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Symposium

Frontosubthalamic Circuits for Control of Action and Cognition

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The subthalamic nucleus (STN) of the basal ganglia appears to have a potent role in action and cognition. Anatomical and imaging studies show that different frontal cortical areas directly project to the STN via so-called hyperdirect pathways. This review reports some of the latest findings about such circuits, including simultaneous recordings from cortex and the STN in humans, single-unit recordings in humans, high-resolution fMRI, and neurocomputational modeling. We argue that a major function of the STN is to broadly pause behavior and cognition when stop signals, conflict signals, or surprise signals occur, and that the fronto-STN circuits for doing this, at least for stopping and conflict, are dissociable anatomically and in terms of their spectral reactivity. We also highlight recent evidence for synchronization of oscillations between prefrontal cortex and the STN, which may provide a preferential "window in time" for single neuron communication via long-range connections.

Key words: **basal ganglia; conflict; oscillations; response inhibition; stopping; surprise**

Introduction

There is burgeoning interest in the subthalamic nucleus (STN) of the basal ganglia. This is driven by a confluence of interests in neurosurgery, neurology, computational modeling, and cognitive neuroscience. A major driver of interest is that research on the STN takes advantage of one of the only regular opportunities to acquire electrophysiological signals from deep within the human brain (i.e., via the implantation of deep brain stimulation [DBS], electrodes in patients with Parkinson's disease). DBS is thought to override or disrupt pathological oscillations, and "free up" the basal ganglia and its associated cortical circuits to better process information (Grill et al., 2004; Wilson et al., 2011). Yet DBS comes with side effects, for example, on speech and cognition (Hershey et al., 2004; Parsons et al., 2006), and there is much interest in optimizing it through better targeting and technical designs (Beudel and Brown, 2016; Kühn and Volkmann, 2016). A better understanding of the STN, its subregions, and its associated circuits (including prefrontal connections) could thus be clinically relevant. Going hand-in-hand with this is the question of what computations does the STN and its circuits do. Much recent research has focused on the idea that the STN plays a role in decision-making. Specifically, it has been proposed that the STN pauses responding by raising the decision threshold, and that it does this by suppressing basal ganglia output (Bogacz and Gurney, 2007; Wiecki and Frank, 2013; Zavala et al., 2015a). Here we put forward the hypothesis that this computational pause function is implemented by different (dissociable) cortico-STN circuits for different behavioral contexts. We mainly focus on the behavioral functions of stopping and conflict in the response domain. We end by considering how an STN-mediated pause might also affect cognition.

Stopping

Stopping is a neurocognitive process that countermands an initiated response tendency. It is typically studied in the laboratory with stop signal and Go/NoGo tasks (Verbruggen and Logan, 2008; Chambers et al., 2009; Chikazoe, 2010; Schall and Godlove, 2012; Bari and Robbins, 2013). On each trial, the subject prepares to Go, and sometimes has to try to stop the incipient response when a stop signal occurs. The go process (initiating a response) activates premotor cortex and downstream striatum, pallidum, thalamus, and M1 (consistent with the direct pathway of the basal ganglia) (Aron and Poldrack, 2006; Schmidt et al., 2013). The stop process activates (and requires the integrity of) specific frontal regions, such as the right inferior frontal cortex (IFC) and the presupplementary motor area (pre-SMA) (for review, see Wiecki and Frank, 2013; Aron et al., 2014; Jahanshahi et al., 2015); it also activates the STN (see below) and the globus pallidus pars interna (GPi) (Aron and Poldrack, 2006; Li et al., 2008; Schmidt et al., 2013; Watanabe et al., 2015) and striatum (Aron and Poldrack,

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2006; Zandbelt and Vink, 2010). Many studies now attest to the STN's role in outright action stopping, including human fMRI (Aron and Poldrack, 2006; Li et al., 2008), human lesion (Obeso et al., 2014), human STN local field potential (LFP) (Kühn et al., 2004; Alegre et al., 2012; Ray et al., 2012; Benis et al., 2014), rat lesion (Eagle et al., 2007), and single-unit studies in humans (Bastin et al., 2014), monkeys (Isoda and Hikosaka, 2008), and rats (Schmidt et al., 2013). While individual approaches have their weaknesses (e.g., 3T fMRI may not be optimal for definitive localization (de Hollander et al., 2015), LFP changes in the STN likely reflect basal-ganglia wide rather than STN-specific signatures (Leventhal et al., 2012) and the rodent lesion study apparently affected going more than stopping), taken together, a strong case is made that the STN is implicated in stopping. Ultimately, however, confirmation requires causal approaches, such as optogenetics.

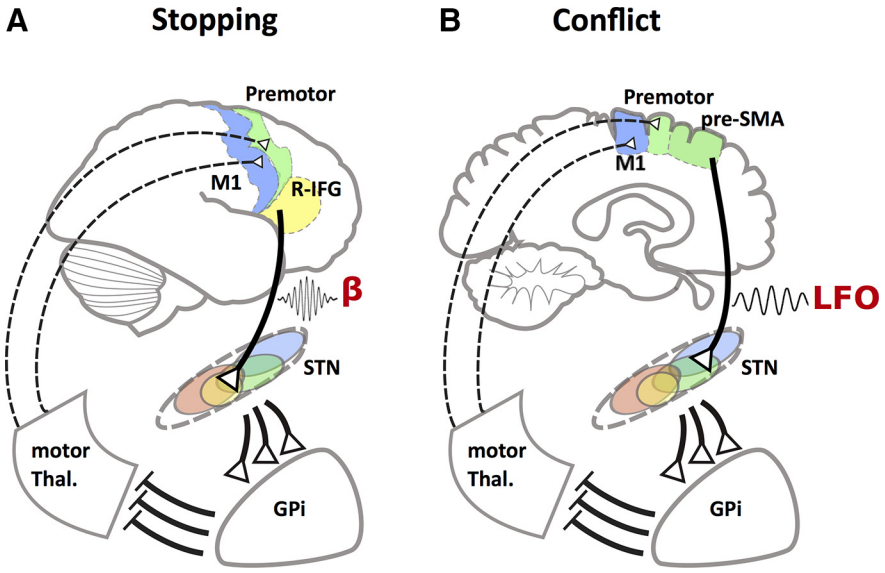

Figure 1. Hypothetical model of different hyperdirect cortico-STN pathways for stopping and conflict processing. ***A***, Stopping is initiated via right inferior frontal gyrus (R-IFG) (possibly in concert with pre-SMA), which projects to the central part of the STN. The STN topography in the figure is based on monkey tracing, with areas color coded by cortical inputs (orange represents ventromedial frontal; region not shown) (Haynes and Haber, 2013). There is a putatively broad effect on the GPi, which broadly suppresses thalamocortical drive, ultimately affecting primary motor and premotor representations. Increases in beta band power are prominent. ***B***, Conflict operates in an analogous way, except it appears to be generated by dmPFC (perhaps pre-SMA), and this projects to a somewhat more dorsal STN territory. Power increases now occur for low-frequency oscillations, LFOs, in the 2–8 Hz band.

As we saw, two prefrontal areas critical for stopping are the right IFC and the pre-SMA. While their relative functional roles are still unclear (Zandbelt et al., 2013; Aron et al., 2014; Herz et al., 2014; Rae et al., 2015; Xu et al., 2016), we suppose that one or both is recruited by the stop signal to trigger the STN via a hyperdirect pathway. The original idea of the hyperdirect pathway was that it has a broad suppressive effect on basal ganglia output (Mink, 1996; Gillies and Willshaw, 1998; Nambu et al., 2002). This was based on tracing studies in the monkey (for review, see Parent and Hazrati, 1995), yet the evidence is weak. Notwithstanding, there is now considerable evidence that stopping action does have broad behavioral/physiological suppressive effects. This was established by studies that use transcranial magnetic stimulation and concurrent motor-evoked potentials: a corticospinal excitability measurement method. Specifically, stopping speech reduces corticospinal excitability of the hand (Cai et al., 2012; Wessel et al., 2016b), stopping the eyes reduces corticospinal excitability of the hand (Wessel et al., 2013a); and stopping the hand reduces corticospinal excitability of the leg (Badry et al., 2009; Greenhouse et al., 2012; Majid et al., 2012). Moreover, stopping one movement leads to large delays in continuing with another (Coxon et al., 2007; MacDonald et al., 2014). Interestingly, the level of global suppression (measured from the hand when stopping speech) has been linked to a "stopping signature" in the STN, viz. increased power of oscillations in the LFP (Wessel et al., 2016b). Notably, the oscillations increased their power in the beta band (13–30 Hz), consistent with several other STN LFP recording studies during stop trials (Kühn et al., 2004; Ray et al., 2012; Bastin et al., 2014; Benis et al., 2014). Moreover, increases in beta band power have been reported for right IFC (Swann et al., 2009, 2012; Wessel et al., 2013b) and pre-SMA (Swann et al., 2012). These increases of beta band power in the STN and in prefrontal regions known to be critical for stopping raise the intriguing possibility that these signatures are linked, and that a prefrontal-STN stopping system operates via "communication" in the beta frequency band (cf. Fries, 2005) (Fig. 1*A*). The evidence for this idea is clearer for tasks that elicit conflict, to which we now turn.

Conflict

Parallel to the research on stopping is research on the topic of response conflict and decision conflict. It was proposed that, when conflict is detected, the STN implements a "hold your horses" pause (Frank, 2006). This can be understood as follows (and see Zavala et al., 2015a). In the standard basal ganglia model, response initiation requires removing the GPi's inhibition of thalamus. However, in situations involving conflict, two or more premotor responses are simultaneously activated. This conflict signal is detected by dorsomedial frontal cortex (putatively the pre-SMA) (Taylor et al., 2007; Wiecki and Frank, 2013), which then recruits the STN via a hyperdirect pathway. The recruitment of the STN increases GPi's (supposedly broad) inhibition of thalamus. To overcome this, the movement-related corticostriatal input needs to be stronger to silence the GPi. The result is that a higher "threshold" of cortical evidence is needed to drive a response. Over time, the premotor representation associated with the correct response will rise, whereas those associated with other response representations will not. Eventually, the correct response will be selected, but with longer reaction time relative to low-conflict trials.

Several studies are now consistent with an STN role during conflict. Oscillatory power increases are seen for high conflict trials in the STN for Stroop, Eriksen Flanker, and decision tasks (Brittain et al., 2012; Cavanagh et al., 2011; Fumagalli et al., 2011; Zavala et al., 2013, 2014). The power increase is in the 2–8 Hz range, which we hereafter refer to as low-frequency oscillations (LFOs). There are also conflict-related LFO increases in scalp EEG sites corresponding to dorsomedial frontal cortex (Cohen and Cavanagh, 2011; Cavanagh et al., 2012). This picture from LFP studies fits with a substantial imaging literature showing that conflict activates dorsomedial frontal cortex, including parts of

the dorsal cingulate and also, notably, the pre-SMA (see meta-analysis) (Ridderinkhof et al., 2004). The observations that LFO increases in the dorsomedial prefrontal cortex (dmPFC, perhaps pre-SMA) and the STN, and that these are connected via white matter (see below), raises the possibility that a prefrontal-STN conflict system operates via intersite coherence in the LFO (as opposed to the beta frequency band for stopping) (Fig. 1*B*). Indeed, coherence for the LFO between the scalp EEG and the STN LFP has been shown for a perceptual decision-making task involving conflicting sensory information, and it was also suggested that the former causes the latter (Zavala et al., 2014).

While the empirical evidence reviewed above has pointed to the putative dorsomedial frontal-STN system, relevant neurocomputational models have also been developed. These make concrete predictions about the STN′s role in elevating decision thresholds so that more evidence is accumulated before responding (Bogacz and Gurney, 2007; Wiecki and Frank, 2013). Consistent with these models, two studies combining computational modeling of decision-making parameters with fMRI found that trial-by-trial variations in STN activity were positively correlated with variations in decision thresholds (Mansfield et al., 2011; Frank et al., 2015). In a recent study, Herz et al. (2016) recorded STN LFPs to further test the involvement of the STN in modulating decision thresholds. They found that LFO preceding the response predicted the adjustment of decision threshold on each trial during two perceptual decision-making tasks. Importantly, the exact relationship depended on the level of cautiousness in the respective task, so that increased LFO predicted increased thresholds only in the task inducing stronger response caution, although it predicted decreased thresholds in the simpler task. A possible neural mechanism underlying this context-specific modulation is the dynamic reconfiguration of distinct neural networks connecting the STN and cortical areas (Fogelson et al., 2006). In particular, as noted above, the dmPFC has been suggested to increase its influence over STN during conflict and increased task difficulty (Ridderinkhof et al., 2011; Wiecki and Frank, 2013). Consistent with this, the extent to which LFO in dmPFC and STN fall in to register is related to elevated decision thresholds and reduced error rates (Herz et al., 2016). The functional role of dmPFC-STN connectivity in setting decision thresholds is further corroborated by a study which found a correlation between decision thresholds and the interaction between STN BOLD activity and LFO in dmPFC EEG (Frank et al., 2015). Of note, this relationship was also specific to trials with high conflict.

Thus, these studies suggest that STN activity determines adjustments of decision thresholds depending on the "effectiveness" of cortical inputs from the PFC. Below we review the single-unit evidence during conflict tasks and explain how optimal alignment of the peaks and troughs in LFO between dmPFC and STN may provide a preferential "window in time" for single neuron communication (Zavala et al., 2015b; Herz et al., 2016). In this schema, adjustments of decision thresholds may then be instantiated through STN-mediated down modulation of movement facilitating corticobasal ganglia feedback loops when cautiousness is warranted, leading to decreased baseline activity and gain of cortical neurons integrating sensory evidence (Hanks et al., 2014; Thura and Cisek, 2016).

Imaging and anatomy

As we saw, research on stopping points to the critical importance of the right IFC and pre-SMA, and research on conflict points to dmPFC, including the pre-SMA. Because stopping needs to be very quick, and perhaps broad in its effects, a hyperdirect cortical-STN system may be recruited; and the same rationale may apply to conflict. Several lines of evidence support the hyperdirect pathway idea

First, studies that stimulate cortex and record from the STN in a rodent reveal a short latency (<10 ms) glutamatergic input (Magill et al., 2004; for review, see Nambu et al., 2002). Second, early tracing studies in monkeys emphasized direct connections to the STN from primary motor, and premotor cortex (including the pre-SMA) (Nambu et al., 1997; Inase et al., 1999). Recently, a large study injected anterograde tracers into multiple sites in macaque primary motor and prefrontal cortex (PFC), including ventromedial prefrontal, orbitofrontal, anterior cingulate, and dorsal prefrontal cortices (Haynes and Haber, 2013). This study revealed a topographically organized hyperdirect pathway: with primary motor cortex projecting to dorsal STN, premotor cortex to a slightly more ventral area, dorsolateral PFC to an even more ventral area and on toward the "limbic" STN tip. This elegant study has significant implications for the current view on the topographic organization of the STN: it suggests that, rather than a simple tripartite motor/associative/limbic organization (Temel et al., 2005), the STN instead represents an overlap over multiple domains based on different cortical inputs (Alkemade, 2013; Alkemade et al., 2015). Third, human studies using diffusion tensor imaging have also provided evidence for connections between PFC and STN. It was shown that both pre-SMA and right IFC project to a midbrain area consistent with the STN (Aron et al., 2007), and several studies have ratified this and showed that white matter variability in these connections relates to stopping speed (Coxon et al., 2012; Forstmann et al., 2012; King et al., 2012; Rae et al., 2015; Xu et al., 2016). Future studies, including ultra-high resolution 7 tesla (or higher) structural MRI and fMRI with submillimeter resolution will provide the opportunity to investigate more fine-grained topological differences within the STN in humans (see, e.g., Keuken and Forstmann, 2015). This could be used to test one implication of our theory, which is that, consistent with the monkey tract tracing results (Haynes and Haber, 2013), stopping (putatively originating in lateral PFC) should activate a more ventral sector of STN than conflict (putatively originating in pre-SMA).

Although there is substantial anatomical and imaging evidence for hyperdirect pathways, it is notable that there is still scant functional evidence that these pathways implement stopping or conflict. Perhaps the only specific evidence to date is a study in nonhuman primates, which showed that the requirement to override a planned saccade produced single-unit STN increases ~10 ms after single-unit increases in the pre-SMA (Isoda and Hikosaka, 2008). This small timing difference is consistent with a hyperdirect pathway without intervening synapses.

Single-unit studies

Although changes in oscillatory power relate to the decision processes in cortex and STN, it is the interaction between oscillations and the firing rate dynamics of the basal ganglia that are ultimately responsible for how an action unfolds. We now turn to single-unit STN recording studies of stopping and conflict.

A recent study of stopping in the rat recorded single-unit activity from multiple basal ganglia nuclei, including STN and SNr (rodent GPi) (Schmidt et al., 2013). In the SNr, the firing rate decreased following the Go signal, consistent with the classic direct pathway view of a striatal GABAergic influence. In the STN, firing increased quickly after the stop signal on both successful and failed stop trials, consistent with the idea that it was being

recruited to stop the action. Strikingly, on successful stop trials, the firing rate in the SNr increased ~16 ms after the STN, consistent with the idea of countermanding the initiated motor command, whereas on failed stop trials this did not happen. The suggestion that STN spiking activity may be involved in stopping has been supported in both primates and humans. In a recent study examining human STN neuronal responses during a stopping task, one population activated during successful inhibitory control, implicating at least some STN neurons in stopping (Bastin et al., 2014). Similarly, in a primate study, a population of neurons exhibited increased phasic spiking activity when switches were made from automatic to volitionally controlled saccades (Isoda and Hikosaka, 2008). These data suggest that STN spiking activity is involved in inhibiting motor responses, but future research is required to establish whether the STN only implements a pause, or can also stop responses outright.

For conflict, several studies have shown that STN spiking activity is modulated when subjects are asked to prevent or delay responses or when they make decisions during high levels of doubt (Zaghloul et al., 2012; Burbaud et al., 2013; Zavala et al., 2015b). In these cases, spiking activity within the STN increases when the behavioral demands require a decision among competing alternatives, which although not identical to the demands required during stopping, nevertheless involves halting a motor signal until enough information or evidence has been acquired to properly proceed. Regardless, whether these decisions involve choices between learned associations (Zaghloul et al., 2012) or simple sensorimotor decisions involving visual conflict (Zavala et al., 2015b), STN spiking activity increased in the presence of conflict. These increases are consistent with the idea that STN spiking activity exerts a suppressive effect on motor signals, and in the context of decisions, would play a role in effectively adjusting the threshold for activating a specific motor command.

These single-unit results raise some puzzles for the classic model of the basal ganglia. This classic model posits that the striatum inhibits firing rate in GPi via the excitatory direct pathway (Go), and that striatum increases the firing rate in the GPi via the GPe (i.e., via the inhibitory indirect pathway, Stop) (Albin et al., 1989; DeLong, 1990)—and also supported by some optogenetic studies, (e.g., Kravitz et al., 2012). Within this classic framework, activity in the STN has been hypothesized to play a role in stopping motor responses via the inhibitory indirect pathway (Bogacz and Gurney, 2007; Isoda and Hikosaka, 2008). Although the traditional model assigns STN firing an antikinetic role over thalamocortical drive, the functional architecture is likely more complex. First, it is not clear whether it is solely changes in firing rate that are important for STN activity or whether it is instead changes in the temporal patterns of activity (Nambu et al., 2015). Second, both direct and indirect pathways are recruited as part of movement (Cui et al., 2013) and different neuronal subpopulations within the STN show opposite patterns of spiking: some populations increase while others decrease with movement (Bastin et al., 2014; Nambu et al., 2015; Zavala et al., 2015b). These contrary responses in STN firing, also seen in songbirds (Goldberg et al., 2013), suggests that neuronal populations within the STN are heterogeneous in their response to movement. One possible explanation, which is not straightforward to reconcile with global suppression, is that motor circuits within the basal ganglia are organized in multiple parallel loops with a center-surround architecture (Mink, 1996; Nambu et al., 2002). In this scheme, decreases in STN activity are specific to circuits involved in a desired motor movement, facilitating a command to move a single finger, for instance, whereas undesired movements, such as those of the other fingers, would be suppressed by increases in the corresponding circuits responsible for those actions within the STN. Better understanding STN spiking, and directly testing, for example, the center-surround idea, will entail more nonhuman animal research, which is better placed to address these questions. Moreover, as the basal ganglia are increasingly implicated in other aspects of human cognition (Weintraub and Zaghloul, 2013), it also remains unclear whether and how this complexity extends to nonmotor processes that may be mediated through parallel associative and limbic loops (Haber, 2003; McHaffie et al., 2005). Given this complexity, how STN firing activity is involved in stopping and conflict, and whether this is mediated through specific interactions with the indirect pathway or through broad suppressive effects in response to cortical signals relayed via the hyperdirect pathway are an active area of investigation.

Thus, conflict induces both firing rate and oscillatory changes in the STN. How are these signatures linked? Recent evidence from other tasks and modeling suggest that oscillations in the LFP modulate firing rates, and that this is a general mechanism of neural computation that also underlies long-range connectivity (Fries, 2005; Sejnowski and Paulsen, 2006; Rutishauser et al., 2010; Buzsáki et al., 2012; Lisman and Jensen, 2013). Indeed, studies of conflict have shown that single-unit activity within the STN exhibits preferential firing during the peaks of theta and beta oscillations in the presence of conflict (Zavala et al., 2015b). As we saw, there is some evidence from conflict studies that cortex and the STN communicate through frequency-specific oscillations. In this scheme, the medial PFC and right IFC may therefore influence the timing of responses during action selection through synchronized oscillations with the basal ganglia that affect STN spiking activity. Addressing how and whether this occurs is important in ascribing functional significance to the putative hyperdirect pathway between these regions, and also of wider interest for better understanding long-range communication in the human brain.

How the STN may impact cognition

The STN "pause" function may be recruited by other behavioral requirements than outright stopping to a stop signal and slowing when conflict is detected. One case is that the STN is also apparently engaged by surprising perceptual events. In one paradigm, subjects got ready to respond to an imperative stimulus, but this was preceded by a tone: mostly it was standard, but occasionally it was surprising. Surprise activated the cortical stopping system (Wessel and Aron, 2013), activated the STN (Wessel et al., 2016a), and produced the same transcranial magnetic stimulation signatures of global motor suppression as outright stopping (Wessel and Aron, 2013).

If an STN-mediated stopping system has a broad effect on the skeletomotor system, it might also have an effect on cognition (at least perhaps those aspects of cognition that relate to the motor system, such as verbal and visuomotor working memory [WM]). This was tested by embedding surprising events within a WM paradigm. On each trial, the human subject encoded a letter string into WM, then held this across a delay, then a standard or surprising tone occurred, and soon after that the subject's WM was probed. Surprising events reduced WM accuracy, activated the cortical stopping system, and activated the STN: the more so, the greater the WM decrement (Wessel et al., 2016a). It was argued that verbal WM (at least) is maintained by "looping" thalamocortical drive, and STN activation by the surprising event pauses this, which dec-

rements WM. Thus, the STN may induce pauses, not just in motor output but also in cognition.

Conclusion

In conclusion, we have focused on how the STN is engaged by stopping, conflict and, as recently shown, surprising events. A general computational function of the STN appears to be to generate a pause. Under some circumstances, this could allow time for more evidence to accumulate to do the "right thing"; in the case of surprise, this putatively interrupts cognition, which could lead to forgetting recent information but also better encoding of new information. Notably, stopping and surprise have a broad suppressive effect on the skeletomotor system, which may relate to the putatively broad impact of the STN on basal ganglia output, although anatomical evidence is still weak.

Stopping recruits prefrontal areas, such as the right IFC and pre-SMA, whereas conflict recruits dmPFC (probably including the pre-SMA). It is thought that these prefrontal areas project to the STN via hyperdirect pathways, for which there is substantial anatomical and imaging evidence, although still scant functional evidence. Stopping (which is an outright form of "response inhibition") is associated with an increase in beta band oscillations in the STN, whereas conflict is associated with an increase in LFOs. Another way of seeing this dissociation is that conflict reflects a need for control (related to LFO) and stopping reflects the implementation of control (related to beta), which could also reflect a cognitive/motor split. We hypothesize that stopping and conflict are implemented by dissociable fronto-STN pathways: stopping engages right IFC and a more ventral part of the STN and involves activity in the beta band, whereas conflict engages pre-SMA and a more dorsal part of the STN, and LFO (Fig. 1). These putatively dissociable circuits and functions could be recruited in close temporal succession, perhaps even in the same trial: for example, a study of the Stroop showed increases in both STN LFO and beta power (Brittain et al., 2012) consistent with recruitment of both conflict (to slow responding) and response inhibition (to prevent the irrelevant response) systems.

Yet the idea of topographical separation of LFO and beta in the STN needs to be further substantiated. Studies of the distribution of the power and reactivity of such activities have not so far provided conclusive evidence, in part because of the relatively poor spatial resolution of LFPs recorded from DBS electrodes, given the small size of the STN (Rodriguez-Oroz et al., 2011; Alegre et al., 2012; Zavala et al., 2014). The question may also be raised why neurons in the STN need to receive different inputs according to their topography when the relevant information is already separated by carrier frequency. We suppose that an organization that uses both systems of keeping information streams separate (frequency band and anatomical location) might help ameliorate problems associated with reliance on just one system (i.e., limits of information coding capacity in the frequency domain and limits of integration across channels in the anatomical domain).

Studies of stopping and conflict show that there are firing rate changes in the STN; and for conflict at least, single-unit activity within the STN exhibits preferential firing during the peaks of theta and beta oscillations in the presence of conflict (Zavala et al., 2015b). This suggests that mPFC (and perhaps similarly inferior frontal gyrus) may therefore influence the timing of responses during action selection through synchronized oscillations with the basal ganglia that affect STN spiking activity.

Our theory of dissociable networks for stopping and conflict could be tested in several ways, including by developments with *in vivo* ultra-high resolution MRI that allows testing these more fine-grained hypotheses about corticosubthalamic networks. When combined with postmortem histology and other data, this could help resolve functional subdivisions in the STN. Moreover, validating the idea of dissociable networks for stopping versus conflict could help to design more focused DBS approaches that optimize decision-making while minimizing side effects on speech and cognition.

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