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The Subthalamic Nucleus, oscillations and conflict

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Abstract

The subthalamic nucleus (STN), which is currently the most common target for deep brain stimulation for Parkinson's disease, has received increased attention over the past few years for the roles it may play in functions beyond simple motor control. In this article we will highlight several of the theoretical, interventional, and electrophysiological studies that have implicated the STN in response inhibition. Most influential amongst this evidence has been the reported effect of STN deep brain stimulation in increasing impulsive responses in the laboratory setting. Yet, how this relates to pathological impulsivity in patient's everyday lives remains uncertain.

Keywords

STN; theta; conflict; decision-making; DBS

Introduction

Over the past two decades deep brain stimulation (DBS) of the subthalamic nucleus (STN) has greatly improved the lives of thousands of patients suffering from Parkinson's disease (PD). The success of DBS underscores the importance of the STN in motor function, particularly when this is disturbed by the distant loss of dopamine neurons. However, recent appreciation of the potential non-motor side effects of DBS of the STN has led to speculation that the importance of this nucleus extends beyond simple motor function, and may also relate to processes involved in inhibiting choices and actions, particularly when

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there may be competing alternatives. Indeed, cross-sectional studies have shown that STN DBS is associated with higher scores on impulsivity rating questionnaires¹ and anecdotal reports suggest that on rare occasions STN DBS may even trigger pathologically impulsive behavior such as hypersexuality and pathological gambling^{2–6}. Understanding the mechanisms underlying the STN's role in cognition, particularly the interactions to be had between the STN and diverse cognitive areas of cortex, is critical if we are to avoid cognitive side-effects in treating motor disorders, or, indeed, turn them to our benefit in the treatment of psychiatric diseases.

Computational models of the STN's role in inhibiting choices and actions

The primary down-stream target of excitation from the STN is the internal segment of the Globus Pallidus (GPi), which sends inhibitory projections to the motor thalamus. Thus, in the context of the traditional models of basal ganglia connectivity^{7,8}, increased firing in the STN is expected to increase the activity of the GPi, which would then lead to disfacilitation of the cortex by the thalamus and thus an inhibition of movement. This view has inspired two major computational models of STN function^{9,10}. Both models posit a crucial role for the STN in response inhibition under conditions in which several responses are entertained, as when conflict information is presented to the subject. Though the mathematical relationships underling the dynamics of STN activity differ between the models, they both predict that the STN is responsible for inhibiting responses during conflict to prevent impulsive actions. They both also, at least by inference, extend this function to inhibiting the wrong choice during conflict, thus implicating the STN in decision-making.

The hypothesized dynamics underlying the models can be summarized as follows. During straightforward action selection that does not involve conflict, the pre-motor cortical activity associated with the correct response initially activates the STN via the fast conducting hyper-direct pathway (figure 1). This activation results in a temporary inhibition of movements due to the broad excitation of GPi by STN neurons. After a brief delay, however, the feed-back inhibition from the external segment of the globus pallidus (GPe) suppresses the STN's net anti-kinetic effect, and cortico-striatal activity corresponding to the correct response inhibits GPi via the "direct" pathway. Once the cortico-striatal activity reaches a certain threshold, the tonically active GPi neurons are inhibited sufficiently to release thalamic facilitation of the cortex.

During situations involving conflict, on the other hand, the models assume that two or more pre-motor responses are simultaneously activated by the conflicting options. This leads to more marked activation of the STN, and thereby GPi (figure 1). In order to overcome this conflict triggered increase in global inhibition, any movement-related cortico-striatal input will need to be stronger to silence the GPi. This effectively results in a higher "threshold" of cortical evidence needed to drive a response. Over time, the pre-motor inputs associated with the correct response will continue to rise, while those associated with the incorrect response will not, eventually resulting in the selection of the correct response. This process will take time, however, resulting in longer reaction times during high conflict trials relative to low conflict trials. Despite the longer reaction times, this proposed process would allow for improved action selection by preventing the selection of the incorrect response. Without

the conflict-triggered increase in global inhibition, the incorrect response would occasionally be selected due to either noise in the system or to pre-potent biases towards the incorrect response. As the STN is crucial in inhibiting responses when two or more potential responses are simultaneously entertained, these models assign to the STN the role of “holding your horses” during high conflict decisions. This has been formalized in the context of the drift diffusion model of decision making in which a noisy neuronal process accumulates information supporting one of two alternatives until there is enough evidence to cross a “decision threshold” and execute the winning response¹¹. During conflict, inhibitory activity from the STN adjusts the amount of evidence the winning alternative will need in order to win the drift diffusion race^{12–15}. According to these predictions, the disruption of STN activity via DBS should result in impulsive behavior in the face of conflict.

Lesion and DBS studies show impaired response inhibition during conflict

Prior to the predictions of the computational models described above, there were several lines of evidence already supporting the claim that the STN is crucial for response inhibition. In a delayed reaction time task where rats were rewarded if they withheld responses until a cue was presented, but not if they responded too early or too late, dopaminergic lesions led to a delay in the response times, similar to that seen in PD patients and resulting in more trials that were missed due to late responses¹⁶. A subsequent lesion of the STN led to a speeding in reaction times, consistent with the effects of DBS on PD. Following the STN lesion, however, the rodents were impaired in their ability to withhold the response until the cue was presented. Thus although the STN lesion produced DBS-like improvements in motor control, it came at the cost of impulsivity in this simple task.

In line with lesion studies in rodents and the predictions made by the computational models, PD patients receiving DBS of the STN have generally been shown to respond more impulsively in the laboratory setting^{12,13,17–23} (but also see^{24–26} and “Paradoxes of deep brain stimulation of the STN” section below). Most of these studies have focused on scenarios in which a fast, pre-potent response must be suppressed in favor of a slower, more controlled response. Though these tasks usually do not require an overt decision, conflict arises between the activity related to the primed incorrect response and that related to the unprimed correct response. Consider, for example, performance on the “Stroop” task. Here subjects must specify the color of the font of printed words, whilst suppressing the pre-potent drive to read the word, which may be for a different color (i.e. the word “red” written in blue font requires the response “blue”²⁷). PD patients with STN electrodes have more errors when their stimulators are turned on^{19,20}. Likewise, when patients perform a Go-NoGo task where they receive a go stimulus on most trials, priming them to respond quickly, but are occasionally presented with a NoGo stimulus in which they must cancel the planned Go response, subjects commit more errors in the DBS ON condition^{21,22}. In line with these results, several other studies using simple action selection tasks involving conflict have shown that STN DBS as well as subthalamotomies induce more errors by impairing response inhibition^{13,15,23,28}.

Several studies have also suggested that the STN may also be involved in more complicated, overt decisions^{12,17,18}. As a follow up to their modeling work, Frank et. al demonstrated that

when DBS stimulators were turned off, patients behaved no differently than healthy controls in a probabilistic paired choice decision task¹⁷. This task involves a choice between two symbols that are associated with differing probabilities of reward. On low conflict decisions, the difference between the two options is sufficiently large that the correct choice is obvious (80% vs. 20%). On difficult decisions, the probability difference is close enough to induce conflict (70% vs. 60%). As would be expected, healthy controls and PD patients in the off DBS state responded significantly more slowly during the high conflict decisions relative to the low conflict decisions. When the STN stimulators were turned on, the patients responded faster during both low and high trials, consistent with the motor improvements associated with DBS. However, in the DBS on condition, the patients actually responded significantly faster during the high conflict trials than they did during the low conflict trials, particularly during win-win scenarios. These differences could not be explained by the motor improvements alone, as faster movements on DBS would not explain why the conflict induced slowing would become conflict induced speeding with DBS. As expected, the faster responses led to suboptimal decision-making and more errors. Similarly, when patients are asked to integrate several lines of evidence to make a decision, STN DBS impairs the usual slowing of reaction time that occurs when the final piece of evidence they receive is contradictory to the previously received evidence¹⁸. Taken together, the rodent lesion and human DBS studies show that the STN plays an important role in response inhibition, which can under some circumstances influence decision-making. Now for insight in to the means by which STN might carry out this function we have to turn to neurophysiological studies.

Electrophysiological evidence supporting a role for the STN in response inhibition: firing rate studies of single neurons

The majority of single neuron studies involve animal models, and so have mostly been restricted to simple response inhibition paradigms. In one study, when non-human primates were primed to make saccades in a given direction and then asked to inhibit that response in favor of making a saccade in the opposite direction, STN neurons exhibited increased firing activity on the switch trials²⁹. More recently, others have attempted to tie the increased firing activity seen in the STN during response inhibition to the activity observed in the rest of the basal ganglia by simultaneously recording neuronal activity in the rodent striatum, GPi, GPe, and STN during a stop signal reaction time task³⁰. This task involves presenting a go stimulus that is occasionally followed by a stop stimulus requiring the cancellation of the initiated movement³¹. Schmidt et al. found that during the stop trials, neurons of the STN always increased their firing after the stop cue. Only on successful stop trials, however, did neurons in the down-stream GPi increase their firing rate. On the failed stop trials, the inhibitory activity of the cortico-striatal inputs managed to suppress the firing rate of GPi neurons leading to the execution of the response (see figure 1). This work provided compelling evidence that response inhibition involves a race between the response-driving activity of the striatum and the braking activity of the STN.

In order to show that STN activity also plays a role in overt decision-making in humans, Zaghoul et al. recorded from the STN of PD patients while they were undergoing DBS implantation surgery³². These recordings were made while subjects performed a

probabilistic paired choice task similar to the one used by Frank et al.¹⁷. In line with the animal studies, STN neurons showed increased firing during the high conflict trials in which the two options contained a similar probability of reward (figure 2a). Furthermore, the firing rate of the STN neurons correlated with the amount of conflict that was present during each trial.

Electrophysiological evidence supporting a role for the STN in response inhibition: synchronized oscillations in the beta frequency (13–30 Hz) band

As much of the electrophysiological literature on the STN focuses on the potential anti-kinetic role of beta oscillations in motor circuits³³, several studies have sought whether beta oscillations might play a similar role in response inhibition and conflict. Kühn et al.³⁴ demonstrated that during a Go-NoGo task, Go trials showed the well-established movement related decrease in beta band activity. NoGo trials likewise showed an initial decrease in beta activity; however, this decrease was quickly reversed to a relative beta increase, posited to inhibit movement. Similarly, during the stop signal reaction time task, stop trials are associated with an increase in beta band activity, with the latency of the beta increase correlating with how quickly subjects react to the stop signal²⁸ (figure 2b). Alegre et al.³⁵ have recently extended this finding to show that beta activity is higher during successful stop trials relative to failed stop trials and that elevated STN beta power is associated with elevated beta band coherence with the motor cortex. These studies all suggest that beta oscillations in the STN and connected structures may play an important role in inhibiting movement, particularly when actions should be prematurely halted.

In order to explore if beta activity is also implicated in a more cognitive task that requires responses during conflict, Brittain et al.³⁶ used the Stroop task to show that high conflict trials exhibit a similar beta band pattern as observed during stopping tasks. Both low and high conflict trials demonstrated a decrease in beta band activity following the stimulus onset, but during high conflict trials, a small relative increase in beta power took place before the response was made (figure 2b). Notably, during error trials the beta band increase still appeared, but it occurred after the response was made. In line with the race model proposed by Schmidt et al.³⁰ the authors interpreted this finding as evidence that when the beta signal arrived too late to inhibit movement, errors occurred.

So far we have considered the role of beta activity in what may be termed reactive response inhibition, in that the movement inhibition follows an imperative cue. However, beta activity may also play a role in pro-active inhibition even during tasks that do not require any movement whatsoever. This was recently investigated in a study in which PD subjects were asked to increase the count of an internally maintained number only when a trial contained a particular visual stimulus³⁷. When the subjects were given an informative warning cue that let the subjects know that the upcoming trial would not contain the relevant stimulus, beta power increased and remained elevated through that trial. This result implicates STN activity in pro-active inhibition, as the increase in beta activity preceded stimuli made irrelevant by the specific warning cue. Importantly, the effect was absent when the patients performed the task after their dopaminergic medication was withheld. Imaging evidence also points to the involvement of STN in pro-active, as well as reactive, response inhibition^{21,38}.

Though the studies we have highlighted suggest an inhibitory role for beta oscillations that may allow the brain to rapidly suppress responses (or updates to working memory), other studies suggest that the role of beta oscillations may be more complex. A recent study contrasting beta band activity in the STN during eye-movements concluded that beta suppression was more pronounced during blocks of trials requiring antisaccades than those requiring prosaccades³⁹. This prompted the authors to suggest that greater beta *suppression*, not enhancement, may be involved in the inhibition of reflexive responses. It should be kept in mind, however, that, unlike the previous studies discussed in this section in which any trial may or may not require a rapid suppression of the incorrect response, this study used a block design in which all of the trials in a given block were of the same type. These are task conditions that will favor pro-active inhibition and perhaps the beta suppression reported here is related to this. Another influential rodent study has suggested that the role of beta activity may extend still further.⁴⁰ These authors argued that beta power is enhanced after cues are used to determine appropriate action, and suggested that beta oscillations reflect a post-decision stabilized state of cortical-BG networks, which normally reduces interference from alternative potential responses. This view that beta activity may play a more general role that includes, but extends beyond response inhibition, finds some traction. Thus the abnormally strong beta seen in PD may reflect over stabilization of cortical-BG networks, producing pathological persistence of the current motor state⁴¹.

Electrophysiological evidence supporting a role for the STN in response inhibition: synchronized oscillations at low (<8 Hz) frequencies

Although the firing rate and beta oscillation studies discussed thus far implicate the involvement of the STN in response inhibition, much of the literature dealing explicitly with decision-making and conflict in healthy subjects focuses on the role of oscillations of lower frequency (< 8 Hz) in the frontal cortex⁴². These are generally termed theta activity, although they often extend to sub-theta (<4 Hz) frequencies as well. During an Eriksen flanker task in which subjects must indicate the direction of a middle arrow flanked by either low (<<<<) or high conflict (>>>>) arrows, theta power increases over the frontal cortex correlate with the prolonged reaction time of high conflict trials⁴³. In a subsequent study, the same authors have used the probabilistic paired choice paradigm and drift diffusion modeling to show that medial pre-frontal cortex (mPFC) theta power correlates with the amount of “evidence” needed to make a decision during conflict¹². Notably, DBS of the STN completely reversed this relationship. These findings are consistent with the general predictions made by the “hold your horses” computational model in that disruption of the STN’s activity leads to more errors. However, rather than assume that the STN calculates conflict based on information it receives from pre-motor cortex, the authors suggested that structures within the mPFC, such as the anterior cingulate cortex (ACC) or the pre-supplementary motor area (pre-SMA), detect conflict and subsequently communicate with the STN through theta activity to inhibit motor responses. Accordingly, they found higher theta power in the STN during high conflict trials. This result has been subsequently bolstered by studies showing elevated theta power during the high conflict trials of the Stroop task³⁶, the flanker task⁴⁴, a conflicting dot movement discrimination task⁴⁵, and even a task in which subjects were asked to indicate whether or not they agreed with various moral statements that involved

conflict (i.e. stealing is right when it is useful to save a human life)⁴⁶. A link between mPFC and STN theta activity was further suggested by the finding that, consistent with the correlations observed in mPFC, STN theta power during the flanker task correlates with individual trial reaction times⁴⁴. Though these correlations suggested that the STN interacts with the frontal cortex during conflict, a direct link was not shown until recently. In a task involving simultaneously recorded mPFC EEG and STN LFP signals, Granger causality analysis was used to demonstrate that theta oscillations in mPFC do actually drive those of the STN during conflict⁴⁵ (figure 2c–d). It remains to be determined whether changes in mPFC-STN connectivity also extends to other contexts in which the mPFC is thought to mediate cognitive control, such as during post error slowing^{47–50}. A possible link is suggested by recent studies showing altered STN activity following incorrect responses^{44,51–53}.

The STN is a point of convergence in a larger response inhibition network

The evidence that mPFC could detect conflict and activate the STN extends beyond studies of beta and theta activity. Many imaging and event related potential EEG studies demonstrate higher mPFC activity during conflict⁵⁴. Moreover, neurons in two key structures within the mPFC, the ACC and the pre-SMA, show STN-like changes in discharge rate during response inhibition and stopping. Isoda and Hikosaka extended their saccade priming task described above to record the firing rates of non-human primate neurons in the STN and pre-SMA during trials that involved conflict between a pre-potent and a controlled saccade^{29,55}. Both structures showed similar firing rate increases during correct trials in which the pre-potent response was successfully inhibited. More recently, others have shown that individual neurons of the human ACC discharge at a higher rate during conflict, and that this correlates with the amount of conflict as it does in the STN⁵⁶.

In light of the evidence highlighting the role of the mPFC during conflict, Wiecki and Frank have proposed a revised computational model of the basal ganglia's activity during decision-making that now also involves various cortical structures⁵⁷. In this model, the ACC detects conflict, subsequently activating the STN to inhibit responses. Wiecki and Frank also posit that the inferior frontal cortex (IFC) plays a role in response inhibition, particularly when all actions must be stopped as in tasks like the Go-NoGo task or the stop signal reaction time task. Support for this model stems from the fact that all three nodes of the stopping network, the mPFC, IFC, and STN are connected and are activated in a similar manner during response inhibition⁵⁸.

As of yet, however, only a handful of studies have analyzed the mechanisms by which the mesial and lateral frontal cortices interact with each other and with the STN during conflict. In addition to the study showing increased mPFC-STN synchrony during conflict⁴⁵, other studies have shown frequency specific synchrony between the two cortical nodes during cognitive processes. For example, high conflict and error trials in the flanker and Stroop tasks are associated with increased theta band synchrony between the mPFC and the IFC^{43,47,59,60}. Beta oscillations also seem to connect the mPFC and the IFC during the Stop signal reaction time task⁶¹, and beta band synchrony increases just before errors are committed by musicians playing the piano⁶². The authors of the latter study suggested that

beta synchrony between the two cortical structures reflected stopping activity trying to prevent errors from occurring, and this was supported by the fact that errors were played at lower volumes. Though there has yet to be a study showing increased coherence between the STN and the IFG, it is possible that beta oscillations play a role in synchronizing the two structures during the stop signal reaction time task. Indeed, similar beta increases as those seen in the STN during this task⁶³ have also been observed over the IFC^{25,61,64}.

Though the above electrophysiological studies suggest that communication between the mPFC, IFG and STN is associated with synchronization of beta and theta oscillations, the factors that determine which frequency is used and in what order the three structures are activated remain unclear. Several electrophysiological recording, transcranial magnetic stimulation (TMS), and functional connectivity studies have suggested that the mPFC detects conflict and subsequently activates the IFC, which then activates the STN to delay actions^{60,61,65}. Against this hypothesis, however, is a recent study suggesting that silencing mPFC activity by repetitive TMS actually enhances response inhibition during conflict and strengthens fMRI determined effective connectivity between the STN and the IFC⁶⁶. Though it remains to be determined why silencing mPFC would lead to enhanced inhibition, the authors suggest that the strengthening of IFC-STN connectivity was compensatory in this paradigm. In light of their findings, the authors endorsed the Wieke-Frank model of response inhibition, where the mPFC and the IFC activate the STN in parallel, not in series. One testable prediction that follows this proposed organization is that theta and beta oscillations may allow both structures to simultaneously activate the STN for different purposes as proposed above by Wieke and Frank. mPFC theta activity may be responsible for delaying responses (such as in the Stroop, flanker, and probabilistic reward task), and IFC beta may be responsible for completely inhibiting them (such as in the Go-NoGo or stop signal reaction time task).

Regardless of the exact organization underlying the response-inhibition network, the expanding literature on the role of oscillatory synchronization within the network suggests that the traditional firing rate models of basal ganglia connectivity are incomplete, as they do not include these important phenomena. This offers a potential explanation for a neglected short-coming of the original 'hold-your-horses' model. As discussed earlier, the core evidence supporting this model is that high frequency DBS of the STN induces a degree of impulsivity, interpreted as resulting from a blocking of conflict related increased firing rates in the STN. Yet, the prevailing evidence now suggests that high frequency DBS actually drives STN output⁶⁷⁻⁷⁰, which should theoretically increase response caution. However, DBS also seems to block or replace patterned output⁷¹⁻⁷³ so the effects of high frequency DBS on key changes in physiological oscillatory synchronization during response inhibition, rather than firing rates, may reconcile the hold-your-horses model with emerging views of DBS effects.

Paradoxes of deep brain stimulation of the STN

Though we have cited some studies demonstrating that DBS to the STN makes patients more impulsive¹, most individuals who receive DBS do not suffer from pathological impulsivity following electrode implantation. There might be several reasons for this,

including compensation by the wider response inhibition network or the nature of the experimental tasks explored. Almost all of the tasks we have highlighted involve very rapid decisions that require quick response inhibition to prevent impulsive responding or to overcome natural biases that would favor the incorrect response. This is why most of the error trials that occur in these tasks have much faster reaction times than correct trials; the inhibition most likely did not arrive in time to prevent the execution of the pre-potent response. We propose that those studies suggesting that STN DBS impairs response inhibition can be reconciled with the clinical reality that pathological impulsivity is only very infrequently seen as a complication of STN DBS, if the response inhibition exerted through the STN is only rapid and not sustained. Indeed, there is evidence that STN DBS only disrupts rapid inhibition that occurs early on in a trial⁷⁴. By examining the behavior of DBS subjects performing the Simon task⁷⁵, Wylie et al were able to show that DBS induces opposing effects depending on the type of inhibition being activated⁷⁴. During trials with very fast response times, they observed decreases in accuracy consistent with the idea that disrupting the STN leads to quick, impulsive errors. During the slowest trials, however, they observed that DBS actually leads to improvements in response inhibition by suppressing the effect of the incorrect response. Thus, STN related inhibition is important in paradigms like Go-NoGo, Stop, Stroop and even the probabilistic reward task where a response is required in each trial. However, many important decisions, whether made over conflicting choices or not, do not require an immediate action. Such delayed actions would not be affected by the type of rapid response inhibition associated with the STN and yet may be it is precisely these delayed action decisions that are affected by the kind of pathological impulsivity that negatively impacts work and relationships. The probable lack of STN involvement in these decisions possibly explains why most DBS patients are able to continue their day-to-day lives without any noticeable signs of pathological impulsivity. Nevertheless, the higher impulsivity scores reported by DBS patients in a questionnaire probing day-to-day impulsivity, albeit in a cross-sectional study¹, and the rare cases of DBS triggered pathological impulsivity²⁻⁶ still implicate the STN in pathological impulsivity in some form.

Another outstanding question relates to the fact that not all experimental studies demonstrate that STN DBS impairs response inhibition, and why some even demonstrate DBS related improvements in inhibition^{24,26,76}. Factors such as task details may again be important, as may be the precise targeting given that the effects of DBS likely vary according to the specific subsections of the STN that are stimulated^{2,35,77,78}. Additionally, patient state also seems to play an important role in determining the outcome of DBS on response inhibition. Ray et al observed that DBS had opposing effects on the stop signal reaction time task when the population of DBS patients was divided into two sub populations²⁸. The patients that had a similar baseline performance as healthy control subjects showed a detrimental effect on stopping when their stimulators were turned on. Patients who were already bad at the task at baseline, however, showed an improvement in response inhibition with DBS. One possible explanation for this may be related to DBS induced modulations of other nodes in the network^{25,76}. This may possibly explain why three other studies have also reported that stop signal reaction time improves with DBS²⁴⁻²⁶. One of these studies²⁵ related the improvement to enhanced theta and beta power increases over frontal cortex (particularly that on the right-side) in successful stop trials made during DBS, leading to the testable

hypothesis that DBS patients who experience improvements in response inhibition may show compensatory increased coupling within the response inhibition network.

A more in depth knowledge of the STN and its connections may also help shed light on recent unexpected findings related to the electrophysiology of patients with impulse control disorders that predate surgery. Rosa et al., recently showed that during a gambling task, Parkinsonian patients with pathological gambling adopted a riskier strategy than patients without pathological gambling⁷⁹. Those that adopted a conservative strategy showed no difference in low frequency STN power (2–12 Hz) between low and high conflict trials (figure 3a). Those that adopted the risky strategy, on the other hand, showed differences between the trial types due to lower amplitude low frequency power during the low conflict trials. Furthermore, in a study comparing the baseline STN activity of Parkinsonian patients with impulse control disorders to the activity of Parkinsonian patients without such symptoms, Rodriguez-Oroz et al. found that the impulsive patients had levodopa-induced increases in theta oscillations in ventral STN as well as in fronto-STN theta coherence⁷⁷ (figure 3b). In addition, the authors reported that patients with levodopa-induced dyskinesias, which may involve impaired inhibition, also show increased STN theta oscillations^{77,80}, although these occurred in more dorsal contacts and were coherent with the motor cortex. A link between impulsivity and dyskinesia is further suggested by studies showing that the presence of the two seem to correlate both across subjects⁸¹ and temporally within a subject⁸². The theta results from the above studies seem to call into question the idea that theta might delay or inhibit responses during conflict. Viewing theta as a conflict related signal as encapsulated in current computational models would predict that impulsive (and dyskinetic) patients should have *decreased* baseline theta levels. One way these findings could be reconciled is if the abnormal theta activity observed in the STN of impulsive patients was not responsible for the symptoms, but rather reflected a break down of the relationship between theta and behavior or even a compensatory mechanism that ameliorates the deficits induced by chronic dopaminergic activation. The latter possibility may also help to explain why STN DBS *per se*, does not seem to treat impulse control disorders, as would be expected if the exaggerated STN theta activity were primarily pathological, and can even, on rare occasions, induce them. Rather it is the associated decrease in dopaminergic medication with chronic STN DBS that leads to improvement in such impulse control disorders³⁸. Together these observations prompt the radical view that interventional therapies should seek to promote local theta and perhaps even beta⁸³ in the STN so as to ameliorate conditions characterized by inadequate response inhibition.

Future Perspectives

We have focused on the role of the STN in response inhibition, acknowledging that this key nucleus may have additional functions that we have not discussed, particularly in limbic domains^{84,85}. Evidence from multiple sources indicates that the STN is an important player in an extensive response inhibition network. Correlative evidence suggests that the STN's operation within this distributed network may involve the graded, task and context-dependent manipulation of oscillatory activities, particularly in the theta and beta frequency bands. Synchronization in these bands is increased during conflict, but whether this relates to decision evidence^{10,44}, conflict detection^{45,57}, response inhibition^{34,36} or post-decision

stabilization⁴⁰ remains unclear, as does the extent to which different spectral activities may differentially underpin these diverse functions. Moreover, as most of the results we have presented only reveal a correlative relationship between electrophysiology and response inhibition, it remains for existing evidence to be complemented by interventional studies demonstrating causal links between oscillatory activities and response inhibition in the frontal cortical-STN network. Such mechanistic studies are attainable, as we can now entrain or induce frequency selective activity through controlled low-frequency stimulation of deep nuclei, using DBS^{86,87}, or of cortical sites, using transcranial alternating current stimulation (TACS)^{83,88}. Finally, the current review has highlighted the need to understand the dynamics of the response inhibition network as a whole, as the STN cannot be considered in isolation. In the future, this will be facilitated by simultaneous electrical and magnetoencephalographic recordings from STN, mPFC, and IFC during decision-making and response inhibition tasks. Nevertheless, the study of PD patients undergoing DBS has already afforded important insights in to the response inhibition network.

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Figure 1.

Basal Ganglia Schematic. Pre-motor cortical inputs project to the STN via the fast conducting hyper-direct pathway. Prior to a decision, these inputs could hypothetically activate the STN to inhibit all responses until the correct response is selected by cortico-striatal activation (via the direct pathway) of the appropriate areas of GPi and cortico-striatal inhibition (via the indirect pathway) of the incorrect response (see text).

Figure 2.

Intra- and post-operative electrophysiological evidence supporting a role for the STN in decision-making recorded in PD patients. **[A]** STN neuronal firing. STN neurons fire more action potentials during high conflict trials in a probabilistic reward task, and degree of firing correlates with the level of conflict. Average across 27 cells recorded from 14 patients. Vertical dotted line indicates stimulus onset. Sp/sec is neuronal spikes/second. **[B]** STN LFP Beta band activity. Top: Stop Signal Reaction Time Task. STN beta power increases during abrupt stopping and is higher for correctly inhibited trials relative to failed stop trials. Average of 9 patients. Vertical solid line indicates go cue onset, and vertical dotted line indicates average stop signal onset. Bottom: Stroop Task. A similar STN LFP beta power increase occurs when subjects ($n=12$) perform high conflict trials (e.g. font-color-text mismatch), but not when they perform low conflict trials that do not contain incongruent information in the stimulus. Vertical dotted line indicates response. Green

shaded regions represent times where paired t tests demonstrate significant difference between congruent and incongruent traces. Note, the early differences in beta power (from -700 to -400 ms) were due to differences in the timing of when the stimulus was displayed relative to the response and do not reflect conflict related activity. [C] STN Theta band (<8 Hz) activity. Left: During a coherent dot motion discrimination task, STN shows increased theta power when two populations of dots are going in opposing directions. Right: Increased STN theta power is associated with increased levels of low frequency (<8Hz) coherence with the mPFC. Average of 13 patients. Vertical dotted line indicates response. Reproduced with permission from ³²[A], ^{36,63}[B], and ⁴⁵[C].

Figure 3.

Theta oscillations and pathology. **[A]** Patients with pathological gambling show abnormal low frequency (2–12 Hz) activity. When PD patients without pathological gambling ($n=6$) perform a probabilistic gambling task, both low and high conflict trials show an increase in STN low frequency power (left). In patients with pathological gambling ($n=6$), the low conflict trials showed impaired theta reactivity (right). Time is expressed as percentage time relative to response. **[B]** One of the side-effects associated with dopaminergic medication for PD is impulsivity. When Parkinsonian patients are at rest in the off medication state (left), the STN demonstrates elevated levels of beta band synchronization (reviewed in ³³). When impulsive patients are given their medication, beta band activity is suppressed as is seen in non-impulsive PD patients, but there is also an increase in low frequency theta band activity (right). The results shown on the left and right panels are from the same patient on and off of dopaminergic medication. Reproduced with permission from ⁷⁹[A] and ⁷⁷[B].