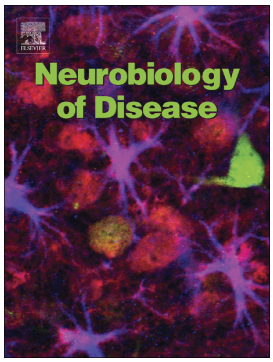

Movement context modulates neuronal activity in motor and limbic-associative domains of the human parkinsonian subthalamic nucleus

Odeya Marmor, Pnina Rappel, Dan Valsky, Atira S. Bick, David Arkadir, Eduard Linetzky, Or Peled, Idit Tamir, Hagai Bergman, Zvi Israel, Renana Eitan

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Movement context modulates neuronal activity in motor and limbic-associative domains of the human parkinsonian subthalamic nucleus

Odeya Marmor [1], Pnina Rappel [1,2], Dan Valsky[1,2], Atira S Bick [1,3], David Arkadir[3], Eduard Linetzky[3], Or Peled[3], Idit Tamir [3,4], Hagai Bergman [1, 2, 3], Zvi Israel [3,4], Renana Eitan [1,3,5,6]

1 Department of Medical Neurobiology (Physiology), Institute of Medical Research – Israel-Canada, the Hebrew University-Hadassah Medical School, Jerusalem, Israel

2 The Edmond and Lily Safra Center for Brain Research, the Hebrew University, Jerusalem, Israel

3 The Brain Division, Hadassah–Hebrew University Medical Center, Jerusalem, Israel

4 The Center for Functional and Restorative Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

5 Neuropsychiatry Unit, The Jerusalem Mental Health Center, Jerusalem, Israel

6 Functional Neuroimaging Laboratory, Brigham and Women's Hospital, Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Corresponding author: Odeya Marmor, Department of Medical Neurobiology (Physiology), The Hebrew University-Hadassah Medical School, Ein Karem Campus, PO Box 12272, 91120 Jerusalem, Israel. E-mail: *odeya.marmor@gmail.com*

Running title: Movement context affects STN activity

Abstract:

The subthalamic nucleus (STN), a preferred target for treating movement disorders, has a crucial role in inhibition and execution of movement. To better understand the mechanism of movement regulation in the STN of Parkinson's disease patients, we compared the same movement with different context, facilitation vs. inhibition context. We recorded subthalamic multiunit activity intra-operatively while parkinsonian patients (off medications, n=43 patients, 173 recording sites) performed increasingly complex oddball paradigms with frequent and deviant tones: first, passive listening to tone series with no movement ('None-Go' task, n=7, 28 recording sites); second, pressing a button after every tone ('All-Go' task, n=7, 26 recording sites); and third, pressing a button only for frequent tones, thus adding inhibition of movement following deviant tones ('Go-NoGo' task, n=29, 119 recording sites).

The STN responded mainly to movement-involving tasks. In the limbic-associative STN, evoked response to the deviant tone (inhibitory cue) was not significantly different between the Go-NoGo and the All-Go task. However, the evoked response to the frequent tone (go cue) in the Go-NoGo task was significantly reduced. The reduction was mainly prominent in the negative component of the evoked response amplitude aligned to the press. Successful movement inhibition was correlated with higher baseline activity.

We suggest that the STN in Parkinson's disease patients adapts to movement inhibition context by selectively decreasing the amplitude of neuronal activity. Thus, the STN enables movement inhibition not by increasing responses to the inhibitory cue but by reducing responses to the release cue. The negative component of the evoked response probably facilitates movement and a higher baseline activity enables successful inhibition of movement. These discharge modulations were found in the ventromedial, non-motor domain of the STN and therefore suggest a significant role of the limbic- associative STN domains in movement planning and in global movement regulation.

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), False Discovery Rate (FDR), Local Field Potential (LFP), Post Stimulus Histogram (PSTH),

Subthalamic Nucleus (STN), Ventromedial Non- oscillatory Region (VMNR).

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 has been 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). Response inhibition is associated with the ventral portion of the STN (Hershey et al., 2010). The ventral portion of the STN receives anatomical projections from associative and limbic areas (Karachi et al., 2005, Haynes et al., 2013) and has a role in emotional processing (Eitan et al., 2013), controlling obsessive compulsive behavior (Rappel et al., 2018) and error monitoring (Bastin et al., 2014). In addition to its role in movement inhibition, the STN is involved in 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 involves the global regulation of readiness for movement which depends on the context of the movement. For example, in the cortex 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 eminently suitable for this 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. Thus, the STN could 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 in parkinsonian and normal state (Kuhn et al., 2004, Aron and Poldrack, 2006, Alegre et al., 2013, Schmidt et al., 2013, Benis et al., 2016, Pasquereau et al., 2017). These studies compared no-go and go trials or successful and 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) and stop vs switch signal (Pasquereau and Turner, 2017), STN-mediated mechanisms of readiness for movement in the context of motor execution or inhibition has not been well studied.

In Parkinson's disease patients, STN electrophysiology may be influenced by the 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 parkinsonian non-human primate model is higher than in normal non-human primates (Bergman et al., 1994, Deffains et al., 2016) and the evoked responses are larger to movement (Filion et al., 1988, Bergman et al., 1994).

In this study we compared human STN multiunit activity in Parkinson's disease patients on oddball tasks with three levels of movement: first, passive listening ('None-Go' task: no movement); second, adding presses to all tones ('All-Go' task: movement within a facilitation context); and third, adding inhibition of movement after the deviant tones ('Go-NoGo' task: movement within an 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 enabled the investigation of the role of the parkinsonian 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 deep brain stimulation (DBS) took part in this study. All patients met the accepted inclusion criteria for DBS surgery and gave their 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, a series of 120 tones with two different pitches were played in a pseudo-random order. The frequent tones (82% of the played tones) were delivered at a high pitch (1200Hz) and the deviant tones (18% of the played tones) were delivered at a low pitch (300Hz). The tone duration was 250ms followed by a 1000ms pause (the total inter trial interval was 1250ms) and the total duration of the task was 2.5 minutes. The difference between the tasks was the instruction to the participants: 1.

'None-Go' task: Participants were awake and were not informed about the task; i.e., the tones were played without any instruction to the participants. 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 not to press the button after the deviant tones.

All patients reported right hand dominance. Participants were asked to press the button using their right thumb or index finger while recordings were collected 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 the patients, the Go-NoGo group of patients were trained on the task prior to surgery. Responses on the All-Go task and following the go cue (frequent tone) on the Go-NoGo task were classified as correct responses whereas the responses subsequent to the no-go cue (deviant tone) on the Go-NoGo task were classified as commission errors (incorrect responses). The experiment had three phases. In the first phase, all subjects performed the Go-NoGo task. In the second phase, all subjects performed the All-Go task. In the third phase, all subjects performed the None-Go task. The patients were not randomized into the study group.

Neuronal data were 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 preferable. However, recordings during surgical navigation are limited by the additional clinical risks 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 recording session. To further minimize the clinical risk, the total recording time for research purposes for each patient was limited to ten minutes. Therefore, each patient was engaged in only one task, which 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).

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 of approximately 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 into 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. 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 recordings included both the dorsolateral oscillatory region (DLOR, sensorimotor domain) and ventromedial non-oscillatory region (VMNR, limbic-associative domain) of the STN. STN DLOR length was 2.0±1.6 mm and 2.1±1.6 mm (mean±SD) for right and left STN, respectively.

Detection of the STN entry and exit as well as differentiating between the DLOR and the VMNR of the STN were automatically delimited by a hidden Markov model (HMM, Zaidel et al., 2009). The sub-division to DLOR and VMNR, based on beta oscillatory activity, has been recently further supported by a DBS lead localization study. This study, has shown that the DLOR area, characterized by LFP beta activity is connected with sensory-motor cortical projections (Horn et al., 2017). Recording locations in the STN subdomains are presented in Fig. 2A-B. Each recording site was classified according to the automatic HMM algorithm and verified / corrected by an experienced electrophysiologist (OM, Fig. 2C). Only 173 out of 196

recording sites that could be defined with certainty within the STN were included in the analysis. Further sub-division was made to recording sites that fell in the border area. We defined the border area as the 1mm that surrounds the DLOR-VMNR transition. The DLOR border area was defined as 0.5 mm above the DLOR-VMNR transition and the VMNR border area was defined as 0.5 mm below the DLOR-VMNR transition. The DLOR border area included 20% of the total DLOR recordings while the VMNR border area included 15% of the total VMNR recordings. These border recording sites exhibited mixed DLOR and VMNR responses (see supplementary Fig. S1). However, the statistical analysis excluding and including the DLOR-VMNR border area yielded similar results and therefore the border area was included in final analysis.

In this study, evoked responses were based on microelectrode multiunit activity recordings. These multiunit STN recordings roughly sense 1-3 nearby cells and smaller background activity of a wider population. The multiunit activity is band-passed filtered in the range of 250-6000 Hz (or 300-9000Hz), enabling good separation from the local filed potentials that are mostly in the low frequencies (below 200Hz). The common source of spiking activity recorded by two STN microelectrodes, separated by 2 mm, is estimated to be about 5% (see Marmor et al, 2017). Therefore, STN microelectrodes enable recordings of activity generated by discrete and small sampling areas.

Signal processing and analysis

Response time: In this study, response time was defined as the time from tone onset to the actual press. Many (5-14%) anticipatory (pre-tone) presses were detected, probably due to the rhythmic nature of the tasks (see Table 1 and Fig 1 C,D). The distribution of the response times showed a second peak of anticipatory presses at 1050-1250ms after the tone on the Go-NoGo and All-Go tasks (Fig. S2). Therefore, a press of 1050ms or longer after one tone was considered an anticipatory press for the next tone. We did not exclude trials with anticipatory presses form the analysis. To avoid bias caused by repeated measures (Vasey et al., 1987), the average response time was calculated for each session (i.e. a series of 120 tones).

Peri-stimulus histogram (PSTH): In each recording site the signal was divided into traces starting 500ms before the tone or press time and ending 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 a 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 the standard deviation (Rousseeuw et al., 1993)). Modified Z-score was chosen because it is less affected by extreme values than Z-score. The data consisted of relatively short trials and long responses that sometimes lasted most of the trial duration; therefore, we chose the more resilient modified Z-score transformation. Trials were aligned to tone onset and to press time and categorized into frequent or deviant tones. The mean of all trials (modified Z-scores of the root mean square as a function of time) was calculated for each recording site. Then, the modified Z-scores were averaged for all recording sites in the same sub-area of the STN. Different analysis methods (median calculated for all recording sites and mean and median calculated for all traces) yielded similar results. In order to measure the evoked response in the different categories for statistical comparison, we quantified two parameters: amplitude and latency. The amplitude of each response was based on the values that fell at constant times, according to the peak and trough of the average response at each category, and not by the peak and trough of each recording site (see Fig. 5A, B, darker dots mark the maximal and minimal points).

The evoked response latency was defined as the time of the maximal peak detected in each recording site in the range of 200ms before tone onset to 1000ms after tone onset, in accordance to the above definition of response time.

The neuronal-motor time lag was defined as the differences between the evoked response peak latency and response time i.e. 'neuronal-motor time lag' = evoked response latency - response time. This measure was set in order to assess whether neuronal responses precede or follow the press.

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

Statistics and software

Patients' demographics in all three groups were compared by one-way ANOVAs. For each session of the All-Go and Go-NoGo tasks, we calculated the average response time, the average press rate and the average early-press rate for frequent and deviant tones. We tested differences in response time, press rate and early press rate by a mixed design ANOVA with the task (All-Go, Go-NoGo) as the between- subject factor and the tone (frequent, deviant) as

the within- subject factor. To test whether there is any clinical effect on behavioral response, we tested the correlation of clinical scores with response time and pressing rate using Spearman's rank-order correlation with a Bonferroni correction for multiple comparisons, for the Go-NoGo task (the largest group size).

Neuronal data: We measured two parameters of the evoked response: amplitude and latency of peak. First, clinical, behavioral and anatomical data were correlated with neuronal response (evoked responses amplitude and latency) using Spearman's rank-order correlation with a Bonferroni correction for multiple comparisons. Next, a two-sample t-test was conducted to compare response amplitude and latency in the left and right recording sites in both DLOR and VMNR sub-domains. We used a two-sample t-test, and not paired-sample t-test, since only 18 out of 43 patients had both left and right recording sites. After verifying that there were no significant differences between left and right STNs, the data from both STNs were united into one group. On the pooled data we conducted a two-sample t-test to compare latency differences of the evoked response peaks between DLOR and VMNR responses. To test whether the neuronal responses precede or follow the press in the DLOR compared to the VMNR we further conducted a two-sample t-test to compare the DLOR and VMNR 'neuronal-motor time lag' (i.e. evoked response latency - response time) differences. To test whether the responses in each domain were evoked by the tone or the press, we compared the evoked response amplitude aligned to tone onset versus press onset using paired sample t-test. To test which parameters best capture the variance of the amplitude aligned to tone, we used a linear mixed model with the following fixed factors: Location (DLOR, VMNR), Tone (Frequent, Deviant) and Task (None-Go, All-Go and Go-NoGo). Random effects of location and task were included, and tone was considered as a repeated effect, all with unstructured covariance. Main effects of Location (DLOR, VMNR), Tone (frequent, deviant), Task (None-Go, All-Go and Go-NoGo) and their pairwise interaction as well as the interaction between location*tone*task were included. The same model was used for the amplitudes of the evoked responses aligned to the press, but with only two task parameters (All-Go and Go-NoGo). A linear mixed model for this analysis was used because the task and location samples were unbalanced, i.e., the Go-NoGo group was larger than the other groups and only 29 out of 43 patients had both DLOR and VMNR locations.

To further compare the pattern of All-Go and Go-NoGo responses, a paired sample t-test on each of the PSTH 50 ms bins in the trial was conducted, followed by FDR correction for multiple comparisons, and repeated for each tone (frequent/deviant) and alignment (tone/press).

In the Go-NoGo task, we further divided the response to the deviant tones into successful (correct rejections) and unsuccessful (commission errors) trials. A paired sample t-test followed by FDR correction for all the PSTH 50 ms bins tested the differences between the correct rejections and commission errors.

All the above analyses were 2 tailed with a significance level of $\alpha = .05$. Data was processed and analyzed using Matlab 2016b (Mathworks, Inc., Natick, MA) and using SPSS 24.0 (IBM SPSS Statistics for Windows Armonk, NY: IBM Corp).

Data availability

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

Results:

Demographics, clinical assessments, medications, number of recording sites and behavioral results are summarized in Table 1. No significant differences were found between the task groups except for disease duration (one-way ANOVA). Post-hoc test revealed that the None-Go group had longer disease duration compared to the other task groups.

Behavioral results

Press rates, anticipatory press rates and response times are presented in Fig. 1 and Table 1. Briefly, press rates were significantly higher for hits than commission errors in the Go-NoGo task (Fig. 1B left, $p<.001$, post-hoc, mixed design ANOVA). Anticipatory press rates tended to be higher for the All-Go task than the Go-NoGo task for frequent tones and tended to be higher on commission errors than hits in the Go-NoGo task (Fig. 1B right). Frequent response times were significantly shorter on the All-Go vs. Go-NoGo task, reflecting the repetitive nature of the All-Go task ($p<.05$, post-hoc, mixed design ANOVA, Fig. 1D). Response times on commission errors (after deviant tones) were faster than response times on hits (after frequent tones) only on the Go-NoGo task ($p<.001$, post-hoc, mixed design ANOVA, Fig. 1C).

We further studied the effect of trial n on the results of trial n + 1 (Gratton-type effect) on the Go-NoGo task. Response times in trials that followed no-go cues (deviant tones) were significantly longer compared to trials that followed go cues (frequent tones) on the Go-NoGo task ($p<0.001$, paired t-test, see Fig. S3 supplemental information). However, no significant differences were found in response times in trails that followed commission errors or correct rejections.

Neuronal results

An example of raw recordings (high-pass filtered) and typical responses to each of the tasks are presented in Fig. 2D-E. Average responses on the three tasks in the STN subdomains (left/right, DLOR/VMNR) are presented in the supplemental information (Fig. S4–Fig. S6). Effects of clinical scores on neuronal evoked response were tested by Spearman's rank-order correlation (Table S2). Most of the correlations were not significant after correction for multiple comparison. A significant correlation was found between the UPDRS motor score (off medication state) and the relative difference of evoked response amplitudes to frequent and deviant tones (Fig. S7). Effects of pressing rate on neuronal evoked responses are shown in Fig. S8.

Similar ipsilateral and contralateral STN evoked responses to tasks

Surprisingly, although patients pressed the button with their right thumb or index finger, evoked responses to movement were observed in both left and right STN (Fig. 3). No statistically significant difference was found between the left and right STN amplitudes aligned to the press time (Fig. 3C-D, $p>.05$, two sample t-test). Therefore, in order to decrease parameter number on comparison across tasks, we pooled the left and right STN recording sites in the next analysis.

The VMNR corresponds with movement planning while the DLOR corresponds with movement execution

Our results indicate that the VMNR response is related to movement planning while the DLOR response is more related to movement execution. This difference is revealed by different timing of neuronal activity (planning occurs before execution) and by differential neuronal activity correspondence to movement planning (hearing the tone) and execution (pressing the button). First, the DLOR and VMNR respond to the tasks with different timing, as can be seen in the example of simultaneous recordings in the DLOR and VMNR (Fig 4A). The evoked response peak latency was shorter in the VMNR than DLOR in all the go cue scenarios ($p<.001$, $p<.01$ and $p<.05$ for the frequent All-Go, deviant All-Go and frequent Go-NoGo, respectively; two sample t-test, Fig. 4B). Similarly, the VMNR evoked response peak latency preceded the response times while the DLOR evoked response peak latency followed the response times ($p<.001$, $p<.01$ and $p>.05$ for frequent All-Go, deviant All-Go and frequent Go-NoGo, respectively; two sample t-test, Fig. 4C).

Second, the evoked response peak amplitude in the DLOR corresponds differently to hearing the tone (movement planning) or pressing the button (movement execution). The DLOR

evoked response peak amplitudes aligned to press was significantly larger compared to evoked response peak amplitudes aligned to tone in the Go-NoGo task (0.62±0.4 vs. 0.72±0.4, paired t-test $p<.001$, Fig 4E). The VMNR evoked response peak amplitudes were not significantly different when aligned to press or tone ($p>.05$, Fig. 4D-E and tended to be larger aligned to tone).

VMNR response to a go cue decreases in the context of movement inhibition

As demonstrated in Fig. 5, in the VMNR, the evoked response amplitude in the Go-NoGo task was modulated by tone, lower for the frequent tones than for the deviant tones ($p<0.001$, post-hoc with Bonferroni correction, linear mixed model, Fig. 5C, F). More interestingly, in the VMNR the evoked response amplitude in response to the frequent tone was modulated by tasks, lower in the Go-NoGo tasks than in the All-Go task ($p<0.05$, post-hoc with Bonferroni correction, linear mixed model, Fig. 5F). In other words, the VMNR evoked response amplitude in response to the go cue (frequent tone) was lower in the context of movement inhibition (Go-NoGo task) comparing to the context of movement facilitation (All-Go task). These results were found both with the evoked responses aligned to tone and press (Fig. 5F, G). This differential response to the go cue in the context of movement inhibition or facilitation was found only in the VMNR but not in the DLOR.

A smaller negative component of the VMNR's evoked response to the go cue in the context of movement inhibition

To further explore the VMNR evoked response in the context of movement facilitation and inhibition, we superimposed the All-Go and the Go-NoGo evoked responses with a normalization to the time before tone or press (Fig. 6 A-D). In the VMNR, the evoked response aligned to the press in the context of movement facilitation (All-Go task) had a large negative component (i.e., a reduction in neuronal activity at 400-600ms on frequent tones and 250-850ms on the deviant tones) that was not observed in the context of movement inhibition (Go-NoGo task, see Fig. 6C-D, lower graphs, marked by gray areas, tested for significance level of $p<.05$, paired t-test after FDR correction). Note that the press in is defined as the time of button pressing, not the usual definition of reaction time that is the initiation of movement.

VMNR commission error responses are associated with lower baseline neuronal activity

We further analyzed the STN evoked responses to the no-go cue (Go-NoGo deviant tones). The differences between tone-locked evoked responses of correct rejections and commission

errors are presented in Fig. 6E. Baseline VMNR neuronal activity (500-100ms preceding the tone) was significantly lower in commission errors than correct rejections (tested for significance level of $p<.05$, paired t-test after FDR correction). The VMNR neuronal activity after the tone (500-1000ms after the tone) was significantly higher in commission errors than correct rejections (tested for significance level of $p<.05$, paired t-test after FDR correction). This implies that VMNR lower baseline neuronal activity is associated with commission errors in response to the no-go cue.

Discussion:

We show here, like previous Go-NoGo studies, that in the context of movement inhibition the human parkinsonian STN multiunit activity response to the inhibitory cue is larger than the response to the release cue. Previous studies have concluded that in the context of movement inhibition the STN increases the response to the inhibitory cue. However, our results suggest that in the context of movement inhibition the STN does not increase the response to the inhibitory cue but selectively decreases the response to the release cue. Our conclusion is supported by the significant changes in STN activity between three versions of oddball tasks. The VMNR response to the go cue in the context of movement inhibition (Go-NoGo task) is smaller than the response to the go cue in the context of movement facilitation (All-Go task). The VMNR response to the no-go cue in the context of movement inhibition (Go-NoGo task) is not significantly different from the response to the go cue in the context of movement facilitation (both frequent and deviant tones in the All-Go task). Further studying the VMNR response in the context of movement inhibition has revealed that the negative component of the evoked response probably facilitates movement and a higher baseline activity enables successful inhibition of movement. We therefore conclude that the associative-limbic STN domain, the VMNR, has an important role in movement planning and in global movement regulation.

VMNR STN corresponds to movement planning while DLOR STN corresponds to movement execution

Although the VMNR is considered the emotional-associative domain, our results indicate clear motor related evoked response. Analysis of both All-Go and Go-NoGo tasks revealed different patterns of responses in the VMNR and DLOR. This difference probably represents the different roles of the VMNR and DLOR in movement planning and movement execution. Our data supports the view that VMNR activity is related to movement planning whereas

DLOR activity is related to movement execution. First, VMNR responses preceded DLOR responses at the 'go' cues (frequent and deviant of the All-Go and frequent of the Go-NoGo). Second, VMNR responses were not correlated to execution of movement. For example, large evoked response amplitudes were observed after deviant tones in the Go-NoGo task, which on most trials, was not followed by movement. Third, DLOR responses on the Go-NoGo task were larger when aligned to the press than when aligned to the tone (Fig. 4E). Finally, DLOR responses were after response time whereas VMNR responses were before response time (Fig. 4C). The bilateral activation in response to the right thumb press (Fig. 3) also support the role of the STN in global bilateral movement regulation and not only contralateral movement execution.

Thus, this study reports the involvement of the ventral STN (non-motor domain) in movement planning that is not restricted to movement inhibition. Our results are in line with previous findings in LFP and single unit recordings. 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 has been associated with LFP activity recorded by ventral-STN located DBS contacts (Hershey et al., 2010, Alegre et al., 2013), in single units recorded from the ventral STN areas of OCD patients (Bastin et al., 2014) and non-human primates (Pasquereau and Turner, 2017). Movement inhibition, a core function in executive functions, is related to the cognitive STN sub-area. However, movement planning was less known as related to cognitive or emotional sub-areas of the STN. In contrast to the classical concepts of parallel and segregated circuits (Alexander et al., 1986), The VMNR role in movement planning implies that STN sub-areas overlap and share functions. These results strengthen recent studies that show an anatomical and functional overlap in the STN projections (Mallet et al., 2007, Haynes and Haber, 2013, Pasquereau and Turner, 2017).

Maximal neuronal response decreases in the context of movement inhibition

Surprisingly, we found that the STN evoked responses to frequent tones in the Go-NoGo task were lower than the evoked responses in the All-Go task. Previous studies that have examined inhibitory paradigms reported a stronger evoked response to an inhibitory signal and thus suggested a mechanism of 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; rather the response to the go cue decreases. We further infer that this differentiation is not due to passive auditory

discrimination process (like mismatch negativity test), but rather related to the movement context, as the evoked responses to the None-Go task had no significant difference between frequent and deviant tones. Below we discuss two possible, non-mutually exclusive explanations for the decreased STN response in the context of motor inhibition. The first focuses on the modulation of STN neuronal activity as a mechanism of facilitation and inhibition of movement. The second relates to the process of error monitoring in the STN.

1. Preparation for movement inhibition decreases the fluctuations in 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") on 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 the current study, the movement in the Go-NoGo task is more restrained due to the ongoing preparation for the no-go cue, whereas in the All-Go task the movement is freer and more rhythmic (i.e. uninterrupted) due to the fixed inter-tone interval that encourages movement anticipation. In the All-Go task, the repetitive nature of the movement is reflected behaviorally by a shorter response time and an increased percentage of anticipatory presses (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. 5B, and Fig. 6 A-D). The late negative response in the All-Go task may be the preparation for the next movement. Due to the repetitive nature of the task, the preparation for the next tone occur immediately after the current tone (Fig. 6 C-D, lower panels). In the Go-NoGo task, the absence of a negative component may reflect ongoing tonic inhibition. Another supporting finding for decreased fluctuations of neuronal activity as a mechanism that facilitates movement inhibition is the correlation between the 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 (commission errors) whereas higher neuronal activity before the inhibitory signal is correlated with the inhibition of movement (correct rejections, see Fig. 6E). Some of the effect of the lower baseline activity before the tone in the commission errors could be a result of the z-score, normalizing by the three preceding averaged frequent tone responses yielded similar results.

Our claim that the level of modulation in STN activity corresponds to the level of action control (i.e. the context of movement facilitation vs. the context of movement inhibition) is

supported by recent studies. Greenhouse et al. (2015) reported that the level of motor-evoked potential inhibition during response preparation was sensitive to response complexity. Fischer et al. (2016) described a cortical mechanism of decreased amplitude in the movement response when adding anticipation of movement inhibition to regular repetitive tapping. They reported that successful motor inhibition was associated with increased beta power activity in the parietal region EEG prior to the inhibitory signal. Benis et al. (2014) reported that unsuccessful motor inhibition trials had relatively lower beta-band (13-35Hz) LFP activity in the STN after cue onset. The level of STN LFP beta power modulation during movement was also reported to be 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, whereas the current results draw on the rate and pattern of multiunit activity.

2. 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 briefly around the prediction and reward times and that 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 play a role in error monitoring of movement feedback (Morris et al., 2006, Joshua et al., 2009a). Although the STN receives only a small fraction of dopaminergic projections compared to the striatum (Rommelfanger et al., 2010), several studies in rats and recently also in human subjects have reported that the STN is also involved 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). Changes in post-press neuronal activity might represent the error monitoring phase in the STN. In the DLOR, the post-press period might represent the motor execution feedback and is characterized by increased neuronal activity both in the context of movement facilitation (All-Go task) and movement inhibition (Go-NoGo task, see Fig. 5D-E and Fig. 6C-D, upper rows). In contrast to the DLOR, the post-press feedback period in the VMNR represents the movement decision feedback (error monitoring). In the context of movement facilitation (All-Go task) the post-press feedback phase is characterized by decreased neuronal activity (Fig. 6 C-D, lower panels, solid line). However, in the context of movement inhibition (Go-NoGo task) the feedback phase is characterized by increased activity in commission errors and decreased activity in correct rejections (Fig. 6E, lower). This differential response might represent the level of error ("oops response" (Lardeux et al., 2009)). In conclusion, motor feedback and correct movement feedback are reflected by

decreasing neuronal activity, while error monitoring feedback is reflected by an increase in neuronal activity.

Study limitations

One limitation of this study is that electrophysiological investigations in Parkinson's disease patients cannot necessarily be generalized to healthy subjects. Parkinson's disease patients exhibit a decline in response inhibition and other deficits that are related to the tasks administered here such as attention shift, error monitoring, the ability to learn from negative decision outcomes, and multitasking (Witt et al., 2004, Frank et al., 2007, Castner et al., 2008, Obeso et al., 2013, Muralidharan et al., 2016). As mentioned above, STN electrophysiology is influenced by the clinical symptoms of Parkinson's disease (Cassidy et al., 2002, Levy et al., 2002, Kuhn et al., 2004, Priori et al., 2004, Eitan et al., 2013, Rappel et al., 2018). Both basal STN neuronal activity and evoked responses are different in parkinsonian model in non-human primates comparing to healthy primates (Filion et al., 1988, Bergman et al., 1994, Deffains et al., 2016). Specifically, the bilateral activation might be due to loss of specificity in the parkinsonian state as was reported earlier in the Globus pallidus (Tremblay et al., 1989). Therefore, 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 changes in dopamine levels. The study results must be carefully interpreted, as they represent the STN activity in Parkinson's disease patients and not necessarily represent the normal STN function.

To avoid learning effects on the different tasks we recorded only one task per participant in this study. A drawback of this decision is that no recordings are available from the same cell or STN domain in the same patient on different tasks. Although patients in the None-Go group had a longer disease duration, a post hoc analysis showed that this difference was between the None-Go and the Go-NoGo group. The behavioral and neuronal results in this study refer to the other two groups, i.e., Go-NoGo and All-Go. Therefore, the difference in disease duration did not affect the behavioral and neuronal results in the Go-NoGo and All-Go groups. The unequal group size was due to the number of error signal after the deviant tone that needed to obtain.

Conclusion

Overall, our findings suggest that the human ventro-medial STN selectively decreases neuronal activity when an inhibitory signal is expected. 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 increases in the response amplitude to the inhibitory (no-go) cue. This

smaller amplitude of the response to the release (go) cue in the context of movement inhibition is mainly due to a smaller negative component in the evoked response. Our results indicate that the limbic and associative domains of the STN play an important role 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
Demographics and clinical state				
Number of participants	7	7	29	
Male : Female	4:3	5:2	16:13	
Age (years) (mean ± sd)	67 ± 6.27	62.14 ± 9.08	62.21 ± 8.33	$F(2,40) = 1.55$, p=.022
Disease Duration (years) (mean ± sd)	14 ± 6.1	9.33 ± 4.03	8 ± 3.37	$F(2,37) = 4.37$, p=.02
UPDRS III Off Medications (mean ± sd)	43 ± 19.6	37.8 ± 12.79	43.17 ± 15.17	$F(2,34) = .77$, p=.47
UPRDS III On Medications (mean ± sd)	16.6 ± 7	11.2 ± 1.64	14.96 ± 11.44	$F(2,34) = .36$, p=.70
LED (mg/day) (mean ± sd)	1014 ± 348	782 ± 27[illegible]	703 ± 453	$F(2,38) = .76$, p=.47
ACE (0-100) (mean ± sd)	80.17 ± 9.43	81.71 ± 13.16	84.09 ± 10.58	$F(2,36) = .64$, p=.53
FAB (0-18) (mean ± sd)	13.75 ± 2.06	13.57 ± 3.15	15.48 ± 3.41	$F(2,34) = 0.99$, p=>.38
Participants and numbers of recording sites				
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 ± 2.47	4.0 ± 2.17	-
Behavioral results				
Press rate (mean ± sd)				
Frequent tone	-	89 ± 14%	94 ± 9%	p < .05(p=0.146)
Deviant tone	-	85 ± 21%	37± 25%	p < .0001
Anticipatory press rate (mean ± sd)				
Frequent tone	-	13.8±12.1%	4.7±6.6%	p < .0001
Deviant tone	-	11.5±11.6%	10.8±20.4%	p >.05 (p=0.916)
Response time (seconds, mean ± sd)				
Frequent tone	-	0.29 ± 0.07	0.39 ± 0.13	p =0.11
Deviant tone	-	0.36 ± 0.13	0.30 ± 0.16	p =0.117

Table 1. Demographics, Number of Participants and Recording Sites and Behavioral Results

Demographics: demographics and the clinical state for each participant were collected and the average and standard deviation were calculated for the participants within each task paradigm group. A one-way ANOVA tested for the effects of the demographics and clinical state between groups. Some of the clinical state data was missing for several patients who were pre-operatively evaluated in other medical centers.

Number of recording sites and participants: each patient participated in only one task paradigm but repeated the task several times while different sites within the STN were recorded. In most cases, two parallel recording electrodes were used, and each electrode was considered as one recording site.

Behavioral results: the behavioral results (press rate, correct / incorrect responses and response time) refer to the total STN recording sites. No significant changes were found between the behavioral results recorded in the DLOR and VMNR. The p values for the behavioral results are for mixed design ANOVA after Bonferroni correction. The variables for the mixed design ANOVA were averages of each recording site (i.e. average press rate, response time or anticipatory press rate for each recording site).

Correlations between the clinical scores and behavioral result are presented in the supplementary information, Table S1.

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

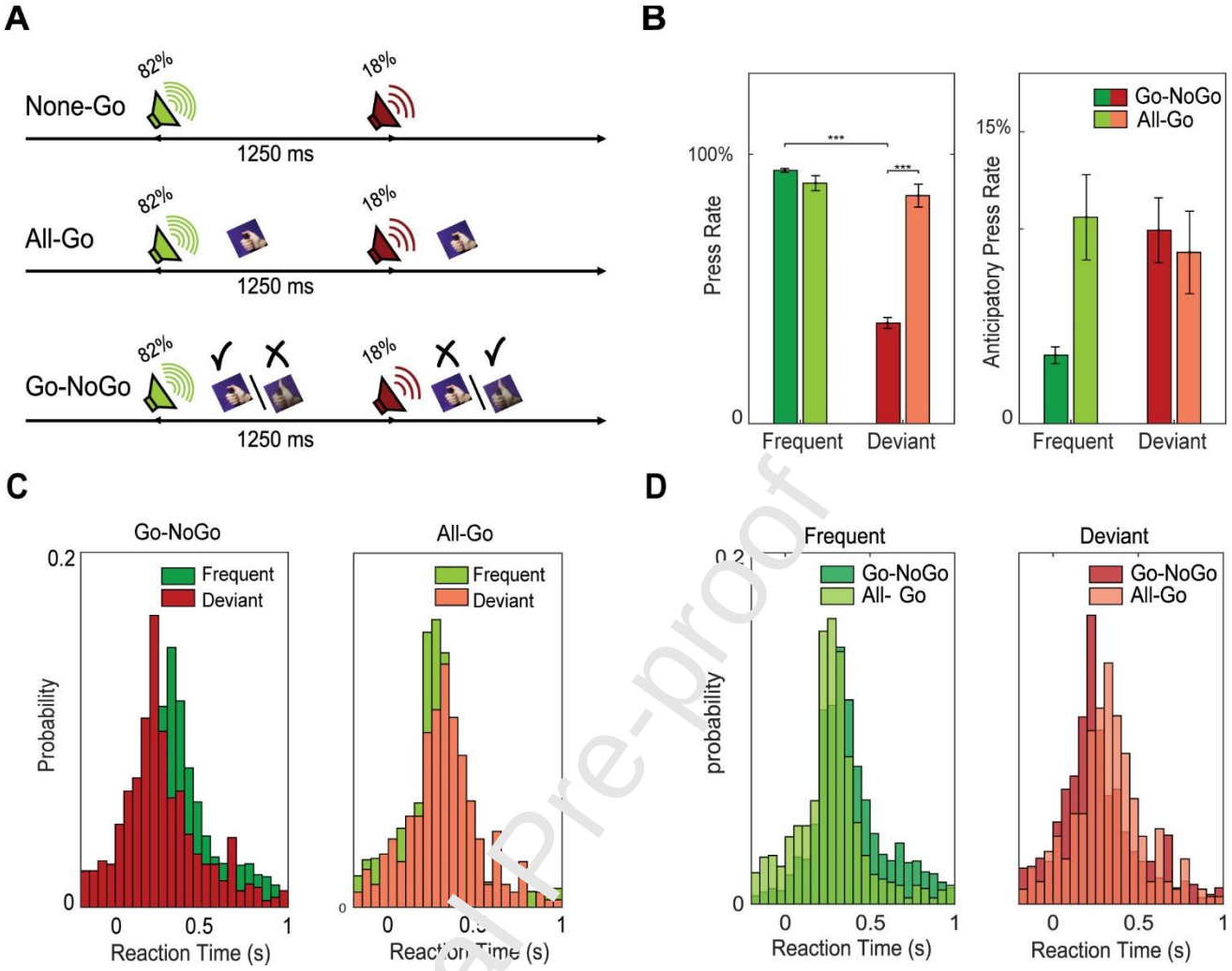

Figure 1. Task Paradigm and Behavioral Results

A. Task paradigm: None-Go - Subjects listened passively to the oddball paradigm. All-Go - Subjects were instructed to press a handed button as fast as possible after each tone of the oddball paradigm. Go-NoGo - Subjects were instructed to press the button as soon as possible only after frequent tones, and not to press after deviant tones. **B.** Press rate and anticipatory press rate to frequent (green) and deviant (red) tones on the Go-NoGo task and to frequent (light green) and deviant (light red) tones on the All-Go task. Anticipatory press was defined as a press that was 0-200ms before tone onset. Left - Press rates were significantly lower for commission errors on the Go-NoGo task than for hits on the All-Go and Go-NoGo tasks ($p<.001$, post-hoc pairwise comparison with Bonferroni correction, mixed design ANOVA). Right - Anticipatory press rates had no significant main effect for tone, task or the interaction of tone and task ($p>.05$, mixed design ANOVA) **C.** Distribution of the response times of the frequent and deviant tones on the Go-NoGo (left) and All-Go (right) tasks. **D.** Distribution of response times to the frequent (left) and deviant (right) tones on the All-Go (light green/red)

and Go-NoGo (green/red) tasks. A significant interaction between tone and task was on response time was found ($F(1,82)=14.63$ $p<.001$, mixed design ANOVA). Post-hoc simple main effects of the tone on each task revealed that response times in commission errors (after deviant tones) were faster than response times in hits (after frequent tones) only on the Go-NoGo task ($p<.001$, Fig. 1C). Post-hoc simple main effects of the task on each tone indicated that the frequent response times were significantly shorter on the All-Go vs. Go-NoGo task $p<.05$, Fig. 1D).

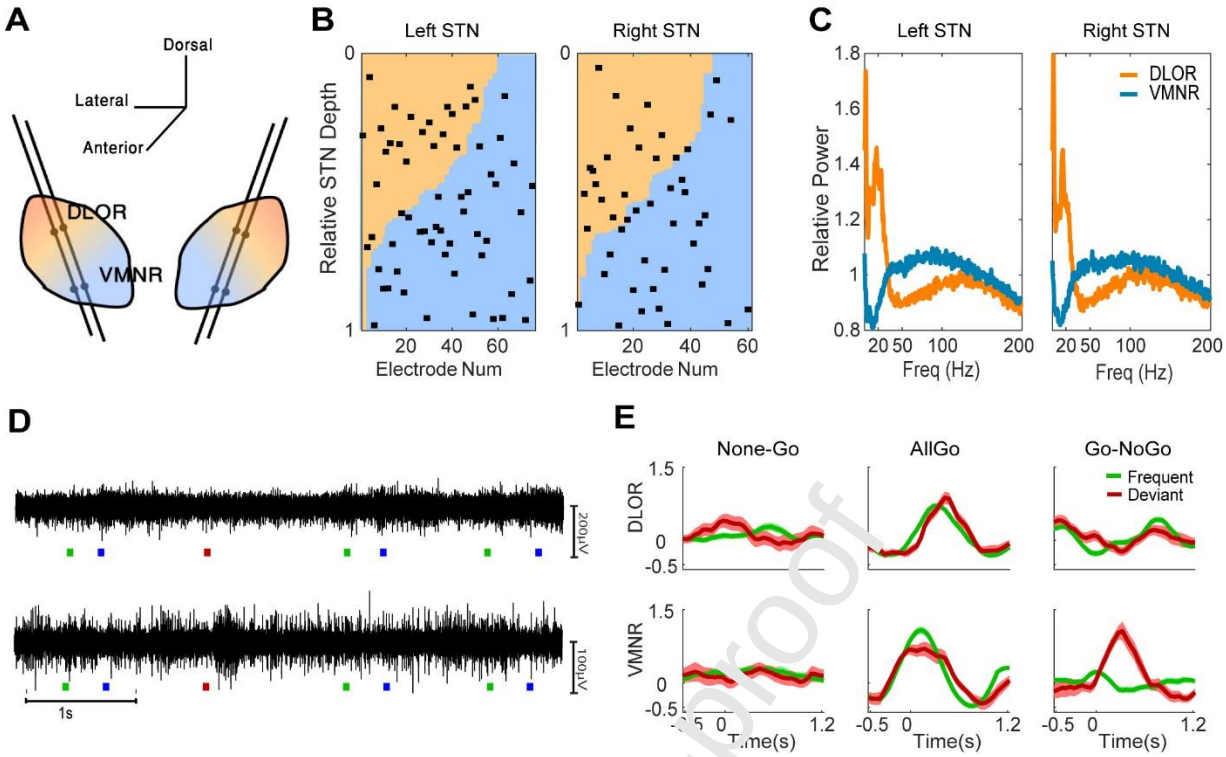

Figure 2. Recording Methods

A. Schema of the recording trajectories locations in the STN. **B.** Distribution of recording locations along the normalized STN trajectories. Electrodes number are arranged by the relative DLOR length. DLOR (orange) and VMNR (light blue) lengths were automatically detected by a 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.** Examples of 5 second microelectrode high filtered signals (300-9000Hz) during the Go-NoGo task. Colored squares at the bottom mark the times of the frequent tone (green), deviant tone (red) and presses (blue). Upper row – signal recorded in the DLOR domain. Lower row- signal recorded in the VMNR domain. **E.** Six examples of the mean post stimulus histogram (PSTH) response on the different tasks in the DLOR (upper row) and VMNR (lower row). Abbreviations: DLOR -Dorsolateral oscillatory region. VMNR – ventromedial non-oscillatory region.

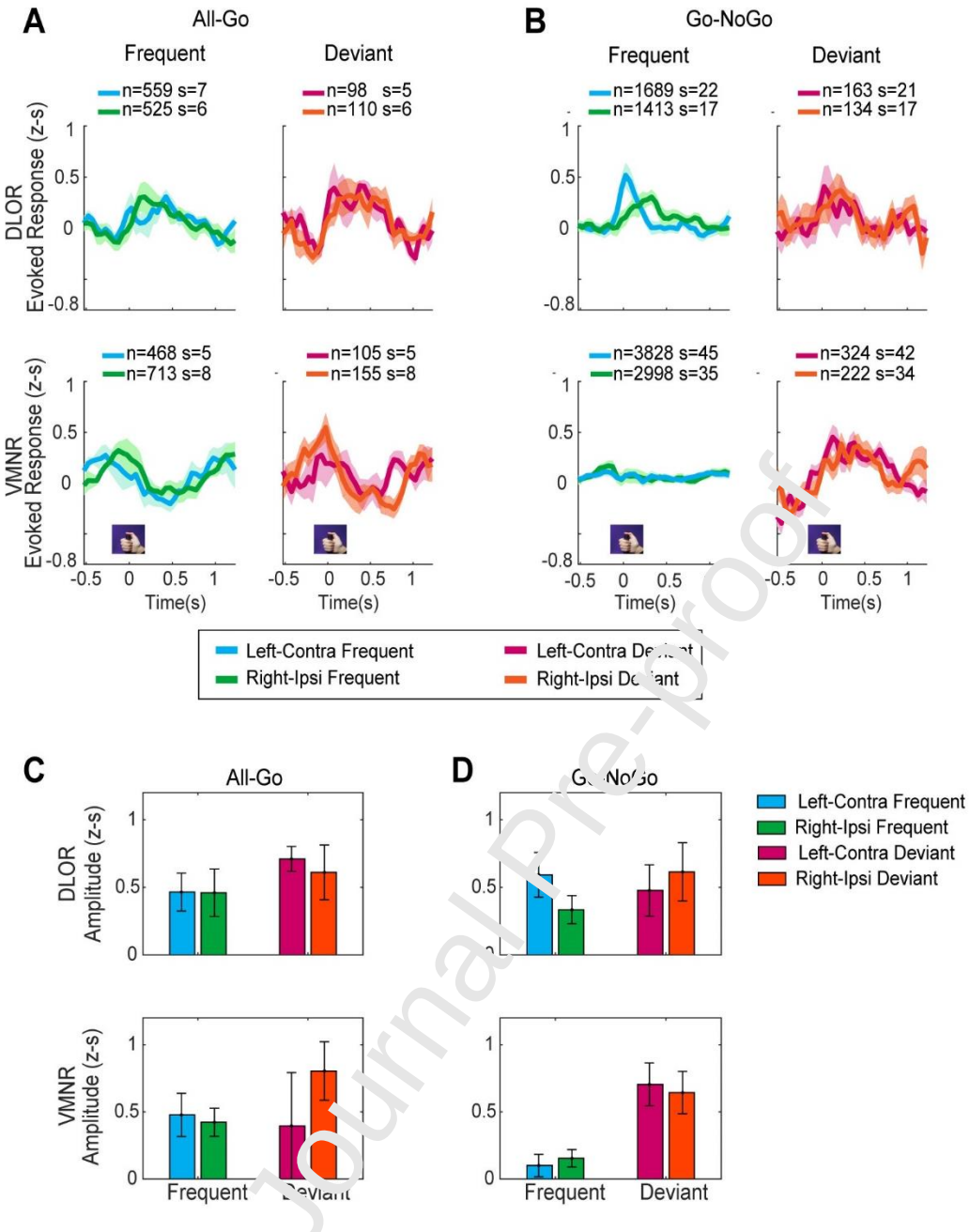

Figure 3. Neuronal Responses in the Ipsilateral and Contralateral STN on the All-Go and Go-NoGo Tasks

A. Mean Z-scored (z-s) post stimulus histogram (PSTH) responses of microelectrode multi-unit recordings ± standard error of mean (SEM) aligned to press in the left (light blue-frequent, magenta-deviant) and right (green-frequent, orange-deviant) STN on the All-Go tasks. **B**. Go-NoGo task, same convention as in A. **C**. Mean amplitudes ± SEM of the averaged evoked response aligned to press in the left and right STN in the All-Go task. **D.** Go-NoGo task, same convention as in C. No significant difference was detected between left and right evoked response amplitudes (two-sample t-test).

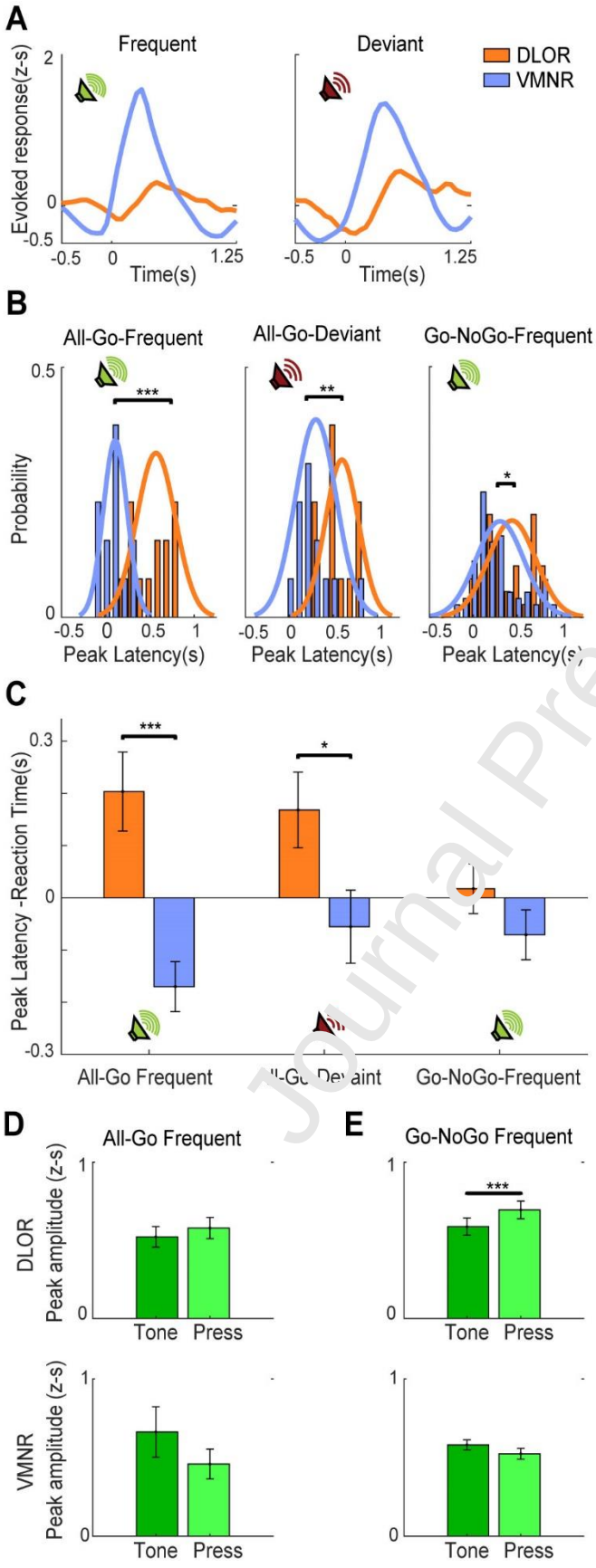

Figure 4. The DLOR Evoked Responses Correspond to Movement Execution and the VMNR Evoked Responses Correspond to Movement Planning

A. An example of evoked responses of frequent (left) and deviant (right) tones from simultaneous recordings from two microelectrodes: one electrode is in the DLOR (orange) and the second electrode is in the VMNR (light blue) during the All-Go task. Note the earlier peak of the evoked response in the VMNR. **B**. Distributions of the evoked response peak latency probabilities in the DLOR and VMNR on the All-Go and go cue of the Go-NoGo tasks. **C**. Averaged difference ±SEM between the mean evoked response peak latency and the mean response time in the DLOR and VMNR on the All-Go and go cue of the Go-NoGo tasks. **D**. The average peak amplitude ±SEM of evoked responses to frequent tones that were followed by press (hits) aligned to tone (darker) and press (lighter) on the All-Go task in the DLOR (upper row) and VMNR (lower row).**E**. Go-NoGo task, same convention as in D. ***Significantly different correlations ($p < 0.001$, paired sample t-test). Number of recording sites (B-D): All-Go DLOR, s=13, All-Go VMNR, s=13, Go-NoGo DLOR, s=39, Go-NoGo VMNR, s=80.

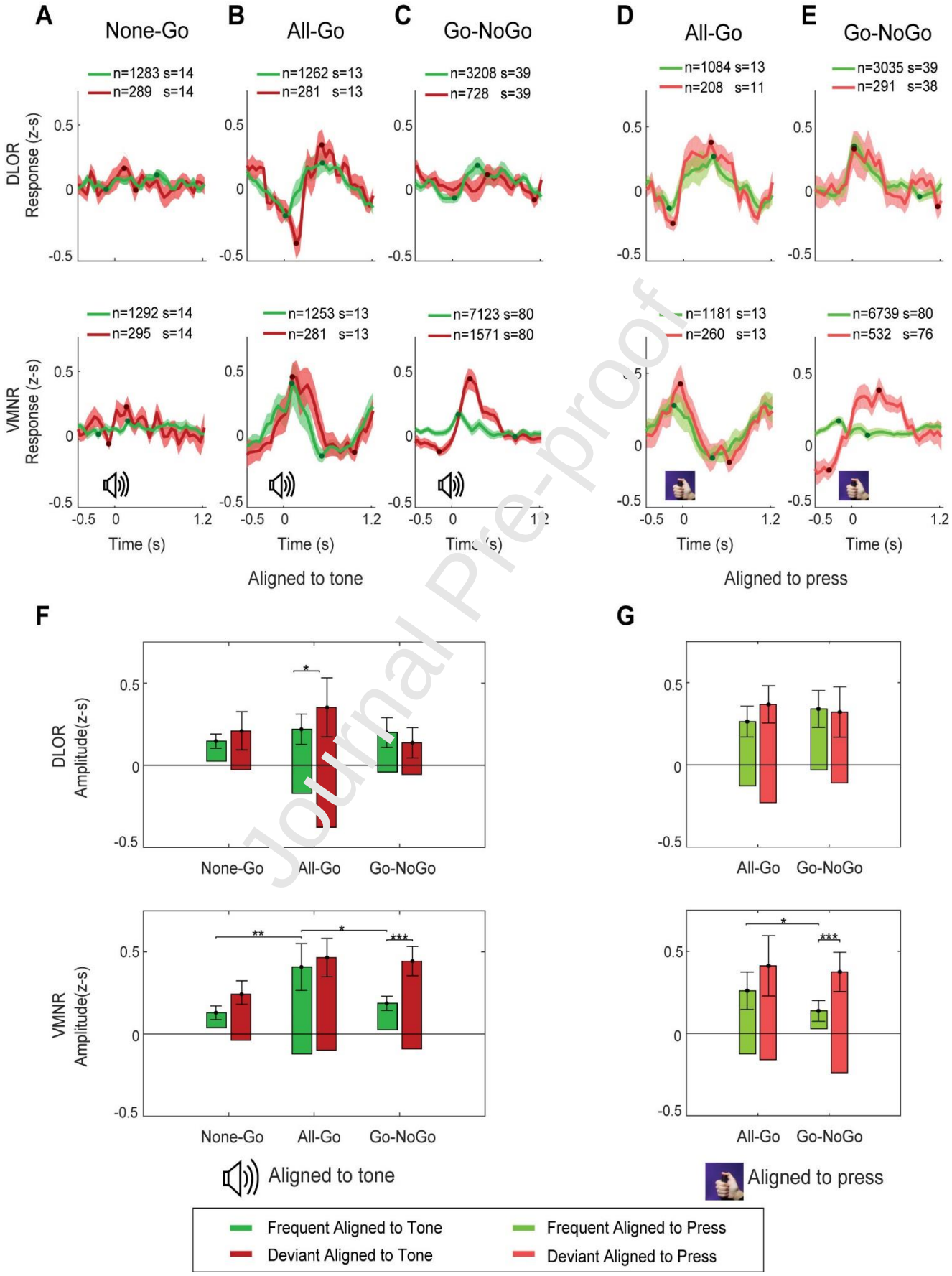

Figure 5. Responses to the Frequent Tone in the VMNR Decrease in the Context of Movement Inhibition

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) on the None-Go task, aligned to tone (speaker icon at time zero). Shaded areas represent the standard error of the mean (SEM). Darker dots represent the time point for the amplitude measure. n, number of trials; s, number of recording sites. **B**. All-Go task, same convention as in A. **C.** Go-NoGo task, same convention as in A. **D.** Average PSTH (post stimulus histogram) response aligned to the press (press icon at time zero) on the All-Go task in the DLOR (upper row) and VMNR (lower row). Same conventions as in A. **E**. Average PSTH (post stimulus histogram) response aligned to the press (press icon at time zero) on the Go-NoGo task. Same conventions as in A **F.** Amplitudes of the average responses aligned to tone in each task in the DLOR (upper row) and the VMNR (lower row). A significant effect on the evoked response amplitude was found to the tone and task, but not to location, and a significant interaction between tone, task and location was found ($F(1,167)=8.01$, $p<.01$, $F(2,73)=5.59$, $p<.01$, $F(2,167)=3.89$, $p<.05$, respectively, linear mixed model). Post-hoc pairwise comparison for each location of the task effect on each tone, revealed that in the VMNR, the amplitude of evoked response to frequent tones was modulated by task, lower in the None-Go and Go-NoGo tasks than in the All-Go task ($p < .01$, $p < .05$, respectively). In addition, post-hoc for each location, of the tone effect on each task revealed that the tone strongly modulated the evoked response amplitude on the Go-NoGo task in the VMNR, lower amplitude to frequent tones than deviant tones ($p<0.001$). In the DLOR, the deviant tone was significantly larger than frequent tone on the All-Go task ($p < .05$). **G.** Amplitudes of average frequent and deviant responses aligned to press on the All-Go and Go-NoGo tasks in the DLOR (upper row) and VMNR (lower row). A significant main effect was found to the tone type, larger on deviant tone press compared to frequent tone press ($F(1,135)=3.99$ $p<.05$). Post-hoc pairwise comparison of the task effect on each tone, revealed that in the VMNR, evoked response to the frequent tone press was significantly lower on Go-NoGo task compared to All-Go task ($p <.05$) and that in the VMNR on the Go-NoGo task the evoked response amplitude for the frequent tone was significantly lower than the evoked response amplitude for the deviant tone ($p <.001$). *p < 0.05, **p < 0.01, ***p < 0.001.

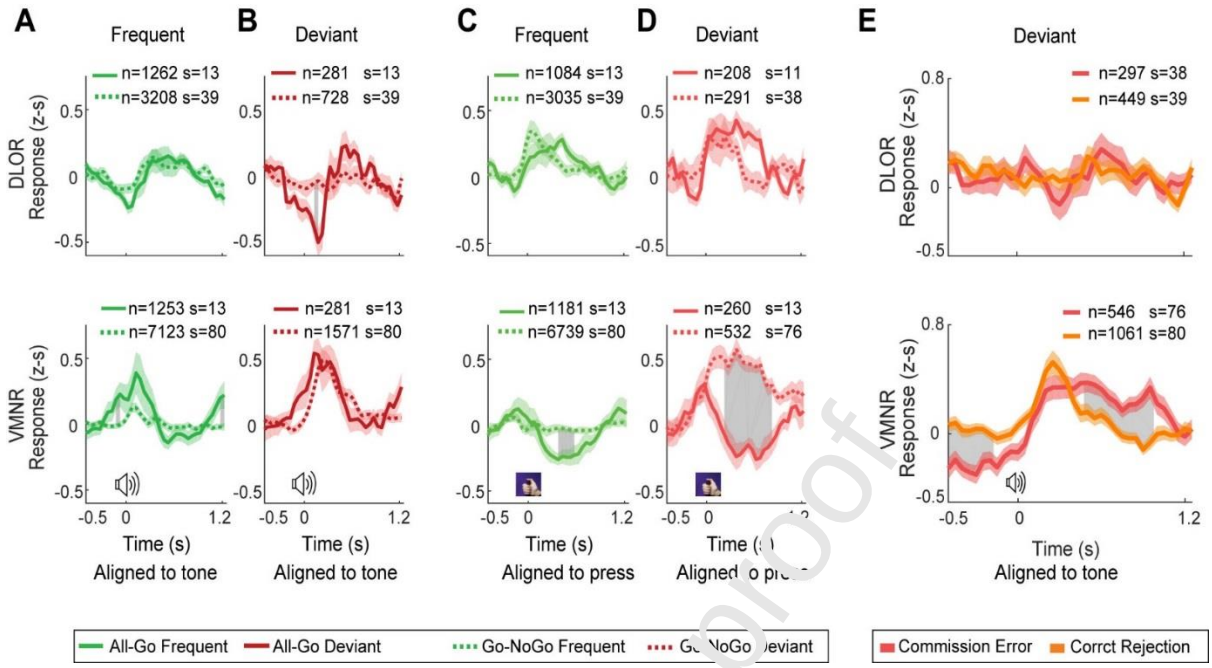

Figure 6. Smaller Negative Phase of Evoked Response Represents Preparation for Possible Movement Inhibition A. Mean PSTH response of all recording sites aligned to the tone in the All-Go (solid line) and Go-NoGo (broken line) for the frequent tones (green). Responses were normalized by subtraction of the mean activity preceding tone/press onset (-500:-100ms). Gray area indicates time bins in which the difference between the All-Go and Go-NoGo tasks was significant (two-sample t-test $p<0.05$ after FDR correction). B. Mean PSTH response of all recording sites aligned to the tone in the All-Go (solid line) and Go-NoGo (broken line) for the deviant tones (red) **C.** Mean PSTH response of all recording sites aligned to press for the frequent tones. Same convention as in A. **D.** Mean PSTH response of all recording sites aligned to press for the deviant tones. Same convention as in A. **E.** 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 on the Go-NoGo task in the DLOR (upper row) and VMNR (lower row). Shadows represent the standard error of the mean. Gray area indicates time bins in which the difference between the commission error and the correct rejection responses was significant (paired-sample t-test $p<0.05$ after FDR correction). n, number of trials; s, number of recording sites. Note that the evoked response in E differ from A - D, A-D are normalized by the preceding 500ms whereas E is without further normalization beyond the Z-score.

Highlights:

- Parkinsonian STN response decreases in the context of movement inhibition
- Unsuccessful movement inhibition is preceded by higher STN baseline activity
- To enable better preparation for possible inhibition STN reduces its evoked responses
- STN acts as a tonic "brakes" with different suppression levels according to context
- Ventral STN is part of movement control network and a future treatment target

Author contributions:

O.M., P.R., D.V., A.S.B., D.A., E.L., O.P., I.T., H.B., Z.I. and R.E. were engaged in study conception and interpretation and contributed to the critical revision of the manuscript. O.M, D.V, A.S.B., I.T., H.B., Z.I., and R.E. were involved in electrophysiological data recordings. Z.I., and I.T. performed the surgery. D.A., E.L., O.P., Z.I., and R.E. were involved in clinical neurology and psychiatry assessment. O.M., and R.E. developed the behavioral tasks. O.M., P.R., A.S.B., H.B., Z.I., and R.E. analyzed the electrophysiological data. O.M., P.R., H.B., Z.I., and R.E. prepared the manuscript. All authors discussed the results, assisted in the preparation of the manuscript and approved the final version.