REVIEW

Parkinson's Disease, the Subthalamic Nucleus, Inhibition, and Impulsivity

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ABSTRACT: Although Parkinson's disease (PD) is primarily considered a disorder of initiation of actions, patients also have deficits in inhibitory control, both in the motor and cognitive domains. Impulse control disorders, which can develop in association with dopaminergic medication in a small proportion of patients with PD, are the symptoms most commonly considered as representing inhibitory deficits. However, there is now also a body of evidence suggesting a role for the subthalamic nucleus (STN), which is ordinarily hyperactive in PD, in inhibitory control. Here, we review evidence from animal studies, imaging studies, and investigations recording STN activity intra- or perioperatively in patients with PD having surgery for DBS of the STN (STN-DBS). We also highlight relevant hypotheses about the role of the STN and consider evidence from studies that have examined the effect of STN-DBS in patients with PD on performance of experimental tasks requiring inhibition of prepotent or habitual responses or decision making under conflict, as well as the psychiatric side effects of STN-DBS. Though the results are not always consistent, nevertheless, this body of evidence supports the role of the STN in inhibitory and executive control. © 2014 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; subthalamic nucleus; inhibition; impulsivity

Given that bradykinesia and akinesia are among the main symptoms of Parkinson's disease (PD), the disorder is commonly considered to involve an initiation and execution deficit, but also reduction of automatic movements, such as blinking, gesturing, or arm swing. However, bradykinesia and akinesia can also be conceptualized as a failure of phasic release of cortical motor and premotor areas from the tonic inhibition of the basal ganglia, which is the way it has been conceptualized in the Albin et al.[1] and De Long[2] models. Excessive inhibition of the intention to move is also reflected by freezing of gait, episodes when initiation of movement is temporarily blocked and patients feel as if their feet are glued to the floor, which are common in PD and induced by turning, fatigue, confined spaces, and stressful situations.[3] In contrast, levodopa-induced dyskinesias, involuntary movements that develop in PD after long-term therapy, represent excessive disinhibition of movement and are considered to reflect reduced inhibitory output from the basal ganglia.[4]

The profile of executive dysfunction in PD includes deficits in inhibitory control.[5] There is evidence from studies using tasks, such as go no-go reaction times (RTs) and stop signal tasks, which respectively

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measure action restraint and motor inhibition, that PD patients have deficits in motor inhibition (e.g., see previous works[6-10]). In addition, PD patients have inhibitory deficits on executive control tasks necessitating inhibition of habitual or prepotent responses for selection of appropriate responses, such as on the Stroop, random number generation, and the Hayling, Simon, or Eriksen flanker tasks.[8,10-13]

PD is characterized by hyperactivity and synchronized oscillatory activity of the STN and the internal segment of the globus pallidus (GPi).[14,15] In PD, inhibitory deficits are commonly considered in relation to impulse control disorders (ICDs) associated with treatment with dopaminergic medication. However, there is now a body of evidence that relates the STN to inhibition and impulsivity (for review, see[16,17]). In this article, our aim is to examine the role of the STN in inhibitory control by reviewing evidence from animal lesion studies, imaging in humans, electrophysiological and behavioral studies following surgery in PD, and consideration of the psychiatric problems encountered after such surgery, which suggest failure of inhibition and impulsivity.

The STN, Inhibition, and Impulsivity

The STN is a small, lens-shaped nucleus, which is part of the indirect pathway and also receives inputs from various frontal areas, including the motor cortex, pre-SMA (supplementary motor area), caudal and dorsal premotor cortex, dorsolateral prefrontal cortex, anterior cingulate, and inferior frontal cortex through the hyperdirect pathway.[18-20] The hyperdirect pathway is the shortest and quickest route for influencing the tonic inhibition of the GPi/SNr over cortical areas and achieving inhibition of action. Dorsal, central, and medial sections of the STN have been related to motor, associative, and limbic functions, respectively, identified in monkeys using anterograde tracing[21] and also in humans with imaging,[22] although, from a meta-analysis of the evidence, this tripartite division has been questioned.[23]

DBS of the STN (STN-DBS) is now established in randomized, controlled trials as an effective therapy for the motor symptoms of PD.[24-26] It has been proposed that, in PD, STN-DBS interferes with the normal function of the STN in situations of conflict, which is to send a "hold your horses" or "no go" signal to temporarily raise the response threshold to allow time for information accumulation before a decision is made and a response is produced. Therefore, alteration of STN activity by STN-DBS in PD is predicted to result in fast, impulsive responding when faced with conflict.[27]

Behavioral inhibition is most commonly studied in terms of its failure. This failure includes impulsivity, perseveration, disinhibition, obsessions, and compulsions, symptoms that are features of different psychiatric disorders. The STN has been shown to play a role in these various forms of inhibitory failure. Impulsivity, one of the symptoms associated with inhibitory deficits, can take many forms. Responding fast without taking time for reflection (impulsive action or reflection impulsivity), a preference for immediate small rewards rather than delayed larger rewards (aversion to delayed gratification), inability to withhold or delayed inhibition of prepotent responses (delayed motor inhibition), and engaging in more risky decision making (risk-taking) are some of the characteristics of impulsive individuals.[28,29] Various types of behavioral inhibition have been distinguished, including reactive (e.g., stopping at a zebra crossing when a motorbike approaches), proactive (e.g., refrain from smoking when trying to quit), global, and selective,[30] with varying degrees of relevance to impulsivity and other symptoms of psychiatric disorders. Inhibition is also relevant to conflict resolution or in decision making and response selection under conflict as these necessitate, inhibition of inappropriate, habitual, or prepotent responses to allow selection of the appropriate response.[16,17]

There are several experimental tasks commonly used to measure motor inhibition. On the go no-go reaction time task, participants respond on go trials when a go stimulus is presented and withhold a response on more infrequent no go trials. The stop signal task provides an estimate of the time for cancellation of a response when a stop signal is presented with a variable delay after a go signal that triggers the response. The Eriksen flanker and the Simon tasks allow assessment of how well participants can ignore irrelevant stimuli and engage in response selection under conflict. A number of cognitive tasks require executive and inhibitory control over prepotent responses in order to generate alternative strategic responses. Tasks such as the Stroop color word interference task (color words such as red, blue, and green are printed in incongruent ink and participants have to name the color of ink they are presented in) requires inhibition of the prepotent response of reading the words to engage in the alternative response of naming the color of ink they are presented in. Similarly, in random number generation, participants have to inhibit the prepotent and habitual response of counting in series and instead generate responses in a random fashion.

Evidence From Animal Lesion Studies

The first study reporting the effects of STN lesions on animal behavior was that by Whittier and Mettler[31] showing ballism in the monkey. STN was little studied before the end of the 1980s, when there was renewed interest in the context of parkinsonism. Then, Bergman et al.[32] showed the beneficial effect

TABLE 1. Animal lesion or electrophysiology studies providing evidence for the role of the STN in inhibition arranged by year of publication

Investigator	Year	STN Manipulation	Task	Effect
Baunez et al.[33]	1995	Bilateral STN lesion	Simple RT	Increased premature responses
Baunez and Robbins[36]	1997	Bilateral STN lesion	5-choice SRTT	Increased premature and perseverative responses
Baunez and Robbins[42]	1999	Bilateral STN muscimol	5-choice SRTT	Increased perseverative responses
Phillips and Brown[37]	2000	Unilateral STN lesion	Simple vs. choice RT	Increased premature responses
Baunez et al.[38]	2001	Bilateral STN lesion	Simple vs. choice RT	Increased premature responses, perseveration on previous response
Desbonnet et al., 2004[43]	2004	Bilateral STN-DBS	Choice RT	Decreased premature responses depending on parameters
Winstanley et al.[125]	2005	Bilateral STN lesion	Delay-discounting	No discounting
Uslaner et al.[39]	2006	Bilateral STN lesion	DRL	Increased premature responses
Baunez et al.[41]	2007	Bilateral STN-DBS	5-choice SRTT	Increased perseverative responses
Eagle et al.[44]	2008	Bilateral STN lesion	Stop-signal RT task	Increased errors (impaired stop of an ongoing response)
Eagle et al.[126]	2008	Bilateral STN lesion	Equivalent Go-NoGo (stop task with 0 delay)	Impaired no-go
Isoda and Hikosaka[78]	2008	Recording STN neurons	Go-NoGo (monkey)	Different responses at NoGo than Go
Lardeux et al.[127]	2009	Recording STN neurons	Reward (4% vs 32% sucrose) cued RT task (rat)	Responses at cue light predictive of future premature response
Aleksandrova et al.[40]	2013	Bilateral STN lesion	Gambling task for rats	Increased premature responses
Schmidt et al.[47]	2013	Recording STN neurons	stop-task (rat)	Delayed response to stop signal
Lardeux et al.[46]	2013	Recording STN neurons	Reward (cocaine vs. sucrose) cued reaction time task (rat)	Responses at cue light predictive of future premature response

SRTT: Serial reaction time task.

of STN lesions in MPTP monkeys, restoring gross motor behavior. When assessing more subtle motor functions, it was established that STN lesions were inducing nonmotor effects that were related to the control of inhibition, given that they increased premature responding and perseverative behavior.[33] Further studies have since shown that STN lesions increased impulsivity, especially impulsive action among the various possible forms of impulsivity (for review of animal evidence, see a previous work[34]).

Animal studies showing inhibitory deficits following STN lesions are summarized in Table 1. The most common measures of impulsive action in the rat are premature or perseverative responses. The 5-choice serial reaction time task (5-CSRTT) is often used to measure impulsive action.[35] Rats are trained to detect a brief visual stimulus presented in one of five apertures and respond by a nose poke in it. The critical issue is that the animal has to withhold its response during a fixed (5s) or variable intertrial interval, leading to the possibility that the animal engages in "impulsive action" while waiting for the imperative cue. Bilateral lesions of the STN increase premature responding on this task,[36] as well as in various forms of RT task[33,37,38] or other behavioral tasks, such as a decision-making task mimicking a gambling task or the differential reinforcement at low rate task.[39,40]

Interestingly, pharmacological blockade or STN-DBS do not always induce entirely similar results to those observed after STN lesions. Muscimol infusion into the STN, as well as bilateral STN-DBS increased perseverative responses with no premature responses in the 5-CSRTT[41,42] or even decreased premature responses depending on the parameters.[43]

In a go no-go RT task, when measuring the ability of rats to withhold a prepotent response to a "no-go" stimulus, STN lesions impaired the equivalent of a no-go response.[44] In the monkey, electrophysiological recording has revealed that STN neurons show the property to respond either specifically to go or no-go trials, highlighting the involvement of STN in the inhibition of undesired saccades and facilitation of selected desired saccades.[45] In a task developed to assess reward-related activity, but measuring RT to withdraw a lever, it was shown that the STN neuronal activity recorded at the presentation of the cue light predicting

TABLE 2. fMRI studies showing significant STN activation in relation to motor inhibition arranged by year of publication

Investigators	N	Task Details	Contrast Showing STN Activity	Main Findings
Aron and Poldrack, 2006[54]	18 HC	2-choice stop signal: 25% stop trials auditory stop signal, staircase tracking procedure	StopInhibit>Null; StopInhibit>go StopRespond>null	Go RTs activated frontal, striatal, pallidal, and motor regions, Stop right IFG, pre-SMA, GP, and STN. Longer stop delays, produced greater STN activation.
Aron et al., 2007[51]	15 HC	*Conditional* stop signal task, 25% stop trials, auditory stop signal, staircase tracking procedure	StopInhibit>go (critical direction) StopRespond>Go (noncritical)	rIFG+rSTN more activated with faster SSRT; pre-SMA more active in conflict trials; IFG-STN role in stopping; STN had correlations with IFG pars triangularis.
Li et al., 2008[53]	30 HC	Simple RT stop signal task, visual stop signal, staircase tracking procedure	Long>short SSRT	STN greater activity in long SSRT and stop errors trials; head of caudate activation with faster SSRT; correlated with pre-SMA
Forstmann et al., 2012[128]	13 HC	Stop signal task, auditory stop signal, staircase tracking procedure	Probability maps of STN peak activation	Medial prefrontal cortex had greater functional connectivity with the STN during response inhibition.

IFG, inferior frontal gyrus.

the reward (sucrose or cocaine) could be predictive of future early withdrawal of the lever in case of an activation, whereas inhibition after the cue was predictive of a correct response.[46] This further supports the role of the STN in the control of inhibition.

On a modified stop signal task, STN lesions in rats impaired the stopping behavior, even when the stop signal was presented very early in the trials (even with zero delay, which is equivalent to a no go trial).[44] A recent electrophysiological study in rats[47] showed that STN neurons had low latency responses to the stop cue, regardless of whether or not the animal was able to stop the go response, suggesting that the STN provides fast signals to stop action. In contrast, SNr neurons only responded to stop signals on successfully inhibited trials, whereas striatal neurons were active on presentation of go, but not stop, signals. It was proposed that the results support the interactive race model, with the relative timing of the distinct inputs to the SNr from the striatum or STN, respectively, determining stopping failure and success. Perhaps a missing component in earlier works is the contribution from the GPi and SNr[47,48] to such a stopping process, given that these final output pathways convey the final signal through the thalamus back to the cortex before an action is withheld or exerted.

Evidence From Imaging and Transcranial Magnetic Stimulation Studies

Previous lesion studies in humans[49,50] investigating inhibition revealed causal roles of the right inferior frontal cortex (IFC), the pre-SMA, and SMA proper. Imaging studies have identified brain networks involved in stopping actions, including frontal regions together with subcortical areas, such as the STN or caudate.[51-54] Table 2 provides a summary of the imaging studies that have revealed activation of the STN during motor inhibition. A functional MRI (fMRI) study used a conditional stop signal paradigm to investigate the functional networks involved in motor inhibition and conflict resolution.[51] They first used diffusion-weighted imaging (DWI) to show connections between the pre-SMA, IFC, and STN.[51] The results showed that a similar network was activated during both response inhibition and conflict resolution, involving the right pre-SMA, right IFC, and right STN regions. The IFC and STN activity correlated with each other, and the measure of behavioral inhibition, the stop signal reaction time (SSRT), and were considered key nodes in the inhibition network. The STN was also shown to be particularly engaged by late inhibition, as reflected by correlations of STN activation with longer stop signal delays.[54]

Some theoretical and computational models predict that stopping is achieved by a top-down control network between the IFC and the STN using the hyperdirect route.[27,55-57] However, there is controversy about this proposal, given that inhibition has also been shown to be implemented through the indirect pathway between the striatum and the output structures of the basal ganglia, by way of the STN.[47,53,58,59] Using effective connectivity, the STN was shown to receive information from the IFC to interrupt activity through the hyperdirect pathway.[56,57] Moreover, joint function of the pre-SMA and striatum[52] as well as the STN[60] become important in highly demanding conditions where speed and accuracy behavioral adjustments are required, which, connectivity analysis suggest, rely on the indirect pathway.[57] Evidence suggests that the striatum and the indirect pathway are involved in stopping behaviors proactively or selectively,[59] whereas global

inhibition may be achieved through the hyperdirect pathway.[48]

To address the question of which corticosubcortical pathways mediate motor inhibition, the use of transcranial magnetic stimulation (TMS) combined with imaging allows for direct testing of causal influences from cortical regions to subcortical networks and pathways during response inhibition. Increased right striatal and decreased motor cortex activity was found after TMS was applied over the right IFC and pre-SMA.[61]. Another combined TMS and imaging study during a stop signal task showed that TMS to the right pre-SMA was associated with significant activation of the left pre-SMA.[62] Finally, a study examined correlations between TMS effect sizes (between motor cortex and the pre-SMA and IFC) and white matter connecting pre-SMA and IFC to STN[63] during a switching task and reported significant correlations with the STN (at a latency of 12 ms).

Several imaging studies have examined the effects of STN-DBS on patterns of brain activation during performance of cognitive tasks requiring inhibitory and executive control in PD patients. These have shown that switching STN stimulation on is associated with significant *decreased* activation in key frontal areas, including the pre-SMA, IFC, dorsolateral prefrontal cortex, and anterior cingulate cortex, during tasks that require inhibitory and executive control for response selection under conflict and suppression of habitual or prepotent responses, such as the Stroop,[64] fast-paced random number generation (RNG),[65] or the go no-go task.[66]

In summary, imaging and TMS studies have identified the pre-SMA and IFC as critical cortical areas and highlighted the importance of both the indirect and hyperdirect basal-ganglia-cortical pathways when an action needs to be cancelled.

Evidence From Electrophysiological Studies in PD Patients Undergoing STN-DBS Surgery

The implantation of electrodes for DBS in the STN has allowed the recording of STN activity in PD patients. Intraoperative microrecordings help to improve STN localization before DBS implantation and offer an excellent window to explore neuronal responses to motor or cognitive tasks. In addition, the DBS electrode can also be used to record local field potential (LFP) activity from the STN during surgery or, more usually, in the immediate postoperative phase before internalizing the connection cables and the implantable pulse generator. Most of the direct neurophysiological evidence of the STN role in inhibition comes from postoperative studies, given that these allow longer recording times.

Recent studies from three groups[67-69] have specifically looked for changes in STN LFP activity during stop signal tasks. The changes observed, which confirm the role of the STN in motor inhibition, involve the three most relevant bands described in STN activity: beta, gamma, and theta.

Despite some methodological differences, the three studies show parallel results in the beta band (Fig. 1A,C.D). A voluntary movement is usually accompanied by a decrease in beta activity in the STN. This decrease begins before the movement, reaches its minimum value shortly after the movement has begun, and is followed by a "rebound" after the movement is completed.[68] This pattern was observed in the three studies in the "go" trials. However, in the "stop" trials, when the patient successfully inhibited the response, the beta decrease was consistently smaller, faster, and shorter. This difference in beta activity between these two types of trials (Fig. 1C, bottom) strongly suggests that beta-band subthalamic activity is involved in reactive inhibition. Similar inhibition or conflict-resolution–related beta changes have been found in go no-go and Stroop tasks, using similar postoperative LFP recordings.[70,71] Additionally, beta activity might also have a role in proactive inhibition. Benis et al.[68] added an additional type of trial to the stop signal task, a group of trials in which the patient knew that there would be no stop signal (named go-fast trials). When beta changes were compared between the go (where occurrence of a stop signal on a proportion of trials was possible) and the go-fast trials, the beta decrease was deeper in the go-fast condition (Fig. 1E). This difference may indicate that a higher level of beta activity is also related to proactive inhibition, given that its decrease is smaller when the patient expects that there may be a stop signal indicating inhibition of the response (go trial), than when he or she knows for certain that there will be no stop signal (go fast trial).

Gamma changes in the STN were also investigated using the stop signal task in two of these studies.[67,69] A voluntary movement is accompanied by a gamma increase in the STN, which is proportional to the motor effort.[72] Alegre et al.[69] found that in the go and failed stop trials in the "on" motor state, there was a gamma increase around the time of the motor response (as expected), whereas in the stop-inhibit trials (successful inhibition trials), there was a decrease in gamma activity (Fig. 1B). In line with these findings, Ray et al.[67] also described a higher gamma increase during failed stop trials than during successfully inhibited trials, although the difference was not statistically significant. These results again suggest the existence of an active process in the STN related to the presence of the stop signal and the successful inhibition of the response. The suppression of gamma activity may be related to the suppression of the intention to move and indeed could represent the physiological marker of the braking or hold your horses

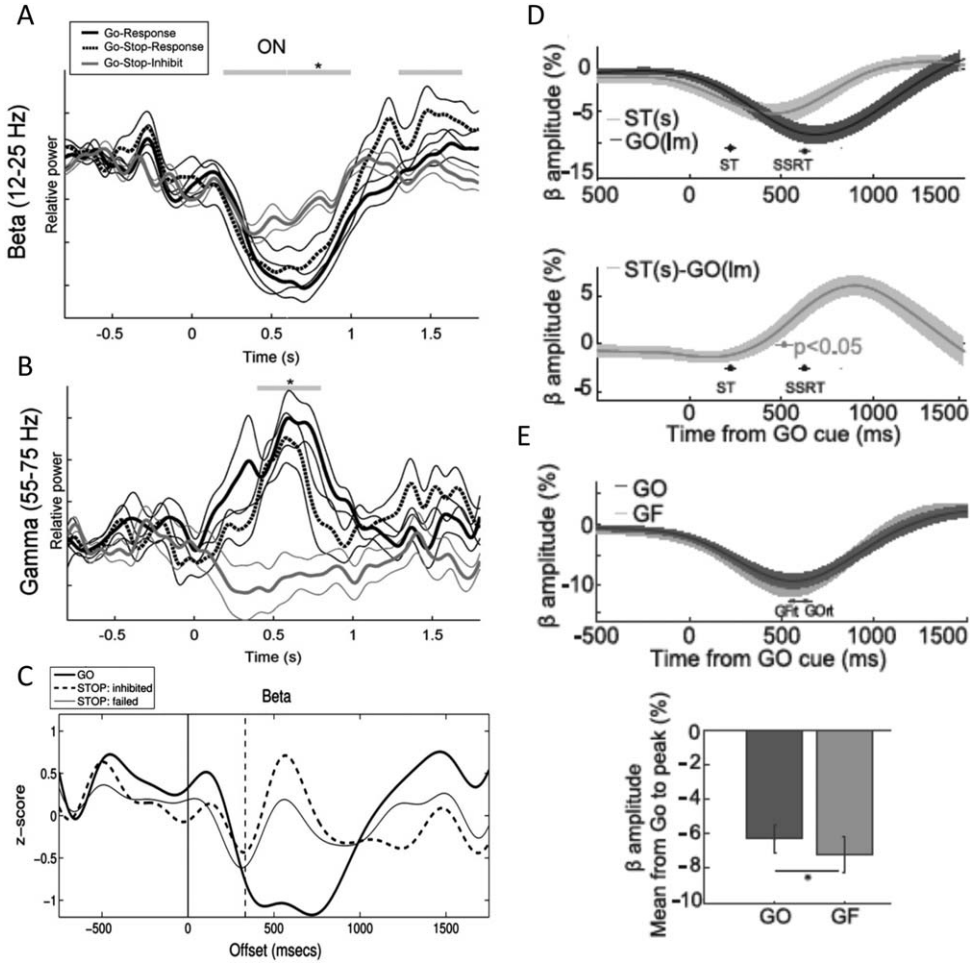

FIG. 1. Beta- and gamma-band activity in LFPs recorded from the STN in patients with PD during performance of stop signal RT tasks. (A and B) Beta (A) and gamma (B) relative power changes during different trial types in Alegre et al. (2013).[69] (C) Beta z-score change values during different trial types in Ray et al. (2012). (D) Beta relative amplitude changes during stop and go trials in Benis et al. (2014). (E) Beta relative amplitude changes in go and go-fast trials in Benis et al. (2014). During the go trials (Go-response in A, Go in C, and GO(lm) in D), in which there is no stop signal, beta activity shows a marked decrease that begins after the go signal and is followed by a small rebound over baseline. During stop trials (Go-stop-inhibit in A, Stop: inhibited in C, and ST(s) in D), in which the response is successfully inhibited after a stop signal, the beta decrease is faster (peaks earlier), shorter, and smaller. In the trials with a stop signal in which the patient could not stop (Go-stop-response in A and Stop: failed in C), the beta changes are intermediate between the other trial types. This result has been consistently observed in different studies despite the differences in paradigms and measures (relative power in A, Z-score in C, relative amplitude in D, go signal as trigger in A and C, and stop signal as trigger in D). Gamma activity in Alegre et al. (2013) (B) showed a different behavior in go and stop trials: Although there was an increase in go trials (go-response), a decrease was observed in successful stop trials (go-stop-inhibit). These differences were only noted in the "on" motor state. Benis et al. (2014) also studied the relationship of beta activity and proactive inhibition, comparing go trials with and without stop signal presentation after the go signal (Go [G] and Go-fast [GF] trials, respectively). When the patient knew that there would not be any stop signal, the beta decrease was more intense (E). Note that panel (A) and (B) trial types refer to Go-Stop-Response or Go-Stop-Inhibit, whereas panel (C) similar trial type is referred as STOP:failed or STOP:inhibited, respectively. (A) and (B) are adapted from Alegre et al. (2013; with permission); (C) is adapted from Ray et al. (2012; with permission). (D) and (E) are adapted from Benis et al. (2014; with permission).[68]

function attributed to the STN.[55] Moreover, whereas beta corticosubthalamic coherence appears to be cortex-driven, gamma coherence is probably STN-driven or bidirectional.[73,74] Additionally, the failure to inhibit gamma activity during successful inhibition on the stop signal task in patients with ICDs[69] may support a direct relationship between modulation of the gamma band and impulsivity.

On two tasks requiring inhibition of inappropriate (verbal fluency) or habitual (random number generation) prepotent responses, increased STN gamma band activity was observed, which positively correlated with measures of switching (verbal fluency) and controlled processing and negatively with measures of automatic processing (random number generation).[75,76] The increased STN gamma band activity observed in these studies may reflect the switch from automatic to controlled processing on these attention- and resource-demanding cognitive tasks, consistent with the proposal that the STN implements a signal from the prefrontal cortex to switch from automatic to controlled processing, as necessitated by task demands or context.[77,78]

TABLE 3. Studies of the effects of DBS-STN in PD on tasks involving inhibition of prepotent or habitual responses, response selection under competition, or decision making under conflict, arranged by year of publication

Investigator	Year	Medication Status	Worse With STN-DBS	Unchanged With STN-DBS	Improved With STN-DBS
Jahanshahi[86]	2000	Off	Stroop interference task		
Schroeder[64]	2002	Off	Stroop interference task		
Hershey[90]	2004	Off	Go no-go RT with high target frequency	Go no-go RTs with lower target frequency	
Van den Wildenberg[92]	2006	On		Go no-go RTs	Stop Signal RT task
Witt[87]	2006	On	Stroop interference task		
Thobois[65]	2007	Off	Fast-paced RNG		
Castner[129]	2007	On		Picture Word Interference Task	Hayling Sentence Completion Task
Frank[27]	2007	On	Probabilistic decision making under high conflict		
Castner[130]	2008	On	Greater errors on noun-noun and verb-verb generation tasks, and latter deficit correlated with item selection constraint		
Campbell[131]	2008	Off		Go no-go RTs	
Ballanger[66]	2009	Off	Go no-go RT		
Ray[91]	2009	On	Stop signal RT Task		
Wylie[95]	2010	On	Simon Task—fast responses		Simon Task—slow responses
Hershey[97]	2010	Off	Go no-go RT—with ventral STN-DBS		
Greenhouse[98]	2010	On		Stop Signal RT Task—DBS of ventral vs. dorsal contacts	
Yugeta[132]	2010	On		Antisaccade task	Memory-guided saccades
Swann[133]	2011	On			Stop Signal RT task
Mirabella[134]	2011	Off			Stop Signal RT task
Cavanagh[89]	2011	?	Probabilisitic decision making under high conflict		
Coulthard[88]	2012	On and Off	Probabilistic decision making requiring integration of conflictual information		
Favre[124]	2013	On			Release of proactive inhibition in unwarned simple RT
Obeso[93]	2013	On	Conditional Stop Signal RT Task		
Green[95]	2013	On	Moving Dots Task		
Pote[96]	2014	On	Moving Dots Task		

Theta-band activity has been related to decision conflict, both in the frontal cortex and in the STN. The potential role of the STN in this regard is also supported by the findings of a conflict-related increase in firing rate in an intraoperative study using a probabilistic decision task.[79] More direct evidence relating STN LFP low-frequency activity to impulsivity and presence of ICD in PD has been provided in two studies. In PD patients with preoperative ICDs, theta activity in the STN was maximal in ventral electrodes, in agreement with impulsivity-related oscillatory changes[80] and behavioral effects of DBS.[81,82] The results of Rosa et al.[83] directly related low-frequency STN activity to adoption of risky strategies in patients with PD and pathological gambling. Thus, the current neurophysiological evidence strongly suggests that the STN is involved in inhibition, but does not conclusively demonstrate that it leads the cortex in inhibition.

Evidence From Experimental Studies of STN-DBS or Subthalamotomy in PD

Major aspects of cognition are not affected by STN-DBS.[25,26,84,85] However, on a range of experimental tasks, a number of studies have reported that STN-DBS is associated with deficits in inhibitory and executive control, resulting in impulsive action. For example, STN-DBS has been associated with deficits on a variety of tasks that require conflict resolution, response selection under conflict, and inhibition of prepotent responses, including the Stroop,[86,87] RNG,[65] probabilistic decision making,[27,88,89] go no-go,[66,90] stop signal task,[91-93] and the Simon effect[94] (for details, see Table 3). In addition, on the "moving dots" perceptual decision-making task, STN-DBS in PD lowered response thresholds, resulting in fast, but errorful, responses with stimulation switched on during high-task difficulty[95] or when acting under time

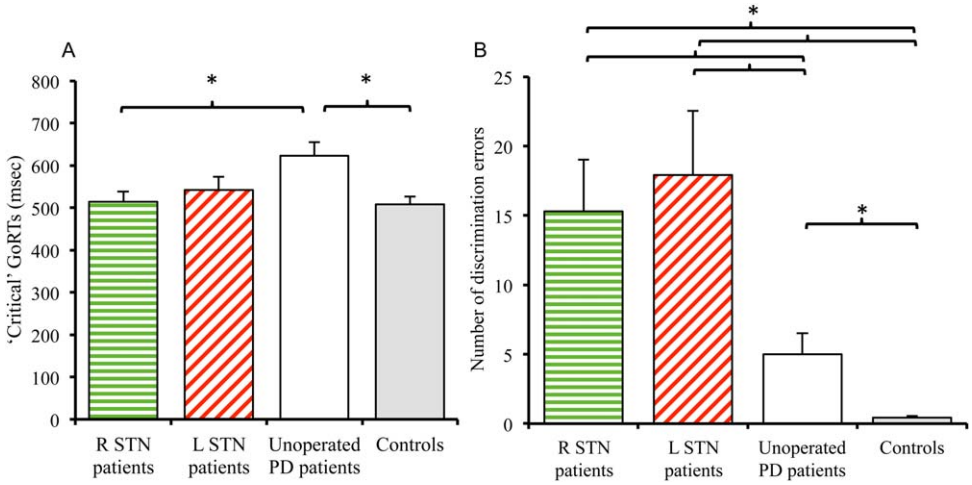

FIG. 2. (A) The mean "critical" Go RTs for the contralesional hand of the patients with PD right or left subthalamotomy (R STN, L STN) and the dominant hand of the unoperated patients with PD and healthy control participants. Error bars are standard errors of the mean. *$P < 0.05$. (B) Mean discrimination errors with the contralesional hand for the patients with PD with right or left subthalamotomy (R STN, L STN) and the dominant hand for the unoperated patients with PD and healthy control participants. Error bars are standard errors of the mean. *$P < 0.05$. Reproduced from Obeso et al. (2014; with permission).[101]

pressure.[96] However, as evident from Table 3, not all studies involving inhibitory processing have shown deficits with STN stimulation. Variations in the nature and prepotency of the response (e.g., percent of go trials in a go no-go or stop signal task) and the precise active contact position in the STN[97,98] are likely to account for some of the differences in results across studies. Another important consideration is the nature of impulsivity being studied. Other than deficits in motor inhibition summarized in Table 3 and increased loss-chasing in a gambling task,[135] investigators have not found any detrimental effects of STN-DBS on other features of impulsivity and risk taking.[136,137]

More direct and "causal" evidence of the role of the STN in inhibitory and executive control comes from a handful of studies of subthalamotomy in PD. Postsubthalamotomy deficits on the Stroop in 30% of the PD patients and deterioration in release from proactive inhibition on a memory test, with normal performance in 98% of the sample before and 50% of the sample after surgery, have been reported.[99,100] In a recent study, Obeso et al.[101] used the conditional stop signal task to investigate the role of the STN in reactive and proactive inhibition and conflict resolution and in adjusting response thresholds and speed-accuracy trade-offs. Patients with right subthalamotomy had significantly faster Go RTs, but made significantly more discrimination errors with their contralesional hand than the unoperated PD patients (see Fig. 2A,B), suggesting that right subthalamotomy influenced speed-accuracy trade-offs. The patients with right subthalamotomy could not engage in late-phase, fast inhibition of the response and showed minimal proactive inhibition when tested with the contralesional hand. These results provide strong evidence that the STN is involved in response inhibition.

Evidence From Psychiatric Side Effects of STN-DBS or Subthalamotomy in PD

STN lesions lead to the "syndrome of the body of Luys," a mixture of hemichorea-hemiballism, typically accompanied by nonmotor behavioral complications.[102] The marked involuntary movements led to the clinical concept of the STN as a motor control nucleus.[103] Hemiballism tends to improve over time, but it can more rarely persist as a permanent sequelae, which can be improved by pallidotomy or pallidal DBS.[104,105]

Behavioral side effects, such as hypomania, hypersexuality, logorrhea and disinhibition of mood and euphoria, impulsivity, and aggression, have been described to accompany hemiballism in spontaneous STN lesions in humans.[106-108] Following bilateral subthalamotomy in PD, "hyperactive" behaviors, such as disinhibiton, euphoria, and irritability, transiently increased and their course of evolution was similar to the postoperative increase in dyskinesias.[109]

In PD patients treated with STN-DBS, disinhibition of complex behavioral programs, such as mirthful laughter, mania, depression, intermittent explosive disorder, kleptomania, emotivity, creativity, and new-onset ICDs (hypersexuality, pathological buying, pathological gambling, and bulimia), are compatible with the role of the STN in control and release not only of motor plans, but also of nonmotor behaviors (for review, see previous works[110,111]). Some of these STN-induced behaviors represent disinhibition or

failure of executive control over prepotent responses. Current spread to the associative and limbic territories have been postulated to explain these stimulation-induced behavioral disinhibitions, in the same way that lesions of the STN motor territory induces hemichorea-hemiballism through the functional inhibition of deafferentation.[110,112,113]

Postoperative apathy as a frequent non-voltage-dependent complication, which appears with chronic STN-DBS in the weeks or months after surgery,[114-117] seems to contradict the theory of "releasing the brake" or disinhibition of nonmotor behavior. However, it can be convincingly shown that postoperative apathy is not directly related to STN-DBS, but rather the consequence of the marked reduction in dopaminergic treatment allowed by motor improvement, which can unmask hypodopmainergic symptoms, such as apathy, depression, and anxiety, related to dopaminergic denervation of the mesolimbic and -cortical dopaminergic projections from the midbrain substantia nigra and ventral tegmental area. The fact that this postoperative withdrawal syndrome is predicted by preoperative nonmotor fluctuations, correlates with the extent of mesolimbic denervation, and is reversible with reintroduction of a D2-D3 dopamine agonist with a relative selectivity for the mesolimbic dopaminergic system clearly indicates that postoperative apathy is not directly related to STN-DBS itself, but rather corresponds to the unmasking of hypodopaminergic nonmotor symptoms of the disease.[117-119]

New-onset ICDs as a stimulation-related side effect have been observed in retrospective series as a complication after STN-DBS surgery in PD.[81,82] Closer examination of the published literature reveals that such "chronic or even permanent" postoperative ICDs mainly occur in those patients who remain on high-dosage dopaminergic treatment after surgery in addition to STN-DBS.[81] In two prospective studies in large patient cohorts, with a marked decrease in dopaminergic treatment, there has been a virtual disappearance of ICDs with the single exception of binge eating.[118,120] This improvement in preoperative hyperdopaminergic behaviors after surgery has been explained by postoperative desensitization following the decrease in dopaminergic treatment.[110]

Behavioral disinhibition with a high incidence of transient appearance of hypomania or even mania has also been reported in patients with obsessive-compulsive disorder (OCD) treated by STN-DBS directly targeting its limbic territory.[113] In OCD, the situation is easier to interpret given that, contrary to PD, there is no simultaneous change in psychotropic dopaminergic treatment. STN-DBS-induced hypomania or mania in OCD are always reversible with a decrease in stimulation parameters, but the therapeutic window may be rather narrow, suggesting that it might be this behavioral disinhibition that allows the patient to become free of obsessions and compulsions,[121] likely mediated by the orbitofrontal cortex directly projecting to the STN through the hyperdirect corticosubthalamic pathway.[21]

Conclusions and Future Directions

As reviewed above, there is now evidence, from a variety of sources, that the STN plays a role in inhibitory control for response selection under conflict and adjusting response thresholds during decision making under conflict or time pressure. Consequently, there is also empirical support indicating that STN-DBS or subthalamotomy in PD can be associated with a host of behavioral and psychiatric problems that reflect deficits in inhibitory control and give rise to certain types of impulsivity.

What remains unclear from the behavioral STN-DBS on versus off studies, imaging, and electrophysiological evidence is whether it is conflict per se,[122] choice difficulty,[79,95] the appetitive/aversive valence of the choices,[27] adoption of a risk-taking strategy,[83] information integration,[88] or acting under time pressure[96] that influence STN activity and adjustment of response thresholds. Future studies are required to refine which contacts or stimulation frequencies alter inhibition and thus will contribute to a better understanding of the current inconsistent results with improvement versus worsening of executive and inhibitory control on different tasks after STN-DBS. Because many of the tasks on which STN-DBS-induced deficits in inhibitory and executive control have been found, as well as necessitate inhibition of automatic prepotent or habitual responses and alternative engagement of strategic response selection,[77] a parsimonious and speculative explanation may be the need for allocation of more attentional resources. Such a formulation would be consistent with the proposed role of the STN in implementation of a frontally signaled switch from automatic to controlled processing, as suggested by Isoda and Hikosaka,[78] the attentional deficit after STN lesion in animals,[33] and the increased gamma-band activity observed in STN LFPs during attention-demanding cognitive tasks,[75,76] as well as the fact that, in some studies, STN-DBS-induced deficits were only observed for tasks with high cognitive control demands[90] or motivational salience.[27]

To date, the main focus has been on the role of the STN in reactive and global inhibition, and few studies have investigated proactive or selective inhibition, with exceptions.[101,123,124] Certainly, this is an imbalance that needs to be addressed in the future. Similarly, despite ample evidence for psychiatric problems suggestive of disinhibition following STN surgery in PD, with the exception of the two studies showing an association between STN LFP activity and ICDs in

PD,[80,83] no efforts have been made to directly link the psychiatric sequelae of STN surgery to deficits in inhibitory control. Provision of such direct evidence is important from both clinical and theoretical perspectives. The results linking low-frequency STN activity functions to ICDs impulsivity in PD[79,82] open up a new avenue of research, which allows for merging the roles of the STN in selection and motivational salience, which could potentially enhance our understanding of ICDs in PD as well as the roles of the STN in humans. ■

References

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989;12:366-375.
2. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281-285.
3. Rahman S, Griffin HJ, Quinn NP, Jahanshahi M. The factors that induce or overcome freezing of gait in Parkinson's disease. Behav Neurol 2008;19:127-136.
4. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, DeLong MR, Olanow CW. Pathophysiology of levodopa-induced dyskinesias in Parkinson's disease: problems with the current model. Ann Neurol 2000;47(4 Suppl 1):S22-S32.
5. Dirnberger G, Jahanshahi M. Executive dysfunction in Parkinson's disease: a review. J Neuropsychol 2013;7:193-224.
6. Cooper JA, Sagar HJ, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. Brain 1994;117:517-529.
7. Gauggel S, Rieger M, Feghoff TA. Inhibition of ongoing responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:539-544.
8. Obeso I, Wilkinson L, Casabona E, et al. Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson's disease. Exp Brain Res 2011;212:371-384.
9. Obeso I, Wilkinson L, Jahanshahi M. Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. Exp Brain Res 2011;213:435-445.
10. O'Callaghan C, Naismith SL, Hodges JR, Lewis SJ, Hornberger M. Fronto-striatal atrophy correlates of inhibitory dysfunction in Parkinson's disease versus behavioural variant frontotemporal dementia. Cortex 2013;49:1833-1843.
11. Dirnberger G, Frith CD, Jahanshahi M. Executive dysfunction in Parkinson's disease is associated with altered pallidal-frontal processing. Neuroimage 2005;25:588-599.
12. Praamstra P, Plat FM. Failed suppression of direct visuomotor activation in Parkinson's disease. J Cogn Neurosci 2001;13:31-43.
13. Wylie SA, Stout JC, Bashore TR. Activation of conflicting responses in Parkinson's disease: evidence for degrading and facilitating effects on response time. Neuropsychologia 2005;43:1033-1043.
14. Kuhn AA, Tsui A, Aziz T, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215:380-387.
15. Vila M, Levy R, Herrero MT, et al. Consequences of nigrostriatal denervation on the functioning of the basal ganglia in human and nonhuman primates: an in situ hybridization study of cytochrome oxidase subunit I mRNA. J Neurosci 1997;17:765-773.
16. Jahanshahi M. Risky choices link the subthalamic nucleus with pathological gambling in Parkinson's disease. Mov Disord 2013;28:1617-1619.
17. Jahanshahi M. Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease. Front Syst Neurosci 2013;7:118.
18. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 1995;20:91-127.
19. Nambu A, Tokuno H, Inase M, Takada M. Corticosubthalamic input zones from forelimb representations of the dorsal and ventral divisions of the premotor cortex in the macaque monkey: comparison with the input zones from the primary motor cortex and the supplementary motor area. Neurosci Lett 1997;239:13-16.
20. Afsharpour S. Topographical projections of the cerebral cortex to the subthalamic nucleus. J Comp Neurol 1985;236:14-28.
21. Haynes WI, Haber SN. The organization of prefrontal-subthalamic inputs in primates provides an anatomical substrate for both functional specificity and integration: implications for basal ganglia models and deep brain stimulation. J Neurosci 2013;33:4804-4814.
22. Lambert C, Zrinzo L, Nagy Z, et al. Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. Neuroimage 2012;60:83-94.
23. Keuken MC, Muller-Axt C, Langner R, Eickhoff SB, Forstmann BU, Neumann J. Brain networks of perceptual decision-making: an fMRI ALE meta-analysis. Front Hum Neurosci 2014;8:445.
24. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
25. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010;362:2077-2091.
26. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009;301:63-73.
27. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318:1309-1312.
28. Evenden JL. Varieties of impulsivity. Psychopharmacology (Berl) 1999;146:348-361.
29. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron 2011;69:680-694.
30. Aron AR. From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry 2011;69:e55-e68.
31. Whittier JR, Mettler FA. Studies on the subthalamus of the rhesus monkey; hyperkinesia and other physiologic effects of subthalamic lesions; with special reference to the subthalamic nucleus of Luys. J Comp Neurol 1949;90:319-372.
32. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436-1438.
33. Baunez C, Nieoullon A, Amalric M. In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. J Neurosci 1995;15:6531-6541.
34. Eagle DM, Baunez C. Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci Biobehav Rev 2010;34:50-72.
35. Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl) 2002;163:362-380.
36. Baunez C, Robbins TW. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci 1997;9:2086-2099.
37. Phillips JM, Brown VJ. Anticipatory errors after unilateral lesions of the subthalamic nucleus in the rat: evidence for a failure of response inhibition. Behav Neurosci 2000;114:150-157.
38. Baunez C, Humby T, Eagle DM, Ryan LJ, Dunnett SB, Robbins TW. Effects of STN lesions on simple vs choice reaction time tasks in the rat: preserved motor readiness, but impaired response selection. Eur J Neurosci 2001;13:1609-1616.
39. Uslaner JM, Robinson TE. Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice—mediation by enhanced incentive motivation? Eur J Neurosci 2006;24:2345-2354.
40. Aleksandrova LR, Creed MC, Fletcher PJ, Lobo DS, Hamani C, Nobrega JN. Deep brain stimulation of the subthalamic nucleus

increases premature responding in a rat gambling task. Behav Brain Res 2013;245:76-82.

41. Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW. Bilateral high-frequency stimulation of the subthalamic nucleus on attentional performance: transient deleterious effects and enhanced motivation in both intact and parkinsonian rats. Eur J Neurosci 2007;25:1187-1194.
42. Baunez C, Robbins TW. Effects of transient inactivation of the subthalamic nucleus by local muscimol and APV infusions on performance on the five-choice serial reaction time task in rats. Psychopharmacology (Berl) 1999;141:57-65.
43. Desbonnet L, Temel Y, Visser-Vandewalle V, Blokland A, Hornikx V, Steinbusch HW. Premature responding following bilateral stimulation of the rat subthalamic nucleus is amplitude and frequency dependent. Brain Res 2004;1008:198-204.
44. Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW. Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cereb Cortex 2008; 18:178-188.
45. Isoda M, Hikosaka O. Cortico-basal ganglia mechanisms for overcoming innate, habitual and motivational behaviors. Eur J Neurosci 2011;33:2058-2069.
46. Lardeux S, Paleressompoulle D, Pernaud R, Cador M, Baunez C. Different populations of subthalamic neurons encode cocaine vs. sucrose reward and predict future error. J Neurophysiol 2013; 110:1497-1510.
47. Schmidt R, Leventhal DK, Mallet N, Chen F, Berke JD. Canceling actions involves a race between basal ganglia pathways. Nat Neurosci 2013;16:1118-1124.
48. Sano H, Chiken S, Hikida T, Kobayashi K, Nambu A. Signals through the striatopallidal indirect pathway stop movements by phasic excitation in the substantia nigra. J Neurosci 2013;33: 7583-7594.
49. Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003;6:115-116.
50. Alexander MP, Stuss DT, Picton T, Shallice T, Gillingham S. Regional frontal injuries cause distinct impairments in cognitive control. Neurology 2007;68:1515-1523.
51. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. The Journal of Neuroscience 2007;27:3743-3752.
52. Forstmann BU, Dutilh G, Brown S, et al. Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci U S A 2008;105:17538-17542.
53. Li CS, Yan P, Sinha R, Lee TW. Subcortical processes of motor response inhibition during a stop signal task. Neuroimage 2008; 41:1352-1363.
54. Aron AR, Poldrack RA. Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 2006;26:2424-2433.
55. Frank MJ. Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 2006; 19:1120-1136.
56. Duann JR, Ide JS, Luo X, Li CS. Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 2009;29: 10171-10179.
57. Jahfari S, Waldorp L, van den Wildenberg WP, Scholte HS, Ridderinkhof KR, Forstmann BU. Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. J Neurosci 2011;31:6891-6899.
58. Sano H, Chiken S, Hikida T, Kobayashi K, Nambu A. Signals through the striatopallidal indirect pathway stop movements by phasic excitation in the substantia nigra. J Neurosci 2013;33: 7583-7594.
59. Majid DS, Cai W, Corey-Bloom J, Aron AR. Proactive selective response suppression is implemented via the basal ganglia. J Neurosci 2013;33:13259-13269.
60. Mansfield EL, Karayanidis F, Jamadar S, Heathcote A, Forstmann BU. Adjustments of response threshold during task switching: a model-based functional magnetic resonance imaging study. J Neurosci 2011;31:14688-14692.
61. Zandbelt BB, Bloemendaal M, Hoogendam JM, Kahn RS, Vink M. Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. J Cogn Neurosci 2013;25:157-174.
62. Obeso I, Cho SS, Antonelli F, et al. Stimulation of the pre-SMA influences cerebral blood flow in frontal areas involved with inhibitory control of action. Brain Stimul 2013;6:769-776.
63. Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF. Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A 2010;107:13240-13245.
64. Schroeder U, Kuehler A, Haslinger B, et al. Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. Brain 2002;125:1995-2004.
65. Thobois S, Hotton GR, Pinto S, et al. STN stimulation alters pallidal-frontal coupling during response selection under competition. J Cereb Blood Flow Metab 2007;27:1173-1184.
66. Ballanger B, van Eimeren T, Moro E, et al. Stimulation of the subthalamic nucleus and impulsivity: release your horses. Ann Neurol 2009;66:817-824.
67. Ray NJ, Brittain JS, Holland P, et al. The role of the subthalamic nucleus in response inhibition: evidence from local field potential recordings in the human subthalamic nucleus. Neuroimage 2012; 60:271-278.
68. Benis D, David O, Lachaux JP, et al. Subthalamic nucleus activity dissociates proactive and reactive inhibition in patients with Parkinson's disease. Neuroimage 2014;91:273-281.
69. Alegre M, Lopez-Azcarate J, Obeso I, et al. The subthalamic nucleus is involved in successful inhibition in the stop-signal task: a local field potential study in Parkinson's disease. Exp Neurol 2013;239:1-12.
70. Kuhn AA, Williams D, Kupsch A, Limousin P, et al. Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. Brain 2004;127:735-746.
71. Brittain JS, Watkins KE, Joundi RA, et al. A role for the subthalamic nucleus in response inhibition during conflict. J Neurosci 2012;32:13396-13401.
72. Tan H, Pogosyan A, Anzak A, et al. Complementary roles of different oscillatory activities in the subthalamic nucleus in coding motor effort in Parkinsonism. Exp Neurol 2013;248:187-195.
73. Lalo E, Thobois S, Sharott A, et al. Patterns of bidirectional communication between cortex and basal ganglia during movement in patients with Parkinson disease. J Neurosci 2008;28: 3008-3016.
74. Williams D, Tijssen M, Van Bruggen G, et al. Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. Brain 2002;125:1558-1569.
75. Anzak A, Gaynor L, Beigi M, et al. A gamma band specific role of the subthalamic nucleus in switching during verbal fluency tasks in Parkinson's disease. Exp Neurol 2011;232:136-142.
76. Anzak A, Gaynor L, Beigi M, et al. Subthalamic nucleus gamma oscillations mediate a switch from automatic to controlled processing: a study of random number generation in Parkinson's disease. Neuroimage 2013;64:284-289.
77. Redgrave P, Rodriguez M, Smith Y, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci 2010;11:760-772.
78. Isoda M, Hikosaka O. Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. J Neurosci 2008;28:7209-7218.
79. Zaghloul KA, Weidemann CT, Lega BC, Jaggi JL, Baltuch GH, Kahana MJ. Neuronal activity in the human subthalamic nucleus encodes decision conflict during action selection. J Neurosci 2012;32:2453-2460.
80. Rodriguez-Oroz MC, Lopez-Azcarate J, Garcia-Garcia D, et al. Involvement of the subthalamic nucleus in impulse control disorders associated with Parkinson's disease. Brain 2011;134:36-49.
81. Lim SY, O'Sullivan SS, Kotschet K, et al. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. J Clin Neurosci 2009; 16:1148-1152.

82. Halbig TD, Tse W, Frisina PG, et al. Subthalamic deep brain stimulation and impulse control in Parkinson's disease. Eur J Neurol 2009;16:493-497.
83. Rosa M, Fumagalli M, Giannicola G, et al. Pathological gambling in Parkinson's disease: subthalamic oscillations during economics decisions. Mov Disord 2013;28:1644-1652.
84. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol 2006;5:578-588.
85. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol 2008;7:605-614.
86. Jahanshahi M, Ardouin CM, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 2000;123:1142-1154.
87. Witt K, Pulkowski U, Herzog J, et al. Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson's disease. Arch Neurol 2004;61:697-700.
88. Coulthard EJ, Bogacz R, Javed S, et al. Distinct roles of dopamine and subthalamic nucleus in learning and probabilistic decision making. Brain 2012;135:3721-3734.
89. Cavanagh JF, Wiecki TV, Cohen MX, et al. Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold. Nat Neurosci 2011;14:1462-1467.
90. Hershey T, Revilla FJ, Wernle A, Gibson PS, Dowling JL, Perlmutter JS. Stimulation of STN impairs aspects of cognitive control in PD. Neurology 2004;62:1110-1114.
91. Ray NJ, Jenkinson N, Brittain J, et al. The role of the subthalamic nucleus in response inhibition: evidence from deep brain stimulation for Parkinson's disease. Neuropsychologia 2009;47:2828-2834.
92. van den Wildenberg WP, van Boxtel GJ, van der Molen MW, Bosch DA, Speelman JD, Brunia CH. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. J Cogn Neurosci 2006;18:626-636.
93. Obeso I, Wilkinson L, Rodriguez-Oroz MC, Obeso JA, Jahanshahi M. Bilateral stimulation of the subthalamic nucleus has differential effects on reactive and proactive inhibition and conflict-induced slowing in Parkinson's disease. Exp Brain Res 2013;226:451-462.
94. Wylie SA, Ridderinkhof KR, Elias WJ, et al. Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease. Brain 2010;133:3611-3624.
95. Green N, Bogacz R, Huebl J, Beyer AK, Kuhn AA, Heekeren HR. Reduction of influence of task difficulty on perceptual decision making by STN deep brain stimulation. Curr Biol 2013;23:1681-1684.
96. Pote I, Torkamani M, Kefalopoulou ZM, et al. Deep brain stimulation of the subthalamic nucleus lowers response thresholds when acting under time pressure. Submitted 2014.
97. Hershey T, Campbell MC, Videen TO, et al. Mapping Go-No-Go performance within the subthalamic nucleus region. Brain 2010;133:3625-3634.
98. Greenhouse I, Gould S, Houser M, Hicks G, Gross J, Aron AR. Stimulation at dorsal and ventral electrode contacts targeted at the subthalamic nucleus has different effects on motor and emotion functions in Parkinson's disease. Neuropsychologia 2010;49:528-534.
99. Patel NK, Heywood P, O'Sullivan K, McCarter R, Love S, Gill SS. Unilateral subthalamotomy in the treatment of Parkinson's disease. Brain 2003;126:1136-1145.
100. McCarter RJ, Walton NH, Rowan AF, Gill SS, Palomo M. Cognitive functioning after subthalamic nucleotomy for refractory Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;69:60-66.
101. Obeso I, Wilkinson L, Casabona E, et al. The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. Brain 2014;137:1470-1480.
102. Martin JP. Hemichorea resulting from a local lesion of the brain (the syndrome of the body of Luys). Brain 1927:637-651.
103. Carpenter MB, Whittier JR, Mettler FA. Tremor in the rhesus monkey produced by diencephalic lesions and studied by a graphic method. J Comp Neurol 1950;93:1-15.
104. Alvarez L, Macias R, Pavon N, et al. Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. J Neurol Neurosurg Psychiatry 2009;80:979-985.
105. Orthner H, Roeder F. [Experiences with stereotactic interventions. I. Pathogenesis and therapy of extrapyramidal movement disorders; successful treatment of cases of severe hemiballism with aimed electrocoagulation of the globus pallidus]. Dtsch Z Nervenheilkd 1956;175:419-434.
106. Trillet M, Vighetto A, Croisile B, Charles N, Aimard G. [Hemiballismus with logorrhea and thymo-affective disinhibition caused by hematoma of the left subthalamic nucleus]. Rev Neurol (Paris) 1995;151:416-419.
107. Absher JR, Vogt BA, Clark DG, et al. Hypersexuality and hemiballism due to subthalamic infarction. Neuropsychiatry Neuropsychol Behav Neurol 2000;13:220-229.
108. Park HK, Kim HJ, Kim SJ, Kim JS, Shin HW. From Jekyll to Hyde after limbic subthalamic nucleus infarction. Neurology 2011;77:82-84.
109. Bickel S, Alvarez L, Macias R, et al. Cognitive and neuropsychiatric effects of subthalamotomy for Parkinson's disease. Parkinsonism Relat Disord 2010;16:535-539.
110. Castrioto A, Lhommee E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol 2014;13:287-305.
111. Temel Y, Blokland A, Steinbusch HW, Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol 2005;76:393-413.
112. Krack P, Kumar R, Ardouin C, et al. Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 2001;16:867-875.
113. Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci U S A 2007;104:10661-10666.
114. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925-1934.
115. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834-839.
116. Drapier D, Drapier S, Sauleau P, et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? J Neurol 2006;253:1083-1091.
117. Thobois S, Ardouin C, Lhommee E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain 2010;133:1111-1127.
118. Lhommee E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. Brain 2012;135:1463-1477.
119. Thobois S, Lhommee E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain 2013;136:1568-1577.
120. Eusebio A, Witjas T, Cohen J, et al. Subthalamic nucleus stimulation and compulsive use of dopaminergic medication in Parkinson's disease. J Neurol Neurosurg Psychiatry 2013;84:868-874.
121. Krack P, Hariz MI, Baunez C, Guridi J, Obeso JA. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;33:474-484.
122. Fumagalli M, Giannicola G, Rosa M, et al. Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions. Soc Neurosci 2011;6:243-256.
123. van Belle J, Vink M, Durston S, Zandbelt BB. Common and unique neural networks for proactive and reactive response inhibition revealed by independent component analysis of funtional MRI data. Neuroimage 2014;103C:65-74.
124. Favre E, Ballanger B, Thobois S, Broussolle E, Boulinguez P. Deep brain stimulation of the subthalamic nucleus, but not dopaminergic medication, improves proactive inhibitory control of

movement initiation in Parkinson's disease. Neurotherapeutics 2013;10:154-167.

125. Winstanley CA, Theobald DE, Dalley JW, Robbins TW. Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. Neuropsychopharmacology 2005;30:669-682.

126. Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology (Berl) 2008;199:439-456.

127. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C. Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. J Neurophysiol 2009;102:2526-2537.

128. Forstmann BU, Keuken MC, Jahfari S, et al. Cortico-subthalamic white matter tract strength predicts interindividual efficacy in stopping a motor response. Neuroimage 2012;60:370-375.

129. Castner JE, Copland DA, Silburn PA, Coyne TJ, Sinclair F, Chenery HJ. Lexical-semantic inhibitory mechanisms in Parkinson's disease as a function of subthalamic stimulation. Neuropsychologia 2007;45:3167-3177.

130. Castner JE, Chenery HJ, Silburn PA, et al. Effects of subthalamic deep brain stimulation on noun/verb generation and selection from competing alternatives in Parkinson's disease. J Neurol Neurosurg Psychiatry 2008;79:700-705.

131. Campbell MC, Karimi M, Weaver PM, et al. Neural correlates of STN DBS-induced cognitive variability in Parkinson disease. Neuropsychologia 2008;46:3162-3169.

132. Yugeta A, Terao Y, Fukuda H, et al. Effects of STN stimulation on the initiation and inhibition of saccade in Parkinson disease. Neurology 2010;74:743-748.

133. Swann N, Poizner H, Houser M, et al. Deep brain stimulation of the subthalamic nucleus alters the cortical profile of response inhibition in the Beta frequency band: a scalp EEG study in Parkinson's disease. J Neurosci 2011;31:5721-5729.

134. Mirabella G, Iaconelli S, Romanelli P, et al. Deep brain stimulation of subthalamic nuclei affects arm response inhibition in Parkinson's patients. Cereb Cortex 2012;22:1124-1132.

135. Rogers RD, Wielenberg B, Wojtecki L, Elben S, Campbell-Meiklejohn D, Schnitzler A. Deep brain stimulation of the subthalamic nucleus transiently enhances loss-chasing behaviour in patients with Parkinson's disease. Exp Neurol 2011;231:181-189.

136. Torta DM, Vizzari V, Castelli L, et al. Impulsivities and Parkinson's disease: delay aversion is not worsened by deep brain stimulation of the subthalamic nucleus. PLoS one 2012;7:e43261.

137. Djamshidian A, O'Sullivan SS, Foltynie T, et al. Dopamine agonists rather than deep brain stimulation cause reflection impulsivity in Parkinson's disease. Journal of Parkinson's disease 2013;3:139-144.