contact on the stimulated side that was in the STN. Using neurophysiological mapping, it was determined that the contact used for stimulation was located in the STN (9 patients) or the dorsal border (1 patient) of the STN.

Experimental paradigm.

Patients performed the Stroop task,²² in which they were asked to name the ink of color words and ignore their meaning. The schematic of this task is presented in Figure 1. One second before presenting color words, the word "READY" was shown in the middle of the

screen to prepare the patient. The imperative cues were any of “RED”, “GREEN”, “YELLOW”, and “BLUE”, written either with the ink of the same color (non-conflict condition) or with a different color (conflict condition). Patients were required to speak the name of the color into a microphone. The ratio of conflict to non-conflict trials was 1:1. After responding, they proceed to the next trial after the inter-trial interval of 3–5s. During the inter-trial interval, a fixation cross was shown. The patients were encouraged to respond as fast if possible.

Event-related stimulation.

There were four stimulation conditions, one on each trial (no stimulation, Ready period, Early response, and Late response period) (Fig. 1A). In the Ready stim condition, stimulation was applied at the time of “Ready” stimuli during the waiting period. Stimulation was applied during the response period in the other two conditions. The timing of these conditions was determined based on an online estimate of RT, to account for changes in RT during the task. The RT forecast method was based on a block-by-block update of conflict/non-conflict RT from previous no-stim trials (6 trials each).²³ We delivered stimulation at two time points either 30% (Early stim) or 70% (Late stim) of the RT estimate. Trials in which responses occurred before Late stimulation were not analyzed. The ratio of stimulation conditions (no-stim, Ready, Early, Late) was 1:1:1:1 and alternated randomly trial-by-trial, the order of which was not known to the patients and the experimenter. The stimulation did not induce any sensation and is therefore not noticeable by the patients. In total, there were 30 trials for each stimulation condition in each trial type (conflict/non-conflict).

Experimental procedure.

Before the task began, patients’ voice amplitude levels (root mean square power) were gauged using the internal microphone of an Apple MacBook (Apple, Cupertino, CA). Calibration was made to detect the voice onset of each patient. Using a custom-made script and Psychtoolbox sound recording system, RT was calculated online. The experiment began with a training block of 16 trials. In the next block, patients completed 48 trials of the Stroop task (except the first two patients recruited who performed 90 trials) in the absence of stimulation to obtain an initial estimate of RT in each condition. Subsequently, patients performed another 5 blocks (total of 240 trials), during which event-related stimulation was applied.

LFP recordings.

LFPs were sampled at 5kHz and filtered between 1Hz to 1,000Hz and amplified using a SynAmp (or SynAmp RT) amplifier (Neuroscan Laboratories, El Paso, Texas, USA) with a gain of 5,000. All the LFP monopolar recordings were transformed to bipolar during offline preprocessing, except for patient 4 who had LFP bipolarly recorded.

Behavioral analyses.

A rater checked the individual speech responses to exclude trials with noise and only trials with clear speech responses were analyzed. Trials with RT>0.3s and <1.8s were included in

the analyses. There were 30 trials for each stimulation condition and trial type (conflict/non-conflict). The number of trials per patient per stimulation condition after exclusion was 51 ± 5.6 (SD) (the sum of conflict and non-conflict trials).

The Stroop effect was measured by subtracting non-conflict RT from conflict RT. The Stroop effect and RT did not significantly deviate from normality based on the Shapiro–Wilk test. The Stroop effect was analyzed by a one-way repeated measures analysis of variance (ANOVA) to assess the effect of stimulation conditions. Mean RT was analyzed using two-way repeated measures ANOVA with within-subject factors of stimulation (no stim/Ready stim/Early stim/Late stim) and trial types (conflict/non-conflict).

For errors, there was a violation of the normality assumption; thus conflict error rates were arcsine transformed²⁴ [note the non-transformed % values are displayed in figures and reported in the main text]. Errors were analyzed by a one-way repeated measures ANOVA to assess the effect of stimulation conditions.

In addition to the onset of speech times, we also measured speech duration by computing the interval in which the squared values of speech responses exceeded 30% of the maximum speech signal in each trial. Speech amplitude values were squared to provide better differentiation between speech and background noise. The response durations were analyzed using two-way repeated measures ANOVA with within-subject factors stimulation (no stim/Ready stim/Early stim/Late stim) and trial types (conflict/non-conflict).

We also compared the RT of correct and error trials and examined whether event-related stimulation affected the RT of error trials. We excluded 4 patients (Patients 2,7,8,10) since they did not show any errors in at least one condition and one additional patient (Patient 5) was excluded as the RT of error trials was longer than the accepted range (0.3s-1.8s). We performed repeated measures ANOVA on RT with factors correct vs. error and stimulation conditions.

Holm-Sidak tests were used for *post-hoc* comparisons, with correction for multiple comparisons. The assumption of sphericity was validated by the Mauchley's test. All values were reported as mean $\pm$ SEM unless otherwise stated. All P-values reported were two-sided.

LFP analyses.

Custom-written MATLAB scripts along with EEGLAB²⁵ and FieldTrip toolboxes²⁶ were used to analyze the LFP data. First, all LFP data were down-sampled to 1,000Hz and bandpass filtered between 1 and 400Hz. The monopolar recordings were converted to bipolar recordings by subtracting signals in adjacent contacts. Trials containing clear artifacts were discarded (on average 2.6 ± 3.1 (SD) % of trials). We chose the contact pair with the highest beta [13–30Hz] power (averaged across all trials) as the one best representing the location inside the STN.^{27,28} We set the baseline interval as –3 to –1s prior to the Word onset and computed the power spectrum using multi-taper frequency transformation with a Hanning window as tapers.

For time-frequency analyses, for each trial, data were transformed into epochs from 3s before to 1.5s after the cue onset. Trials with RT greater than 1.8s or less than 0.3s, and those with noise or unclear speech responses were excluded from analysis. The remaining trials were decomposed into the time-frequency domain. This decomposition used a product of the data and a set of Morlet wavelets after applying fast Fourier transform. This approach in the frequency domain is equivalent to convolution in the time-domain but is computationally faster. Since there is a trade-off between time and frequency resolution, Wavelet analyses consider a ratio of frequency f and spectral resolution σ_f that is f/σ_f to be constant. This constant ratio was set to 5, which is a standard value given the range of frequencies investigated here. For each frequency between 2 to 100Hz in steps of 0.05Hz, we calculated the product between the wavelets and our LFP data in steps of 10ms, a time-scale sufficient to address oscillatory dynamics for the current study. The epochs were either locked to the word onset (word-locked) or locked to the response (response-locked). They were then normalized to the baseline of 3 to 2s prior to the response onset for the response-locked and the baseline of 2 to 1s prior to word onset for the word-locked, using the formula: Normalized power=[Power values-mean (baseline power)]*100/mean (baseline power).

Analyses of LFO power.

Statistical differences between the power of conflict and non-conflict trial types were assessed by cluster-based permutation tests,²⁹ which is a solution to multiple comparisons with optimal sensitivity. We had *a priori* frequency band of interests based on mounting evidence showing pre-response LFO (2–8Hz) modulation in conflict situations.^{6–8} The clustering dimensions were in the range of 0s to 1.5s for the word-locked and the range of –1s to 0s for the response-locked epochs (time domain) and the range of 2 to 8Hz (frequency domain). For every data point, we compared conflict and non-conflict conditions with a sample-wise paired t -value. Data points were only considered and clustered if their t -values exceeded a threshold of 0.05. This threshold, however, did not have any influence on the false alarm rate, because the significance probability was computed by a Monte Carlo technique and corrected for multiple-comparisons by exceedance mass testing.²⁹ Accordingly, conditions within subjects were randomly shuffled 1,000 times to yield the permutation distribution. Based on this distribution, the clusters were considered significant with $P < 0.05$ two-sided.

Results

Behavioral effects of unilateral STN stimulation

We report results for speech onset latencies (reaction time, RT), the duration of speech responses (i.e., the duration for which the speech signal increases above baseline) and errors, in that order.

For speech onset latency (RT), ANOVA was run with the four stimulation conditions. Event-related DBS reduced the classic Stroop effect ($F(3,27)=3.97$, $P=0.018$, $\eta^2=0.31$). Holm-Sidak *post hoc* tests comparing each stimulation condition to the no-stim condition revealed a significant effect for the Ready stim ($t=2.96$, $P=0.019$, Cohen's $d=0.91$) and a trend for the

Late stim ($t=2.26$, $P=0.063$) (Fig. 1B), but no effect for the Early stim. Next, to determine whether stimulation affected conflict or non-conflict trials or both, we performed a two-way ANOVA with the factors trial type (conflict, non-conflict) and stimulation (no stim, Ready, Early, Late) with RT as the dependent measure. Typical of the Stroop effect, RT was longer for conflict compared to non-conflict trials (main effect of trial types, $F(1,9)=123.9$, $P<0.0001$, $\eta^2=0.93$) (Fig. 1C). There was no main effect of stimulation ($F(3,27)=1.82$, $P=0.167$), but there was a significant interaction between stimulation and trial type ($F(3,27)=3.97$, $P=0.018$, $\eta^2=0.31$) (Fig. 1E, for individual patients). We followed up with Holm-Sidak *post hoc* tests corrected for comparisons between each stimulation condition and no-stim (3 tests per trial type). In the conflict condition, stimulation in the Ready period decreased RT compared to no-stim (Fig. 1C, $t=2.6$, $P=0.044$, Cohen's $d=0.82$), while the other comparisons were not significant. Thus, stimulation speeded RT only in the conflict condition, especially for the Ready condition, while it did not change RT in the non-conflict condition.

For speech duration, there was a significant main effect of stimulation ($F(3, 27) = 4.26$, $P=0.014$, $\eta^2=0.09$) and trial type ($F(1,9) = 5.19$, $P=0.049$, $\eta^2=0.03$), and a significant interaction between stimulation and trial type ($F(3, 27) = 6.90$, $P=0.001$, $\eta^2=0.43$) (Fig. 1D). Holm-Sidak *post hoc* tests revealed that the response durations for both Ready and Early stimulation were overall longer than the no-stim condition (no-stim vs. Ready stim: $t=2.74$, $P=0.025$, Cohen's $d=0.87$; no-stim vs. Early stim: $t=2.84$, $P=0.025$, Cohen's $d=0.9$). To explore the significant interaction, *post hoc* tests revealed that in the no-stim condition, response durations were significantly longer in conflict than in non-conflict trials ($t=2.68$, $P=0.036$, Cohen's $d=0.85$), but in the Ready stim condition the response durations were shorter in the conflict compared to the non-conflict trials ($t=3.15$, $P=0.016$, Cohen's $d=1.0$). Thus, for speech duration, stimulation in the Ready period reversed conflict-related slowing to conflict-related speeding.

Next, we analyzed errors. For the non-conflict condition, errors were rare (<2% for each stimulation condition, no-stim: 0%, Ready stim: 1.81%, Early stim: 1.21% and Late stim: 0.6%; 5 of 10 patients did not make any non-conflict errors). Therefore, errors in non-conflict trials were not analyzed further, and we focused on errors in the conflict trials. A one-way repeated measures ANOVA with the factor of stimulation showed a main effect, with stimulation increasing errors compared to no-stim ($F(3,27)=3.68$, $P=0.024$, $\eta^2=0.29$, Fig. 2A). *Post hoc tests* with Holm-Sidak corrections, performed between the stimulation conditions and no-stim, revealed that the error increase occurred with stimulation in the early response period compared to no-stim (difference: 9%, $t=2.71$, $P=0.034$, Cohen's $d=0.85$) (Fig. 2B for individual data).

A follow-up analysis compared RT for error vs. correct trials in the conflict condition alone. RT for error trials was significantly faster than for correct trials ($F(1,4)=70.73$, $P<0.005$, Fig. 2C) and there was a trend for the main effect of stimulation ($P=0.08$), but there was no significant interaction between stimulation and trial type.

Aligning stimulation timing to STN LFO dynamics

Event-related stimulation was done from the right STN and we recorded the LFP from the left STN. We analyzed the left STN LFP in the trials without stimulation to assess the timing of conflict-related power increase and compare the results to the timing of right STN stimulation. A previous LFP study showed STN LFO signatures for the Stroop task are similar in the left and right STN.⁸ We assessed the LFP power changes in the response period (Fig. 3A) and tested whether changes in the LFP in conflict trials (the early increase in LFO in the response period), would correspond to the period when stimulation influenced accuracy (i.e., in the early period). Consistent with several studies of STN LFP during conflict,^{6–8} there was an increase in the power of low-frequency oscillations (2–8Hz) about 0.6s before the response for the conflict compared to the non-conflict trials (Cluster-based permutation test: $P < 0.05$ cluster-corrected; Fig. 3A inset).

We then tested the relation between LFO increases and the stimulation timing. First, we averaged LFO power (from 2.1Hz to 4.37Hz– the significant band from the cluster-corrected test of conflict vs. non-conflict, as above). Second, stimulation was timed to the cues. In order to compare with response-locked LFO, we calculated the timing of stimulation relative to response initiation. For this, we subtracted the timing of each stimulation condition from the corresponding RT of the conflict and non-conflict trials. The overall range of stimulation timing (for the conflict and non-conflict) was 0.73 ± 0.14 (SD)s before the response for the Early stimulation and 0.33 ± 0.06 (SD)s before the response for the Late stimulation. Finally, we aligned these stimulation times relative to the LFO power increase. As Fig. 3B shows, the significant LFO power increase corresponded to the Early stimulation period. Thus, the Early stimulation that led patients to make more errors occurred around the same time as the LFO response to conflict.

Discussion

We used a novel method of event-related DBS to test whether and when brief stimulation of the STN would impact Stroop task performance. We found that event-related stimulation reduced the overall Stroop effect, and more specifically it speeded RT on conflict trials, especially in the Ready period. Stimulation also increased errors in the conflict condition, especially in the early period after the word cue and this corresponded to the time of conflict-related increase in the STN LFO observed in the absence of stimulation. These results confirm that the STN and its related circuitries are involved in conflict-related behavioral adjustments. Importantly, they clarify the timing of conflict processing and demonstrate, for one of the first time to our knowledge, the feasibility of event-related DBS in cognitive tasks in humans.

Event-related stimulation in the response period

We found that stimulation delivered at particular points within the trial had effects on RT, speech durations, and accuracy in the conflict condition. While we are mindful that event-related DBS of the STN could have an impact on wider circuitry via diaschisis, these findings are consistent with classical models of the role of the STN in motor suppression.¹ They are also in line with more recent computational models that the STN raises the

threshold during conflict leading to slower and more accurate responses^{30,31} and other theoretical accounts.^{32,33} Our results are also consistent with studies using permanent lesions or sustained DBS to manipulate the STN – which induced premature responses and errors in rats^{34–36} and humans.^{10,37–39}

One may wonder if these results in the response period relate to a speed-accuracy tradeoff.^{40,41} Similar to previous studies, RT was faster in error trials than in correct trials. Stimulation appeared to decrease RT in error trials (Fig. 2C) but this change was not significant. This is likely because there were few error trials and five patients who made no error in some conditions were excluded from this analysis. These findings raise the possibility that stimulation may alter speed-accuracy tradeoff with a reduction in RT for error trials particularly with Early stimulation, but future studies are needed to address this issue.

Event-related stimulation in the Ready period

To summarize the above findings, short trains of stimulation time-locked to task events speeded conflict RT and decreased the duration of speech response without changing error rates when applied during the preparation period, and increased errors when applied early in the response period. While the impact of stimulation on errors fit our initial expectations, regarding RT, it was surprising that there is an effect of stimulation (on conflict) in the Ready period, but not in the early response period, and only a trend for the later response period. We had included stimulation in the Ready period because previous work recorded movement-related potentials from the STN between the ready and the imperative cue (go), beginning from the ready cue, corresponding to the well-known contingent negative variation (CNV) potential recorded from scalp EEG electrodes.¹⁶ The CNV amplitude is increased on trials that may involve stopping which requires engagement of proactive inhibitory control in advance, compared to go trials in which no stopping was required.⁴² Thus, these lines of evidence implicating the basal ganglia in the preparatory period motivated us to stimulate in the Ready period. Since subjects could not anticipate which cue type would occur (given the 50/50 ratio of conflict/no-conflict), Ready stimulation probably did not affect conflict processing per se. Instead, it might indirectly influence response control by augmenting preparatory processes involved in ‘clearing’ the response system – something that led to subsequently faster speed with no increase in errors. Thus, we speculate that the speeding of RT that occurred with stimulation in the Ready phase relates to an alteration of an STN function that prepares the system to respond, for example by clearing or suppressing response alternatives. This putative function of the STN to clear the response alternatives by broadly exciting the GPi is suggested by theoretical accounts¹ and by STN lesion studies in rats (that lead to premature responses during a ready interval).³⁵ Moreover, recent TMS studies in humans measuring corticospinal excitability observed preparatory inhibition, consistent with the broad suppressive effect by the STN.⁴³ Thus, the relative RT speeding on conflict trials in the Ready period that we observed for stimulation might fit this ‘clearing alternatives’ view. Moreover, this RT speeding in the absence of any impact on errors suggests that Ready stimulation may have improved performance. We note however that this putative augmentative effect of DBS during Ready period seems contradictory to its disruptive effect early in the response period, which led to more errors.

Previous studies have reported mixed results with improvement^{13–15} or worsening of response control with long-train STN DBS^{10–12}, suggesting that the effects of DBS likely depend on the task and the type of response control. Our findings suggest that the effects may also depend on when the stimulation is applied during the task. Future studies are needed to study the putative involvement of the STN and related circuitries in the preparatory period, especially in conditions where conflict is impending.

Conflict-induced LFO coincided with the timing at which event-related stimulation disrupted response accuracy

Event-related stimulation in the early phase of the response period increased errors in the conflict condition. Notably, this coincided with the time of increased LFO in conflict compared to non-conflict trials, consistent with previous studies,^{40,41} suggesting that LFO activity is possibly involved in accuracy adjustments under conflict. In line with this, a study showed a linkage between the LFO and enhanced decision threshold when the emphasis of the task was on accuracy, but not on speed.⁴¹ Conflict-triggered LFO, which is likely first generated by medial frontal cortex, signals the need for executive control.^{44,45} It may then communicate to other brain regions such as the STN to implement the control.³² Our STN LFO findings are consistent with previous studies that reported elevated LFO power (in the range of frequencies found in the current study) from STN LFP recordings during various conflict paradigms including the Stroop task.^{4–8} Previous studies also reported that STN LFO activity⁴⁰ and STN activity measured with fMRI, and mid-frontal LFO activity detected with EEG are linked to the decision-threshold.⁴⁶ However, these oscillatory signatures do not provide causal evidence that the STN and its associated circuits are involved during conflict. Our results, obtained via a temporally precise causal manipulation, go further by suggesting that these LFO increases for conflict are functionally significant. Moreover, we interpret the increased error rate induced by stimulation on conflict vs. non-conflict trials in terms of a disruptive effect of event-related DBS and suggests a specific role for LFO enhancement period in resolving conflict. It thus appears that this mode of stimulating the STN unilaterally at the therapeutic frequency for 80ms is not augmentative but instead disruptive of concurrent behavioral functions.

Clinical implications

Our findings have implications for the design of closed-loop DBS. Most previous closed-loop DBS studies in PD focused on beta oscillations as the control signal,^{47,48} but our findings suggest that LFO may also be important. STN LFO has been linked to the presence of impulse control disorders in PD.⁴⁹ The knowledge from our study of apparently improved performance (reduced Stroop effect without any increase in errors) by Ready stimulation and apparently disrupted performance by Early stimulation could be leveraged to design event-DBS protocols that improve cognitive performance while reducing the side-effects of stimulation.

More generally, our results contribute to a small but growing literature that monitors LFP to delineate distinct phases of cognitive control processing. A recent study showed that adaptive DBS reduced STN beta oscillations and disrupted its relationship to adjustment of decision threshold.⁵⁰ Our findings point to the prospect of delivering low-frequency (~ 4 Hz)

stimulation during periods of increased LFO – indeed, four Hz stimulation was recently shown to improve cognitive control in PD patients.⁵¹

Limitations

The study has several limitations. First, recordings were made in PD patients and their STN activities may be different from normal subjects. However, we studied PD patients on dopaminergic medications, which may partially normalize STN activities. Second, stimulation of the contact deemed to be within the STN did not allow comparison of the effects of dorsal versus ventral STN stimulation, a subject for future study. Third, we only stimulated one side rather than both sides. We stimulated the right STN and examined LFP recordings from the left STN in trials without stimulation due to signal saturation on the side of stimulation when the stimulator was connected. We note that a previous study found similar power modulations in the right and left STN in a vocal Stroop task.⁸ Thus, it is possible that bilateral stimulation would produce greater behavioral effects. Fourth, we found that the effects of STN stimulation coincides with the elevation of conflict-related LFO power. Our study was not designed to determine whether event-related DBS perhaps suppresses LFO in the presence of conflict. This can be addressed in future studies with appropriate stimulation-recording techniques. Fifth, we targeted stimulation in the response period relative to RT by tracking RT throughout the experiment. To more precisely target the LFO activities, future studies could titrate stimulation to the timing of LFO increases through real-time estimation. Sixth, our sample size was relatively small compared to most cognitive neuroscience studies. We note, however, the technical challenges of such experiments in PD patients who are recovering from surgery and that this sample size is similar to other studies in the same field.^{6,8} Finally, our results present a puzzle in that Ready period stimulation apparently augmented a ‘suppress alternatives’ function, while stimulation in the early response period apparently impaired a conflict processing function. Future research is required to better understand if these are true augmentations and impairments and why it varies as a function of phase of the trial.

Conclusion

Using a novel approach of event-related DBS of STN in humans during a cognitive control task, we showed that the STN and its associated circuitry is critically involved in conflict-related behavioral adjustments. Moreover, the stimulation timing that disrupted accuracy coincided with the occurrence of a conflict-triggered increase in low-frequency activities, supporting the idea that these slow frequency oscillations mark cognitive control processes in the cortical-basal ganglia system,⁵² in which the STN plays a critical role. The findings of this study have theoretical relevance for better understanding the dynamics of the STN and related circuits in response control and, also, potential clinical significance for helping the design of event-related DBS approaches.

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Figure 1. Event-related deep brain stimulation affects the onset times and duration of speech in the conflict condition.

A. Stroop Task. Each trial begins with a 'Ready' cue displayed for 1s, after which a color word appears on the screen. Subjects experience conflict trials (where word and word color do not match) and non-conflict trials (where they do match). On each trial, a burst of high-frequency stimulation (130Hz, ~80ms, indicated by black boxes) was applied at one of three different time points: the preparation phase (ready), and early or late in the response phase. B. The Stroop effect was significantly decreased by event-related stimulation. C. Stimulation applied in the preparation phase (Ready) selectively decreased RT during conflict trials

while the non-conflict RT was unchanged. D. Speech response durations were longer for conflict compared to non-conflict trials in the no stimulation condition. However, with event-related stimulation in the Ready period, the response duration became shorter in the conflict trials compared to non-conflict trials. E. Individual patients' data. Each dot represents one patient. RT in stimulated trials is plotted against RT in the absence of stimulation for non-conflict (left) and conflict (right) conditions. There was speeding of RT in conflict but not in non-conflict trials. Mean $\pm$ SEM are shown. * $P<0.05$

Figure 2. Effect of event-related stimulation on error trials in the conflict condition

A. Group mean error data. Stimulation increased the error rate, especially when applied early in the response period. B. Individual data. C. Error trials were significantly faster than correct trials in the absence of stimulation. Early stimulation appeared to make the error trials even faster, but the changes were not significant ($N=5$). $*P<0.05$. Mean $\pm$ SEM are shown.

Figure 3. Mapping of stimulation timing to STN activities during conflict.

A. Both conflict and non-conflict trials show a response-locked increase in gamma power at the time of response. Conflict trials additionally show an increase in low-frequency power (2–8Hz) early in the response period. The dotted box indicates the a priori band of interest to examine low-frequency oscillations. Inset, the contrast between conflict and non-conflict conditions in the 2–8Hz range. The difference is significant ($P < 0.05$, red unmasked area). Time 0 represents the response onset. B. Stimulation timing (Mean $\pm$ SD) in the pre-response period relative to significant LFO power changes. LFO power significantly increased in the conflict compared to the non-conflict trials in the timing interval that covers the Early, but not the Late stimulation. The vertical dotted lines represent the range of stimulation timing. The grey-shaded area represents the timing of the significant difference between conflict and non-conflict trials extracted from panel A-inset.

Table 1.

Clinical details

Patient	Age (years)/Sex	Disease duration (years)	UPDRS off (III)	UPDRS on (III)	Main motor features	LED(mg/d)	Stimulation current intensity (mA)
1	50 M	7	41	30	dyskinesia, motor fluctuations	1800	-
2	64 M	9	40	20	tremor, bradykinesia	1910	-
3	73M	14	38	27	peak dose dyskinesias, motor fluctuations	750	1.6
4	62F	6	30	16	dyskinesia, freezing of gait	900	2.5
5	63M	16	41	18	dyskinesia, tremor	1160	2
6	44 F	6	23	11	left sided tremor, bradykinesia	525	0.5
7	56 M	14	28	16	tremor, bradykinesia	2213	2
8	57 M	9	42	17	motor fluctuations	950	2
9	65 F	9	35	5	motor fluctuations, tremor, rigidity	1550	1.74
10	73 F	13	32	15	rigidity, bradykinesia, freezing of gait	1200	2
11	64 M	11	55	35	dyskinesias	1225	1.8
12	56 M	8	36	15	bradykinesia, rigidity, dyskinesia	975	2.8
13	58 M	10	36	12	rigidity, dyskinesia	1925	2.2

Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III) assessed preoperatively; F, female; M, male; LED, levodopa equivalent dose calculates as 100 mg of standard levodopa = 133 mg of controlled-release levodopa or 75 mg of levodopa plus entacapone or 1 mg of pramipexole or 5 mg of ropinirole.