Title:

Human Subthalamic Nucleus Selectively Decreases its Response to the Go-Signal in a Motor Inhibition Context

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Running title: Movement context affects STN activity

Abstract:

To understand the mechanism of movement facilitation and inhibition in the subthalamic nucleus (STN), we recorded intra-operatively subthalamic multiunit activity while parkinsonian patients (n=43 patients, 173 recording sites) performed increasingly complex oddball paradigms: auditory task, simple movement task and movement inhibition task.

We found that the human STN responds mainly to movement-involving tasks: movement execution at the motor STN and movement planning at the limbic-associative STN. At the limbic-associative STN, responses to the inhibitory cue (deviant tone) in the movement inhibition task were not significantly different from the simple movement task. However, responses to the go cue (frequent tone) were significantly decreased in the movement inhibition task. Successful motor inhibition was correlated with a higher baseline activity before the inhibitory cue.

We therefore suggest that the subthalamic nucleus adapts to movement inhibition context by selectively decreasing the amplitude of neuronal activity. Smaller fluctuations might enable better preparation for possible inhibition.

Key words: Movement inhibition, Movement planning, Subthalamic nucleus, Multiunit activity, Parkinson's disease, Deep brain stimulation.

Abbreviations: Deep Brain Stimulation (DBS), Dorsolateral Oscillatory Region (DLOR), Post Stimulus Histogram (PSTH), Subthalamic Nucleus (STN), Ventromedial Non-oscillatory Region (VMNR), False Discovery Rate (FDR), Local Field Potential (LFP).

Introduction:

Neural circuits of response inhibition are associated with the Subthalamic nucleus (STN). Classical models of the basal ganglia (DeLong, 1990, Mink, 1996), describe an excitatory input from the cortex to the STN via the hyper-direct pathway (Nambu et al., 2002). The STN exerts an excitatory influence on the output nuclei of the basal ganglia which in turn inhibit the thalamus and the cortex. Activation of the STN during inhibition of movement was found in many fMRI, local field potential (LFP) and single unit studies in both animals and humans (Aron et al., 2006, Forstmann et al., 2012, Ray et al., 2012, Alegre et al., 2013, Schmidt et al., 2013, Bastin et al., 2014, Rae et al., 2015, Fischer et al., 2017a). The STN is also involved in response inhibition of non-motor modalities such as working memory and decision making (Brittain et al., 2012, Zaghloul et al., 2012, Wessel et al., 2016b, Herz et al., 2018).

Besides the role of the STN in movement inhibition, the STN is also involved in both the planning and execution of movement (Thobois et al., 2000, Cassidy et al., 2002, Levy et al., 2002, Foffani et al., 2004, Kuhn et al., 2006, Androulidakis et al., 2007, Oswal et al., 2013, Fischer et al., 2017b). Part of the movement planning process is a global regulation of readiness for movement that depends on the context of the movement. In the cortex for example, a subconscious readiness potential precedes the time of voluntary movement and regulates movement execution or inhibition (Libet et al., 1983, Keller et al., 1990, Schultze-Kraft et al., 2016).

The role of the STN in global movement regulation has not been well explored although its physiology makes it very suitable for such a function. The STN has a high spontaneous firing rate (Wichmann et al., 1994) and it tonically inhibits the thalamus via the output nuclei of the basal ganglia. Therefore, the STN can potentially be involved in the regulation of global readiness for movement.

Many studies have examined STN-mediated motor inhibition using classical versions of stop signal tasks (Kuhn et al., 2004, Aron and Poldrack, 2006, Alegre et al., 2013, Schmidt et al., 2013, Benis et al., 2016). These studies compared no-go to go trials or successful to unsuccessful stop trials. Although several studies have compared different levels of anticipation to the inhibitory signal (Ray et al., 2012, Benis et al., 2014, Fischer et al., 2016), STN-mediated mechanisms of readiness for movement in the context of motor execution or inhibition has not been well studied.

In this study we compared human STN multiunit activity for oddball task with three levels of movement: first, passive listening (‘None-Go’ task: no movement); second, adding presses to all tones (‘All-Go’ task: movement with facilitation context); and third, adding inhibition of movement following the deviant tones (‘Go-NoGo’ task: movement with inhibition context). We used a similar auditory paradigm in all tasks to control for the auditory passive listening process and to directly compare simple motor planning (All-Go task) to inhibitory motor planning (Go-NoGo task). This enables the investigation of the role of the STN in the execution of movement in the context of no movement, movement facilitation and movement inhibition.

Methods:

Patients

Parkinson’s disease patients (n=43) undergoing STN DBS participated in this research. All patients met the accepted inclusion criteria for DBS surgery and gave a written informed consent. This study was authorized and supervised by the IRB of Hadassah Medical Center (reference code: 0168-10-HMO). All recordings were performed while the patients were awake and off medications (over-night washout).

Study paradigm

We used three tasks as illustrated in Fig. 1, A. In all three tasks, series of 120 tones with two different pitches were played in a pseudo-random order. The frequent tones (82% of played tones) were delivered at high pitch (1200Hz) and the deviant tones (18% of played tones) were delivered at low pitch (300Hz). The tone duration was 250ms followed by 1000ms pause (total inter trial interval was 1250ms) and the total duration of the task was 2.5 minutes in all three tasks. The difference between the tasks was the instruction to the participants: 1. ‘None-Go’ task: Participants were not informed about the task, i.e., the tones were played without any instruction to the participants (but we verified that the patient was awake). 2. ‘All-Go’ task: Participants were instructed to press a hand button as fast as possible after each tone (both frequent and deviant tones). 3. ‘Go-NoGo’ task: Participants were instructed to press a hand button as fast as possible after the frequent tones and to avoid pressing the button after the deviant tones.

Neuronal data was recorded in different areas along the left or right dorsolateral-ventromedial STN axis (see details below) while the participants performed the tasks. Recordings of all three tasks (None-Go, All-Go and Go-NoGo) in all four recording sites (right dorsolateral STN, left

dorsolateral STN, right ventromedial STN, left ventromedial STN) would have been the preferable method. However, recordings during surgical navigation is limited by the additional clinical risk for the patient as well as by the patient's attention span. Prior to each recording session, the neurosurgeon (ZI) verified the clinical state of the patients (for example, no excessive increased cerebrospinal fluid leak) and approved carrying out the research recording session. To further minimize the clinical risk, the total recording time for research purpose for each patient was up to 8 minutes. Therefore, each patient participated in only one of the tasks that was repeated in the four STN recording domains. Tones and press times were saved with neuronal data on the same data acquisition device (MicroGuide or NeuroOmega, AlphaOmega, Nazareth, Israel). All patients reported right hand dominance. Participants were asked to press the button using their right thumb or index finger while recording in the left (contra-lateral) or right (ipsi-lateral) STN. Since the Go-NoGo task instructions were thought to be too complex for some of our patients, the Go-NoGo group of patients were trained with the task prior to surgery.

Surgery

The surgical technique is described elsewhere (Zaidel et al., 2009). Briefly, surgery was performed using the CRW stereotactic frame (Radionics, Burlington, MA, USA). STN target coordinates were chosen as a composite of indirect targeting based on the anterior commissure-posterior commissure atlas-based location and direct targeting with three Tesla T2 magnetic resonance imaging (MRI), using Framelink 5 or Cranial software (Medtronic, Minneapolis, USA). A typical trajectory was ~60° from the axial anterior commissure-posterior commissure plane and ~20° from the mid-sagittal plane. Final trajectory plans were slightly modified to avoid the cortical sulci, ventricles and blood vessels (as seen in T1 scans with contrast media).

Electrophysiological recordings

The microelectrode recording data were acquired with the MicroGuide or the NeuroOmega systems (n= 19 and 24 patients respectively, AlphaOmega Engineering, Nazareth, Israel) as previously described (Marmor et al., 2017). Neurophysiological activity was recorded via polyamide coated tungsten microelectrodes with an impedance around 0.5 MΩ (measured at 1000Hz). For the MicroGuide system, the signal was amplified by 10,000, band-passed filtered from 250 to 6000 Hz using a hardware four-pole Butterworth filter, and sampled at 48 kHz by a 12-bit A/D converter (using ±5 V input range). For the NeuroOmega system, the signal was amplified by 20, band-passed filtered from 300 to 9000 Hz using a hardware four-pole

Butterworth filter, and sampled at 44 kHz by a 16-bit A/D converter (using ±1.25 V input range).

Typically, two parallel electrodes separated by 2mm for each STN trajectory were advanced simultaneously along the planned trajectory. Recording began 10 mm above the presumed target (estimated by the pre-operative imaging). Electrodes were advanced in the STN in discrete steps of ~0.1 mm. The task was performed several times (2.4±1.2, mean±SD) along the tract in the STN while maintaining the electrodes stationary.

Detection of the STN entry and exit as well as differentiating between the dorsolateral oscillatory region (DLOR, sensorimotor domain) and ventromedial non-oscillatory region (VMNR, limbic-associative domain) of the STN were automatically delimited by a hidden Markov model (HMM, Zaidel et al., 2009). Recording locations in the STN subdomains are presented in Fig. 2A-C. Each recording site was classified according to the automatic HMM algorithm and verified / corrected by an experienced electrophysiologist (OM). Only locations that could have been certainly defined within the STN were included in the analysis (173 out of 196 recording sites). Total STN axis length was 4.6±2.0 mm and 4.8±2.1 mm (mean ± SD) for right and left STN, respectively. STN DLOR axis length was 2.0±1.6 and 2.1±1.6 (mean ± SD) for right and left STN, respectively.

Signal processing and analysis

Reaction time: Reaction time is usually defined as the time from tone onset to the start of the movement, but we refer to the time from tone onset to the actual press. Because of the rhythmic nature of the tasks and many anticipatory (pre-tone) presses (see Table 1), anticipatory press was defined as a negative reaction time (200-0ms before tone onset). i.e. a press more than 1050ms after the tone was considered as an anticipatory press to the next tone. To avoid bias of repeated measures (dependency between reaction time from the same patient) in the statistical comparison (Vasey et al., 1987), the average reaction time was calculated for each session (i.e. series of 120 tones). The averaged reaction time and its statistical comparisons are detailed in Table 1. Reaction time distribution in all the trials of All-Go and Go-NoGo tasks are presented in Fig. 1C, D. Reaction time in the All-Go task and following the go cue of the Go-NoGo task represents correct responses while the reaction time following the no-go cue of the Go-NoGo task represents the behavior of commission errors (incorrect responses).

Peri-stimulus histogram (PSTH): In each recording site the signal was divided to traces from 500ms before to 1250ms after the tone or press time. The root mean square (RMS) of the signal

was computed in windows of 100ms, with an overlap of 50% between windows, resulting in a time resolution of 50ms bins. After calculating the root mean square values of all windows each trace was normalized by modified Z-score. The modified Z-score was based on the median and MAD (median absolute deviation) corrected by 1.4826 (a scaling factor to equal standard deviation (Rousseeuw et al., 1993)). The modified Z-score was chosen because of the relatively short trials and long responses that sometimes lasted most of the trial length. Trials were aligned to tone onset and to press time and categorized to frequent and deviant tone. The mean of all trials (modified Z-scores of the root mean square as a function of time) in each recording site was calculated before averaging all recording sites for the same sub territory of the STN. Different analysis methods (median calculated on all recording sites and mean and median calculated for all traces) yielded similar results. Examples of the raw data (high-pass filtered) and PSTH averaging of single recording site in each of the tasks and recording sites are presented in Fig. 2, D,E. In order to measure the evoked response in the different categories for statistical comparison, we defined the magnitude of each response as the difference of the evoked response between the maximal peak time and minimal trough time of the averaged evoked response. The maximal and minimal point are determined according to the averaged response within each category (see Fig. 6A, B, darker dots that marks the maximal and minimal points).

Artifact removal: artifacts in the raw data were detected by automatic rejection criteria of an absolute amplitude higher than 20 times standard deviation (SD). Epochs with artifacts were removed from the database and analysis. Speaker's echo of the auditory signal picked up by the recording electrodes was filtered using a narrow filter at the auditory signal's pitch frequencies and its harmonics and verified by human expert (OM). Trials with Z-scored PSTH responses greater than 6 times the standard deviation of the signal were excluded from the analysis.

Statistics and software

Patients' demographics across the three tasks' groups were compared by one-way ANOVA test ($\alpha = 0.05$). For each session of the All-Go and Go-NoGo tasks, we calculated the average reaction time, the averaged press rate and the average anticipatory press rate for frequent and deviant tones. Two sample t-test was conducted to test differences in reaction time and press rate between frequent and deviant tones and between All-Go and Go-NoGo tasks. The frequent reaction time and the deviant reaction time in both tasks were compared using two sample t-test (2 tails, $\alpha=0.05$). Two sample t-test was conducted to test differences in the time of the

amplitude's peak between responses recorded in dorsal and ventral locations (2 tails, $\alpha=0.05$). The task effect on the amplitude of neural responses was compared by a one-way ANOVA test (3 groups: None-Go, All-Go, Go-NoGo) and repeated for each tone (frequent, deviant) and for each subdomain (DLOR, VMNR). If significant effects were found, we used post-hoc simple main effect analysis with Bonferroni correction for multiple comparisons. For the All-Go and Go-NoGo tasks, in the aligned to press trials, a two sample t-test was conducted to test differences of neuronal response amplitude. The tone effect on the amplitude within each task was conducted by paired t-test. To detect any significant change in neuronal response between the successful and unsuccessful stop trials and between All-Go and Go-NoGo trials, we used two sample t-test (2 tails, $\alpha=0.05$) with FDR (false discovery rate) correction for all the PSTH bins (50ms windows).. All data was processed and analyzed using Matlab 2016b (Mathworks, Inc., Natick, MA),

Data availability

Data will be available at http://basalganglia.huji.ac.il/links.htm

Results:

In this study we recorded neuronal activity using microelectrode recordings during DBS surgery targeting the STN. A total of 43 patients participated in this study. Each patient participated in one of the following tasks: 7 patients participated in the None-Go tasks (28 recording sites), 7 patients participated in the All-Go task (26 recording sites) and 29 patients participated in the Go-NoGo task (119 recording sites). Demographic details, clinical assessments and active medications are listed in Table 1. No significant changes were found between the task groups except a difference in disease duration (one-way ANOVA). Number of recording sites and behavioral results in the different tasks are summarized in Table 1.

Behavioral results

The reaction time after frequent tone is significantly shorter in the All-Go task compared to the Go-NoGo task (0.29s and 0.41 s respectively, $p=0.0105$, $d=-2.62$) (Fig. 1B). The pre-tone press rate is significantly increased in the All-Go task compared to the Go-NoGo task (10% and 4% respectively, $p<0.0001$ $d=-5.16$). The reaction time after the deviant tone (no-go cues) in the Go-NoGo task represents only the commission errors (incorrect responses) and is shorter than the reaction time to frequent tone (go cue) (0.31s and 0.41s respectively, $p<0.0001$ $d=4.17$).

The reaction time of commission errors in the Go-NoGo task is not significantly different from the reaction time after deviant tone in the All-Go task (0.31s and 0.36s respectively, p=0.11, d=-1.16)

The STN subdomains respond to the All-Go task (motor activation) with different timing

The recording locations in the STN subdomains and example of raw recordings (high-pass filtered) and typical responses to each of the tasks is presented in Fig. 2. The Averaged responses to the three tasks, in each of the STN subdomains (left, right, DLOR, VMNR) are presented in Fig. 3 – Fig. 5. The electrophysiological recordings show a small response to the auditory cues in the None-Go task, as presented in Fig. 3. No significant difference between the frequent (.12±.18) and deviant tone (.23±.44) was detected in the DLOR (paired t-test, p=0.41, d=-0.85) and a small but significant difference in the VMNR STN ((.09±.14, .29±.27 frequent and deviant, p=0.028, d=-2.46, paired t-test).

Larger responses were recorded for both frequent (.53±.52,.39± .33, DLOR and VMNR) and deviant (.56±.42,.73±.65, DLOR and VMNR) tones in the All-Go task, as presented in Fig. 4. No significant differences were detected between the responses amplitudes to frequent and deviant tones in the All-Go task in both DLOR (p = .06 d = -2.1) and VMNR STN (p=.76 d=-0.31, paired t-test). However, the timing of the evoked responses' peak to the frequent and deviant tones in the All-Go task was earlier in the VMNR than in the DLOR: peak response times were 0.15s and 0.25s for the frequent and deviant tones respectively in the VMNR and 0.55s for both the frequent and deviant tones in the DLOR (two sample t-test on peak's times p=.0037 d= 3.21, p=.057, d= 1.99, respectively).

Differential responses to the Go vs NoGo cues at the limbic-associative domain of the STN

In contrast to the All-Go task, the Go-NoGo task was characterized by disparate responses to the frequent tone (go signal) and deviant tone (no-go cue) in both VMNR and DLOR (Fig. 5). In the VMNR, the amplitudes of the evoked responses to the frequent tone (.16±.39) were significantly smaller than the evoked responses to the deviant tone (.53±.8, p<.0001, paired t-test; amplitude was defined as the difference between the time points of the peak and trough of the averaged evoked response). As in the All-Go task, the timing of the evoked responses' peak of the frequent and deviant tones in the Go-NoGo task was earlier in the VMNR than the

DLOR, but not significantly different. Peak response time were 0.1s and 0.25s for the frequent and deviant tones respectively in the VMNR and 0.4s and 0.55s for the frequent and deviant tones respectively in the DLOR (two sample t-test, p=.068 d=1.84, p=0.61 d=-0.5 frequent and deviant, respectively). In the Go-NoGo task, the evoked responses were larger in alignment with press in the DLOR. In the VMNR, the evoked responses were more locked to the tone rather than the press (Fig. 5, lower row).

Evoked response to a Go cue decreases in the context of movement inhibition in the limbic-associative domain of the STN

Although the patients pressed the button in their right thumb or index finger, evoked response to movement were observed in both left and right STN. Therefore, in order to have better statistical comparison between the responses to the different tasks and between the frequent and deviant tones, we united left and right STN responses (Fig. 6). To test the difference in response to the frequent and deviant tone in each of the tasks we conducted a paired t-test and repeated the analysis for the VMNR and DLOR sub regions of the STN. VMNR response to the deviant tone in the Go-NoGo task and in the None-Go task was larger than its response to the frequent tone ($p<0.0001$, d=-4.83, p=0.028, d=-2.46, respectively) (Fig. 6A, C). All other comparisons did not detect a significant effect (p=.41, d=.86; p=.058 d=-2.1; p=.63 d=-0.29; p=.76 d=.32, None-Go, All-Go and Go-NoGo in the DLOR, and the All-Go task in the VMNR, respectively).

To test the effect of task context on STN responses, we conducted one-way ANOVA on the responses to the tone with the task context as a parameter (None-Go, All-Go, Go-NoGo), and repeated the analysis for the frequent and deviant tone and for the VMNR and DLOR sub-regions of the STN. VMNR response to the frequent tone was modulated by task context ($F(2,104)=5.56$, p=.005). Post-hoc comparisons revealed that the evoked responses to the frequent tone were lower in the None-Go and Go-NoGo tasks compared to the All-Go task (p=0.01 and p=.006, respectively). Surprisingly, there was no effect of task context on the responses to the deviant tone ($F(2,104)=2.7$ p=.07). Expectedly, task context did not modulate response to the frequent tone in the DLOR, while it did affect response to the deviant tone ($F(2,63)=1.08$, p=0.34, $F(2,63)=4.37$, p=0.016, respectively). Post-hoc pairwise comparisons for the deviant tone showed larger responses in the All-Go task (85% of these tones were followed by a press) compared to the Go-NoGo (only 37% of these tones were followed by a

press, p=.014) but not to the None-Go tasks (p=.069) or between the Go-NoGo and None-Go tasks (p=.98).

The smaller amplitude after Go cue in the Go-NoGo task is mainly due to deficiency of the amplitude's negative component

To further compare the differences between the response pattern of the All-Go and Go-NoGo tasks, we superimposed the All-Go and the Go-NoGo responses with a normalization to the time before tone or press (Fig. 7). In the VMNR, the All-Go task evoked response aligned to the press has a large negative component (i.e. reduction in neuronal activity) at 400-600ms after press in the frequent tone trials and 400-850ms after tone in the deviant tone trials that does not appear in the Go-NoGo task (marked by gray areas, tested for significance level of p<.05, paired t-test after FDR correction). In the DLOR, the negative component of the All-Go response is more prominent when the responses are aligned to tone, and significantly different from the Go-NoGo for the deviant tone at 150-250ms after tone onset

Commission Errors responses are associated with lower neuronal activity before tone onset

Analysis of the no-go cue (deviant tone) in the Go-NoGo task detected a change in the neuronal activity between the correct rejection (omission) and commission error trials (Fig. 8). In the VMNR, the neuronal activity of the trials with commission error was significantly lower compared to the neuronal activity of the trials with correct rejection at 500-100ms before the tone (tested for significance level of p<.05, paired t-test after FDR correction). The commission error trials displayed significantly elongated phase of increased neuronal activity 500-1000ms after tone.

Discussion:

In this study we found significant changes in human STN multiunit activity between the three levels of an oddball task. The ventro-medial STN adapts the response to movement inhibition context by selectively decreasing neuronal activity. While the response to the deviant tone remains the same in the context of motor facilitation (All-Go task) and motor inhibition (Go-NoGo task), the response to the frequent tone (go cue) decreases in the context of motor inhibition (Go-NoGo task). The decrease in amplitude of response in the Go-NoGo task was

mainly in the negative component of the response. Along with these findings, we noticed that commission error responses (incorrect responses to an inhibitory signal) display a larger negative component before the tone and an elongated positive phase after the tone compared to the omission responses (correct responses to an inhibitory signal).

The ventromedial STN correspond to movement planning while the dorsolateral STN correspond to movement execution

Analysis of both All-Go and Go-NoGo tasks reveals different responses in the VMNR and DLOR that probably represent their different roles in movement planning and movement execution. Our data support the view that the VMNR activity is related to movement planning while the DLOR activity is related to movement execution. First, VMNR responses precede the DLOR responses. For example, the peak of the evoked response to frequent tone is earlier in the VMNR compared to the DLOR (0.2s vs. 0.55s after tone, respectively) and the evoked response starts before the press time in the VMNR, both in the All-Go and Go-NoGo tasks (0.125s and 0.175s before press respectively, Fig. 6, right bottom row). Second, the VMNR responses are not correlated to whether movement was executed or not. For example, large evoked response's amplitude is seen to the deviant tone in the Go-NoGo task, which in most trials, is not followed by movement. Third, DLOR responses are larger when aligned to press than aligned to tone (Fig. 4, Fig. 5, upper row). Last, the peak of the DLOR responses are usually around the mean reaction time (most prominent in left DLOR, Go-NoGo task, aligned to tone, see Fig. 5, upper row, left). Finally, the bilateral activation in response to right thumb press might hint that the STN role is of more global movement regulation and not the execution of specific muscle.

Our study shows for the first time the involvement of the ventral STN (non-motor domain) in movement planning that is not restricted to movement inhibition. These results are in line with previous reports in LFP. Motor execution has been associated with dorsal STN located DBS contacts exhibiting high beta power (Kuhn et al., 2004, Androulidakis et al., 2008, Zaidel et al., 2010, Greenhouse et al., 2011). Movement inhibition, that is part of the movement planning process, was associated with ventral-STN located DBS contacts (Hershey et al., 2010, Alegre et al., 2013) and also in single units recorded from ventral STN areas of OCD patients (Bastin et al., 2014).

Maximal neuronal response decreases in the context of motor inhibition

The None-Go task is a passive auditory discrimination process, i.e., detection of change in the auditory pitch similar to a miss-match negativity test. The None-Go task elicited small STN evoked responses with small but significant difference between the frequent and deviant tones in the VMNR (p=0.0.028, d=-2.46). This might contribute small effect to the STN responses in the two other tasks (All-Go and Go-NoGo tasks).

Surprisingly, we found that the STN evoked responses to the frequent tone in the Go-NoGo task are lower than the evoked responses in the All-Go task. Previous studies that examined inhibitory paradigms detected a stronger evoked response to an inhibitory signal and thus suggested a mechanism of an increased activation of the STN to the inhibitory signal (Aron and Poldrack, 2006, Isoda et al., 2008, Benis et al., 2016, Wessel et al., 2016a). Our results suggest that the response to the inhibitory cue does not increase, but rather the response to the go cue decreases. Here we discuss three possible, non-mutually exclusive, explanations for the decreased STN response in the context of motor inhibition. The first explanation is resource allocation in the STN following an increased cognitive load. The second explanation is modulation of STN neuronal activity as a mechanism of facilitation and inhibition of movement. The third explanation relates to the process of error monitoring in the STN.

1. *Allocation of neuronal resources to the different cues compensates for the STN capacity constrains*

The decreased STN responses in the motor inhibition context (the most complex of the three tasks in this study) may represents a limitation of the computational capacity of the STN neurons. We suggest that this limited capacity produces a selective integration of data, i.e. concentration on relevant stimuli and filtering out of non-relevant stimuli. If a motor task also requires preparation for possible movement inhibition, the neuronal capacity reserve decreases, and the allocation of resources to the frequent and deviant tones reflects the main aim of the task. In the simpler task (All-Go) the neuronal responses to the frequent tone are similar to the deviant tone in the VMNR. The aim of the All-Go task is motor planning and execution; therefore, the discrimination between the frequent and deviant tones is not relevant to the completion of the task. In the more complex task (Go-NoGo) the neuronal responses in the VMNR (that is associated with movement planning) are smaller to the frequent tone than the deviant tone (amplitude response ratio is 0.3:1, frequent to deviant tone respectively). The major aim of the Go-NoGo task is inhibition of action (press) at the deviant tone (no-go cue). Thus, more neuronal resources should be allocated to the no-go cue. Since increasing the

response to the no-go cue is not possible due to the limited neuronal capacity, the discrimination between go and no-go cues is accomplished by the reduction of the responses to the go cue. The notion that the STN can prioritize the most relevant process is in line with previous reports (Baunez et al., 2001, Wessel et al., 2016a).

2. *Preparation for movement inhibition decreases the fluctuations of STN activity during movement*

In the classical model of the basal ganglia, the role of the STN is to provide ongoing continuous (tonic) inhibition ("brakes") for movement execution. The high spontaneous STN firing rate represents the baseline tonic inhibition and the decreased STN firing rate represents a release of this tonic inhibition. In our study, the movement in the Go-NoGo task is more restrained due to the ongoing preparation for the no-go cue, while in the All-Go task the movement is more free and rhythmic (i.e. uninterrupted) due to the fixed inter tone interval that encourage movement anticipation. In the All-Go task, the repetitive nature of the movement is reflected behaviorally by a shorter reaction time and an increased percentage of early press (before tone onset). In line with these behavioral changes, in the All-Go task there is a larger negative component (i.e. lower neuronal activity) that precedes the evoked response which may represent a release of tonic inhibition (see Fig. 6A, and Fig. 7A,). In the Go-NoGo task, the absence of a negative component may reflect ongoing tonic inhibition. Beside the absence of the negative component, the evoked responses are also narrower in the context of movement inhibition than the same evoked responses with the context of movement facilitation (see Fig. 7B, upper row). This shorter response might represent the readiness of the STN to the anticipated inhibitory signal. Another supporting finding for decreased fluctuations of neuronal activity as a mechanism that facilitate the movement inhibition is the correlation between level of neuronal activity before the tone and the ability to inhibit movement in the Go-NoGo task. Decreased neuronal activity before the inhibitory signal in the Go-NoGo test is correlated with the inability to inhibit the movement, i.e., commission error, while higher neuronal activity before the inhibitory signal is correlated with the inhibition of movement, i.e., correct rejection (see Fig. 8).

Our interpretation that the level of modulation in STN activity correspond with the level of action control (i.e. context of movement facilitation vs. context of movement inhibition) is supported by recent studies. Greenhouse et al. (2015) reported that the level of motor-evoked potentials inhibition during response preparation is sensitive to response complexity. Fischer

et al. (2016) described a cortical mechanism of decreased amplitude in the movement response when adding anticipation to movement inhibition to regular repetitive tapping. They reported that successful motor inhibition is associated with increased beta power activity in the parietal region EEG prior to the inhibitory signal. Benis et al. (2014) reported that un-successful motor inhibition trials have relatively lower beta-band (13-35Hz) LFP activity in the STN after cue onset. The level of STN LFP beta power modulation during movement is also correlated with motor performance (Androulidakis et al., 2007, Tan et al., 2015, Fischer et al., 2017b). However, these reports are based on STN or cortical LFP, while our results represent the rate and pattern of multiunit activity.

3. Error monitoring in the STN in the context of movement inhibition

The basal ganglia play a major role in reinforcement learning by monitoring the error between the prediction and the actual outcome. Animal studies suggest that dopaminergic neurons fire shortly around the prediction and reward times and the magnitude of their firing rates encodes the difference (error) between the prediction and the actual outcome (Wise et al., 1989, Schultz et al., 1992, Pizzagalli et al., 2008, Joshua et al., 2009b). More specifically, dopaminergic neurons have a role in error monitoring of movement feedback (Morris et al., 2006, Joshua et al., 2009a). Although the STN receives only small fraction of dopaminergic projections compared to the striatum (Rommelfanger et al., 2010), several studies in rats and recently also in human subjects reported that the STN also participates in error monitoring (Lardeux et al., 2009, Baunez et al., 2011, Lardeux et al., 2013, Bastin et al., 2014, Tan et al., 2014, Breysse et al., 2015). The analysis of responses that are aligned to press in our study allows a focus on the post-press neuronal activity changes that represent the error monitoring phase in the STN. The DLOR post-press period probably represents the motor execution feedback. The post-press period is characterized by an increased neuronal activity both in the context of movement facilitation (All-Go task) and movement inhibition (Go-NoGo task, see Fig. 6B and Fig. 7B, upper rows). In contrast to the DLOR, the post-press feedback period in the VMNR depends on the movement context. In the context of movement facilitation (All-Go task) the feedback phase is characterized by a decreased neuronal activity. However, in the context of movement inhibition (Go-NoGo task) the feedback period has additional meaning of whether the press was correct or not (error monitoring). In presses after no-go cue, the press is incorrect, therefore there is an error feedback and the after press period is characterized by increased activity (Fig. 6B lower rows). Although we do not have alignment to press after correct rejection response (because there is no press) the response aligned to tone shows an elongated increased amplitude

in commission error response compared to correct rejection response (Fig. 8 B). This differential response may represent the level of error ("oops response"(Lardeux et al., 2009)). The feedback to the go cue in the Go-NoGo task is on the one hand motor feedback or preparation for the next press (= decreasing neuronal activity, as in the All-Go context) and on the other hand error monitoring feedback (whether the press was correct or not) that is mediated by an increase in neuronal activity. Therefore, the net response to the go cue in the Go-NoGo task is no change in neuronal activity.

Study limitations

The most obvious limitation of our study is that electrophysiological investigations in Parkinson's disease patients cannot necessarily be generalized to healthy subjects. Beside the motor symptoms, Parkinson's disease patients exhibit a decline in response inhibition and other deficits that are related to our tasks like attention shift, error monitoring, ability to learn from negative decision outcomes and multitasking performance (Witt et al., 2004, Frank et al., 2007, Castner et al., 2008, Obeso et al., 2013, Muralidharan et al., 2016). STN electrophysiology might be influenced by Parkinson's disease's motor, emotional and cognitive symptoms (Cassidy et al., 2002, Levy et al., 2002, Kuhn et al., 2004, Priori et al., 2004, Eitan et al., 2013, Rappel et al., 2018). The basal STN neuronal activity in Parkinson's disease might be higher than healthy subjects. The STN capacity may be more limited in Parkinson's disease, the processes of movement facilitation and inhibition may be impaired and the error monitoring activity may be altered due to the change in dopamine level.

To avoid learning effects of different tasks we recorded only one task per participant in this study. A limitation of this method is that no recording from the same cell or STN domain in the same patient in different tasks is available. However, the advantage of this study over many LFP studies in the STN is microelectrode recordings with a discrete, small and accurate sampling area and the differentiation to sub-territories of the STN.

Conclusions

In conclusion, we show here that the human ventro-medial STN prepares for a possible inhibitory signal by selectively decreasing the activity modulation associated with movement. In the context of movement inhibition, the response amplitude to the release (go) cue decreases (compared to the same signal in the All-Go task) rather than increase in the response amplitude to the inhibitory (no-go) cue. The reduced response amplitude to the go signal might represent an STN mechanism for discrimination between go and no-go cues when a further increase in

the response to the no-go cue is limited. The smaller amplitude of the response to the release (go) cue in the context of motor inhibition is mainly due to a smaller negative component in the evoked response. The smaller negative component may result from two possible mechanisms. First, a larger negative component (decrease in neuronal activity) represents movement facilitation while a smaller negative component enables a preparation for possible movement inhibition. Second, the smaller negative component may result from the error monitoring process that occurs after the press and mediated by the level of increase in neuronal activity. Finally, our results reveal that the non-motor domain of the STN participates in movement control and therefore should not be completely avoided during targeting of DBS contacts for the treatment of Parkinson's disease.

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Tables and Figures:

	None-Go	All-Go	Go-NoGo	p value
Demography and clinical state				
Number of participants	7	7	29	
Males:Females	4:3	5:2	16:13	
Age (years) (mean ± sd)	67 ± 6.27	62.14 ± 9.08	62.21 ± 8.33	p = .22, F(2,40) = 1.55
Disease Duration (years) (mean ± sd)	14 ± 6.1	9.33 ± 4.03	8 ± 3.37	p = .02, F (2,37) = 4.37
UPDRS III Off Medications (mean ± sd)	43 ± 19.6	37.8 ± 12.79	43.17 ± 15.17	p = .52, F(2,34) = .66
UPRDS III On Medications (mean ± sd)	16.6 ± 7	11.2 ± 1.64	14.96 ± 11.44	p = .70, F (2,34) = .36
LED (mg/day) (mean ± sd)	1014 ± 348	782 ± 274	703 ± 453	p = .47, F (2,38) = .76
ACE (mean ± sd)	80.17 ± 9.43	81.71 ± 13.16	84.09 ± 10.58	p = .53, F(2,36) = .64
FAB (mean ± sd)	13.75 ± 2.06	13.57 ± 3.15	15.48 ± 3.41	p = .27, F(2,34) = 1.37
Participants and recording sites numbers				
Dorso-lateral oscillatory region (DLOR)				
Participants no.	5	5	23	-
Recording site no.	14	13	39	-
Ventro-medial non-oscillatory region (VMNR)				
Participants no.	45	5	26	-
Recording site no.	14	13	80	-
Total STN				
Participants no.	7	7	29	-
Recording site no.	28	26	119	-
Recording site per participant (mean ± sd)	4 ± 1.9	3.71 ± 2.473	4.0 ± 2.17	-
Behavioral results				
Press rate				
Frequent tone	-	89%	94%	p = .025 d = -2.26
Deviant tone	-	85%	37%	p < .0001 d = 8.95
Reaction time (seconds, mean ± sd)				
Frequent tone	-	0.291 ± 0.07	0.413 ± 0.16	p = .0105 d = 2.62
Deviant tone	-	0.367 ± 0.13	0.307 ± 0.19	p = .11 d = -1.61
Pre-tone press rate				
Frequent tone	-	10.6%	3.6%	p < .0001 d = -5.16
Deviant tone	-	8.8%	9.9%	p = .78 d = .269

Table 1. Demographic Details, Number of Participants and Recording Sites and Behavioral Results in Different Tasks

Demographic details: demographic details and clinical state for each of the participants were collected and the average and standard deviation values were calculated for the participants within each task paradigm group. Comparison for any effect of the demographic details and clinical state between the groups was conducted by one way ANOVA. Some of the data about clinical state was missing for several patients that were evaluated by other medical centers.

The numbers of recording sites and participants: each patient participated only in one of the task paradigm, but repeated the task several times in different recording sites within the STN. In most cases, in each session that the participant preformed the task, there were two parallel recording electrodes and each electrode was considered as one recording site.

Behavioral results: the behavioral results (press rate, correct / incorrect responses and reaction time) refer to the total STN recording sites. No significant changes were found between behavioral results recorded in the DLOR and VMNR. p values of the behavioral results are for two sample t-test. The variables for the two-sample t-test are the average of each recording site (i.e. average press rate, reaction time or pre-tone press rate for each recording site).

Abbreviations: UPDRS-III- Unified parkinsonian rating scale, part III; LED-Levodopa equivalent dosage; ACE- Addenbrook's cognitive examination; FAB-Frontal assessment battery.

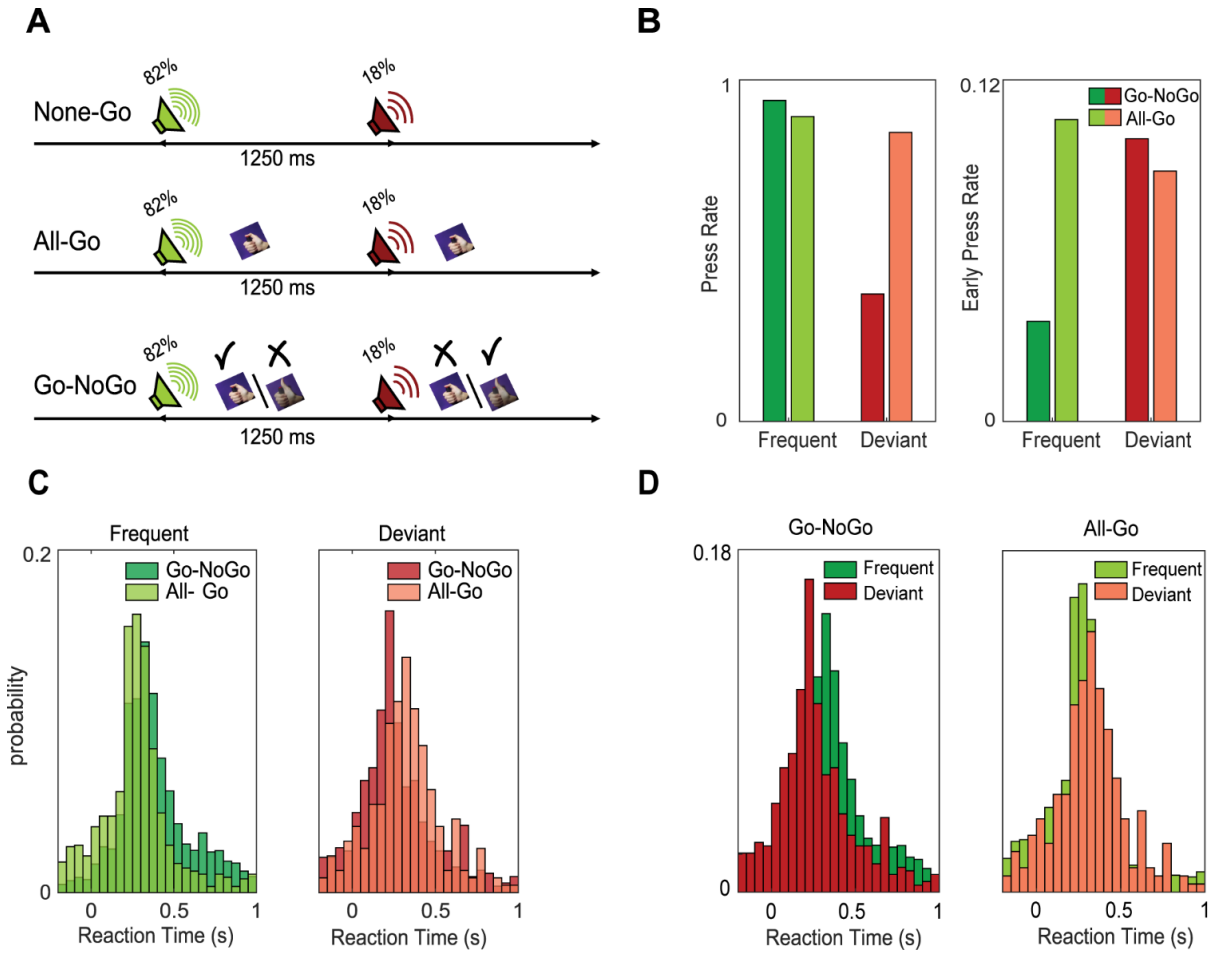

Figure 1. Task Paradigm and Behavioral Results

A. Task paradigm: None-Go - The subject passively listened to a played oddball paradigm. All-Go - The subject was also instructed to press a handed button as fast as possible after each tone of the played oddball paradigm. Go-NoGo - The subject was instructed to press the button as soon as possible only after the frequent tone, and to avoid press after deviant toe. **B.** Press rate and early press rate to the frequent (green) and deviant (red) tone in the All-Go (light) and Go-NoGo (dark) tasks**.** Early press was defined as press that was 0-200ms before tone onset**.** **C.** Distribution of the reaction times in the All-Go (light green/red) and Go-NoGo (dark green/red) tasks to the frequent (left) and deviant (right) tones. **D.** Distribution of the reaction times of the frequent and deviant tones in the GoNoGo and All-Go tasks. Reaction time statistics was calculated on the mean reaction time from each recording site to avoid repetitive measures. Reaction time was significantly different for the frequent tones (p=.025 two sample t-test) and non-significantly different for the deviant tones (p=.11, two sample t-test).

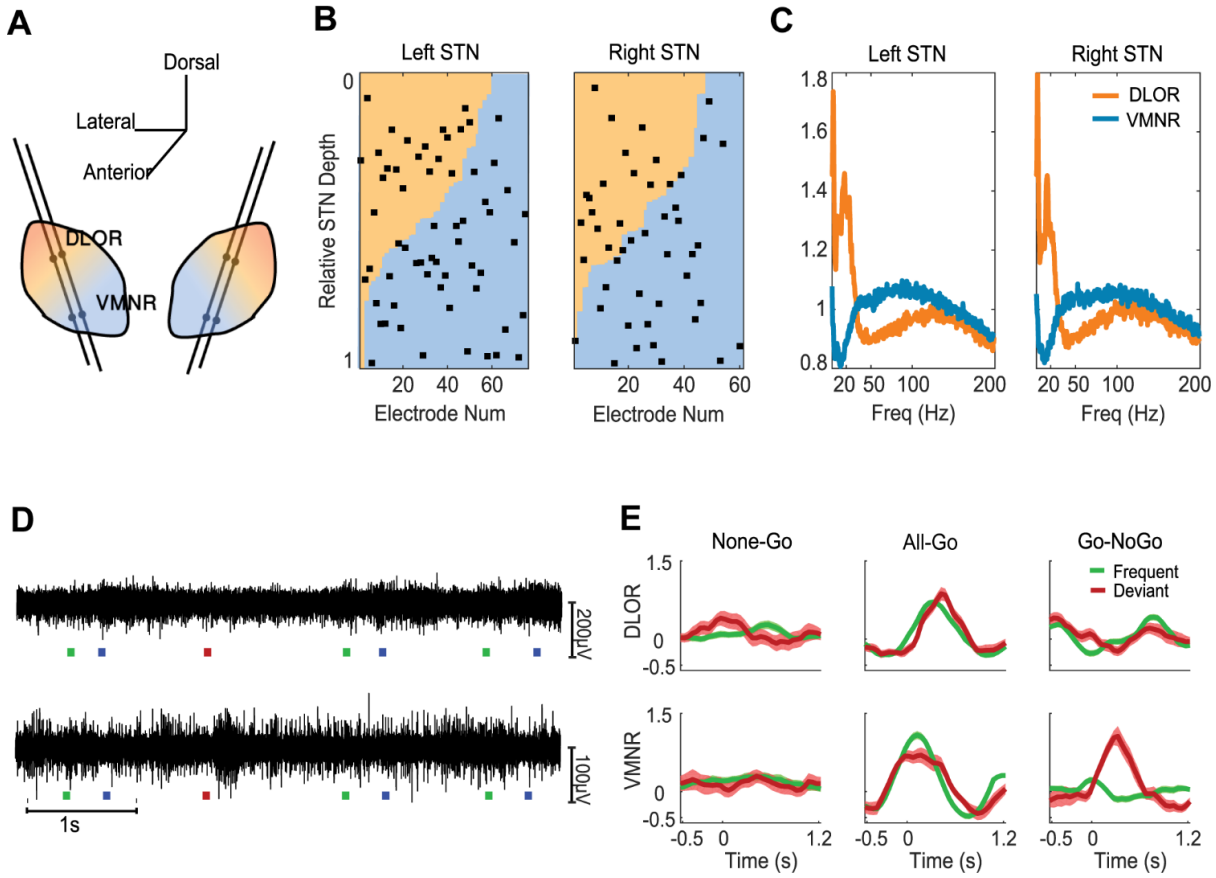

Figure 2. Recording Methods

A. Scheme of the recording trajectories location in the STN. **B.** Distribution of recording locations along STN trajectories. Recording locations are presented by decreasing DLOR proportion and normalized by STN length. DLOR and STN length were automatically detected by hidden markov model (HMM) algorithm. **C.** The mean power spectral density (PSD) of all recording depths that were categorized as DLOR (orange) and VMNR (light blue). D&E show recording sites and trajectories in the Go-NoGo task. The recording sites were similarly distributed in the All-Go and None-Go tasks (data not shown). **D.** Examples of 5 seconds microelectrode high filtered signal (300-9000Hz) during the Go-NoGo task. Colored squares in the bottom mark the times of the frequent tone (green), deviant tone (red) and presses (blue). Upper row – signal recorded at the DLOR domain. Lower row- signal recorded at the VMNR

domain. **E.** Six examples of mean post stimulus histogram (PSTH) response from one electrode (each from different electrode) in the different tasks at the two sub-regions of the STN. Upper row - recordings from the DLOR domain. Lower row - recordings from the VMNR domain. Abbreviations: DLOR -Dorsolateral oscillatory region. VMNR – ventromedial non-oscillatory region.

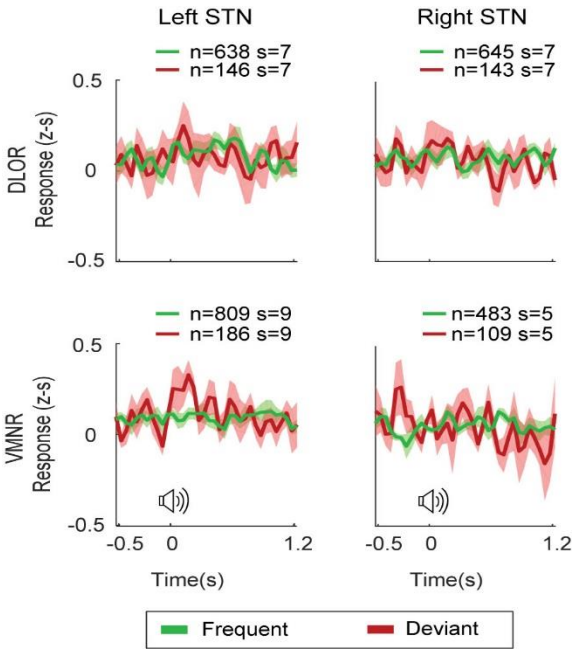

Figure 3. Small Response in the None-Go Task

Mean Z-scored (z-s) post stimulus histogram (PSTH) responses of microelectrode multi-unit recordings ± standard error of mean (SEM) aligned to tone in the left and right DLOR (upper row) and VMNR (lower row). n, number of trials; s, number of recording sites.

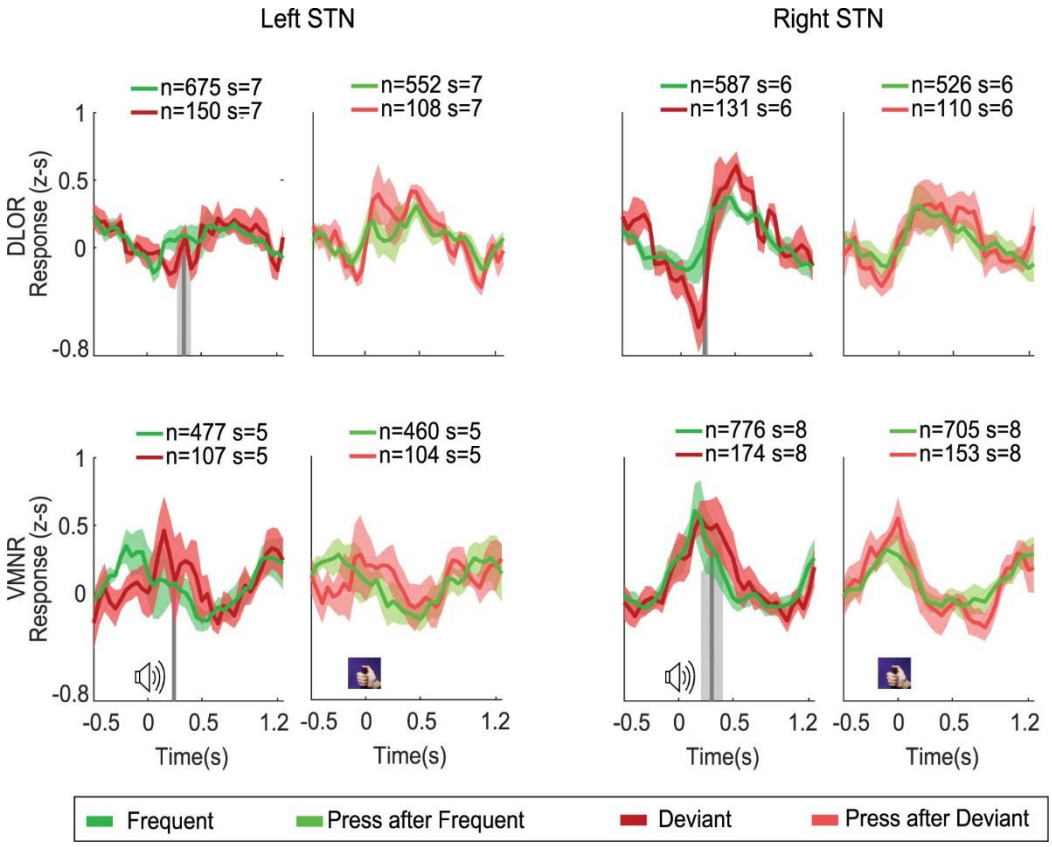

Figure 4. Similar Responses to the Frequent and Deviant Tones in the All-Go Task

Mean Z-scored post stimulus histogram (PSTH) responses of microelectrode multi-unit recordings ± standard error of mean (SEM, shadow) aligned to the time of tone (left) and time of press (right) in the left and right STN, DLOR (upper row) and VMNR (lower row). Gray vertical lines are the mean reaction time of the frequent tone with its standard deviation (shadow). Green and red lines are the frequent and deviant tones respectively aligned to the time of the tone; light red and light green lines are the frequent and deviant tones respectively aligned to the press. n, number of trials; s, number of recording sites.

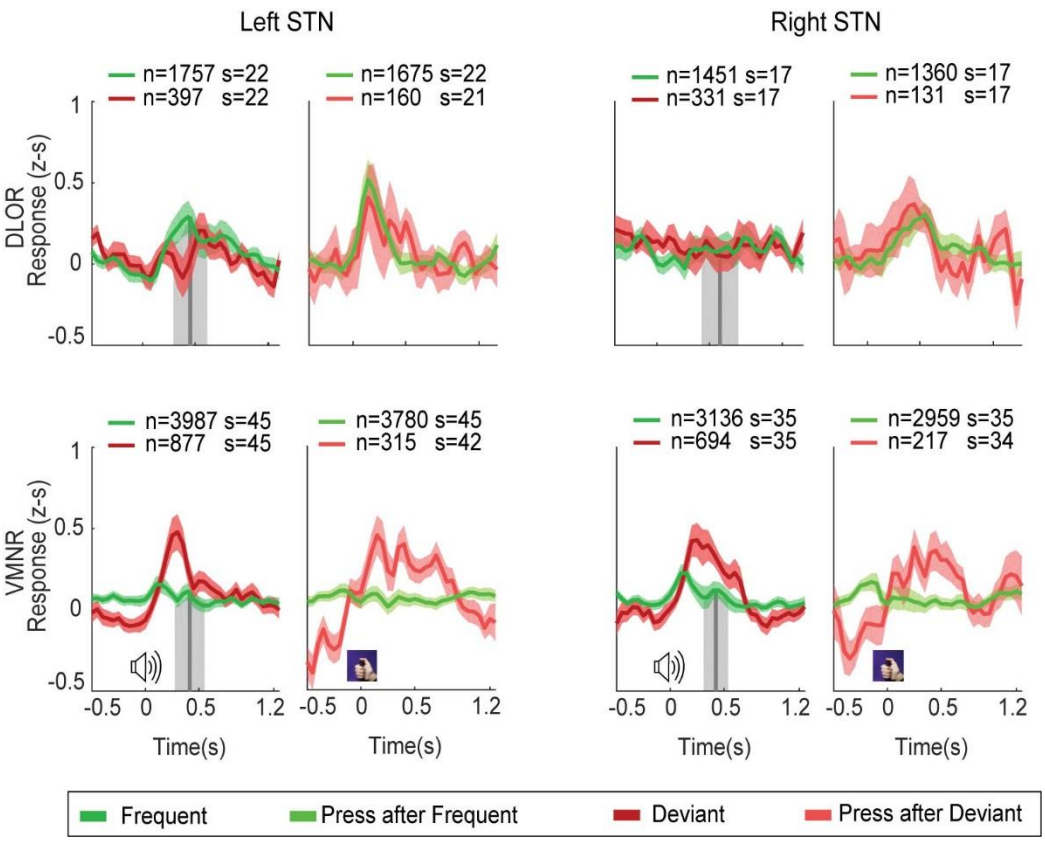

Figure 5. Smaller Response to the Frequent Tone in the Go-NoGo Task, in the Ventro-medial STN

Mean Z-scored post stimulus histogram (PSTH) responses of microelectrode recordings± standard error of mean (SEM, shadow) aligned to the tone (left) and to the press (right) in the left and right STN, DLOR (upper row) and VMNR (lower row). Gray vertical lines are the mean reaction time of the frequent tone with its standard deviation (shadow). Green and red lines are the frequent and deviant tones respectively aligned to the time of the tone; light red and light green lines are the frequent and deviant tones respectively aligned to the press. n, number of trials; s, number of recording sites.

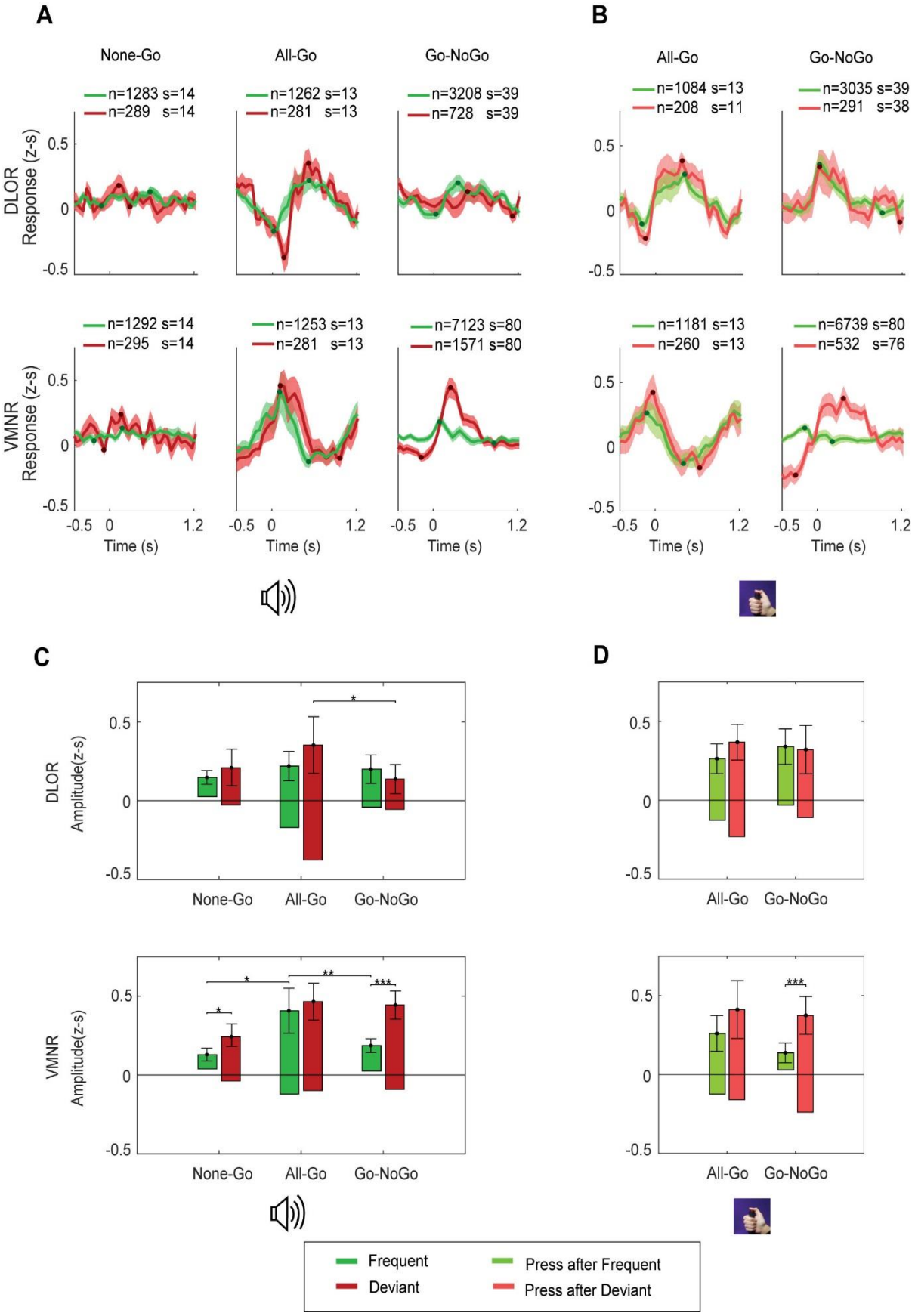
A
None-Go
All-Go
Go-NoGo
n=1283 s=14
n=289 s=14
n=1262 s=13
n=281 s=13
n=3208 s=39
n=728 s=39
DLOR Response (z-s)
n=1292 s=14
n=295 s=14
n=1253 s=13
n=281 s=13
n=7123 s=80
n=1571 s=80
VMNR Response (z-s)
Time (s)
B
All-Go
Go-NoGo
n=1084 s=13
n=208 s=11
n=3035 s=39
n=291 s=38
n=1181 s=13
n=260 s=13
n=6739 s=80
n=532 s=76
C
DLOR Amplitude(z-s)
VMNR Amplitude(z-s)
None-Go
All-Go
Go-NoGo
D
Frequent
Deviant
Press after Frequent
Press after Deviant

Figure 6. Response to the Frequent Tone in the VMNR Decrease in the Context of Movement Inhibition

A. Average PSTH (post stimulus histogram) response to the tone in the DLOR (upper row) and VMNR (lower row) from all recording sites (left and right STN together) in the three tasks, aligned to tone. Shadows represent standard error of the mean. Darker dots represents the times taken for amplitude measure. N, number of trials; s, number of recording sites. **B.** Average PSTH (post stimulus histogram) response aligned to the press. Same convention as in A. **C.** Amplitudes of the averaged responses aligned to tone in each task at the DLOR (upper row) and the VMNR (lower row). **D.** Amplitudes of frequent and deviant averaged responses aligned to press for the All-Go and Go-NoGo tasks at the DLOR (upper row) and VMNR (lower row). The amplitude of the averaged signal is defined as the difference between the maximal peak and the minimal trough of the evoked response. Statistical difference between the tasks is calculated by a one-way ANOVA on the amplitudes of each response at the times of the averaged response's maximal and minimal points. Post Hoc statistical analysis is calculated with bonferroni correction. Statistical differences between the tones in each task are calculated by paired t-test.

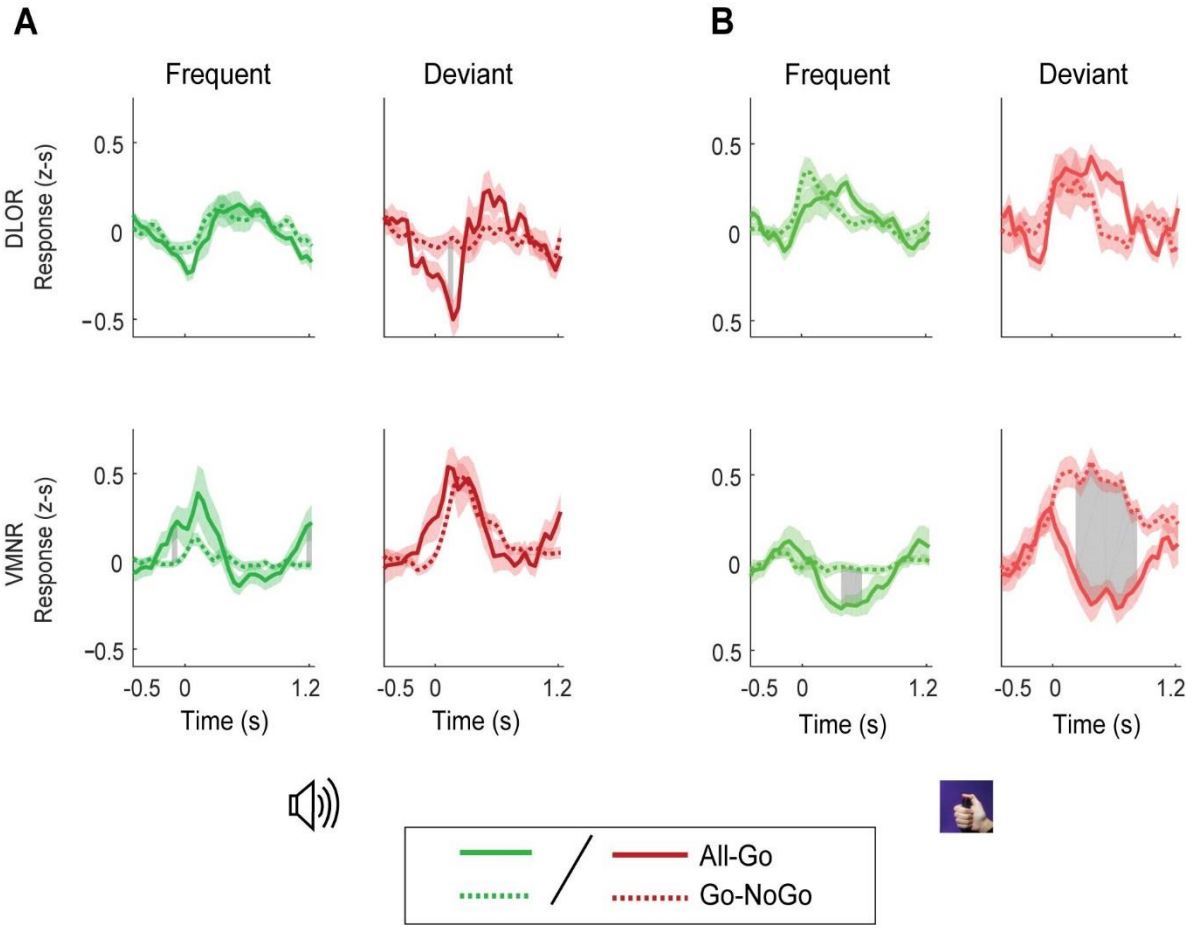

Figure 7. Disappearance of the Responses' Negative Phase in the Context of Movement Inhibition

A. Mean PSTH response of all recording sites aligned to the tone in the All-Go (solid line) and Go-NoGo (broken line) for the frequent (green) and deviant (red) tones. The responses are normalized by subtraction of the mean activity at the time before tone onset (-500:-100ms). **B.** Mean PSTH response of all recording sites aligned to the press. Same convention as in A. Gray area indicates time bins in which the difference between the All-Go and Go-NoGo tasks is significant (paired t-test $p<0.05$ after FDR (false discovery rate) correction).

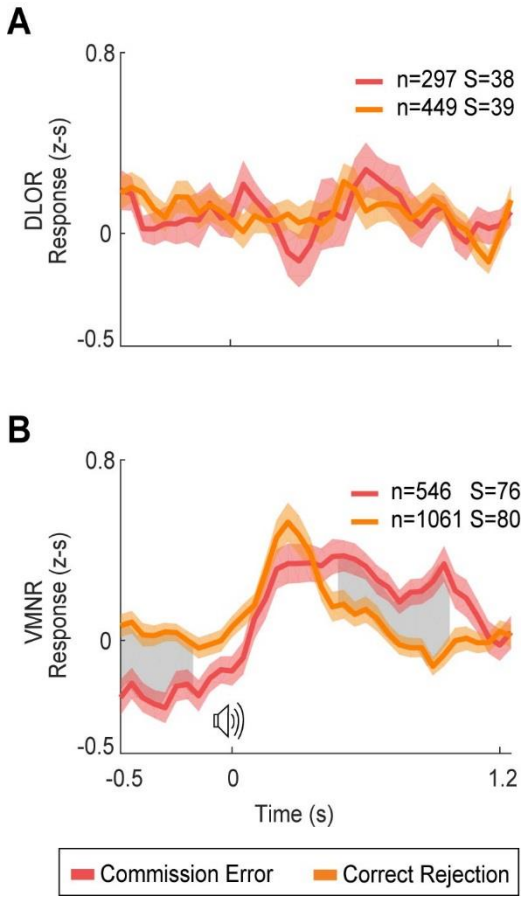

Figure 8. Differences between Correct Rejection and Commission Error Responses in the Go-NoGo task

Mean PSTH responses of all recording sites for trials of correct rejection (orange) and commission errors (pink) in response to the No-Go signal in the Go-NoGo task in the DLOR (A) and VMNR (B). Shadows represent standard error of the mean. Gray area indicates time bins in which the difference between the commission error and the correct rejection responses is significant (two sample t-test $p<0.05$ after FDR (false detection rate) correction). n, number of trials; s, number of recording sites.