Review article

The Subthalamic Nucleus: Unravelling New Roles and Mechanisms in the Control of Action

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How do we decide what we do? This is the essence of action control, the process of selecting the most appropriate response among multiple possible choices. Suboptimal action control can involve a failure to initiate or adapt actions, or conversely it can involve making actions impulsively. There has been an increasing focus on the specific role of the subthalamic nucleus (STN) in action control. This has been fueled by the clinical relevance of this basal ganglia nucleus as a target for deep brain stimulation (DBS), primarily in Parkinson's disease but also in obsessive-compulsive disorder. The context of DBS has opened windows to study STN function in ways that link neuroscientific and clinical fields closely together, contributing to an exceptionally high level of two-way translation. In this review we first outline the role of the STN in both motor and non-motor action control, and then discuss how these functions might be implemented by neuronal activity in the STN. Gaining a better understanding of these topics will not only provide important insights into the neurophysiology of action control but also the pathophysiological mechanisms relevant for several brain disorders and their therapies.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is one of only a few clinical treatments that is based on targeted modulation of known pathophysiology in

defined circuits, highlighting the translational nature of this field. STN DBS has proven strikingly efficient in addressing motor symptoms (Deuschl and others 2006; Limousin and others 1995), though the effects on non-motor functions, such as cognition, emotion and motivation, are less understood (FasanoDaniele and Albanese 2012; KimJeon and Paek 2015). Driven by the motivation to optimize treatment and minimize side effects, there has been an emerging clinical and neuroscientific interest in understanding the functions and the neural dynamics of the STN. Local recording and stimulation in the context of the operative DBS procedure constitute a unique window to study neural network dynamics of the human brain. In this framework, STN function can be linked to several well-established fields of neuroscience, such as motor control, cognitive control, decision making and reward. At the same time, STN DBS treatment for different diagnoses is an inherently collaborative technique that spans multiple clinical disciplines across surgical, neurological and psychiatric fields. This translational relevance and interest largely increases the possibility of understanding the role of STN and developing insights that intersect, connect and synergize diverse fields of neuroscience and clinical medicine in ways that have been previously difficult.

Functional anatomy and dynamics of the STN

The basal ganglia generally exert motor control by keeping the motor cortex under inhibitory control. Processing in the basal ganglia in general, and the STN in particular, leads to adjustments of inhibition from the output nuclei GPI/SNR (internal globus pallidus / substantia nigra pars reticulata), which in turn selectively release the motor cortex from inhibitory control in order to execute actions (AlexanderCrutcher and DeLong 1990).

The canonical basal ganglia loop and movement inhibition

According to the classical view (AlexanderCrutcher and DeLong 1990), the striatum constitutes the main input structure of the basal ganglia, receiving input from the cortex and projecting output either via the direct or indirect (via external segment of the globus pallidus & STN) pathway to the output nuclei GPI/SNR. These nuclei in turn project

back to the cortex via the thalamus (Figure 1A). The direct pathway is thought to facilitate movements by cortical excitation, and the indirect pathway inhibits movements by inhibiting cortical excitation. The balance between the direct and indirect pathway is regulated by dopamine modulation of two striatal cell populations with different dopamine receptor profiles. In this scheme, the STN is a projection nucleus in the indirect pathway, and increased activity of the STN should lead to increased activity of the indirect inhibitory pathway, which would subsequently lead to inhibition of the cortex and therefore inhibition of movement (AlexanderCrutcher and DeLong 1990).

The hyperdirect pathway

More recent models of the basal ganglia have highlighted a direct cortical input to the STN, the hyperdirect pathway, which would render the STN an input structure to the BG (NambuTokuno and Takada 2002) (Fig 1A). The hyperdirect pathway is faster than the striatal pathways, and the STN projection to the GPI/SNR has been found to be more diffuse than the more specific striatal projection (Hazrati and Parent 1992), but see also (Kelly and Strick 2004) . This has led to a race model of motor control, involving a center-surround inhibition of the output nuclei (Mink 1996; NambuTokuno and Takada 2002) (Figure 1A). In this model, an intended action will cause cortical excitatory input to both the striatum and the STN, but the STN will cause a fast and global activation of the SNR/GPI before the striatal input arrives, causing a broad inhibition of movement. Only after sufficient excitation of one specific action has been built up in the striatum does the direct pathway activate the selected motor program, antagonized by the indirect pathway. A recent experimental study supports central aspects of this model (SchmidtLeventhalMalletChen and Berke 2013).

Parallel circuits in the basal ganglia

The basal ganglia, including the STN, are not only involved in motor control, but also in cognitive, motivational and emotional functions (Haber and Behrens 2014; Weintraub and Zaghloul 2013). Anatomically, this is supported by the existence of parallel circuits throughout the basal ganglia; the canonical circuit between structures is maintained, but

the type of information processed in each parallel loop is reflected by the cortical origin of the loop involved in sensorimotor, associative or limbic processes (AlexanderDeLong and Strick 1986). The types of input gradually changes along the dorsolateral-to-ventromedial axis (Haber 2003; Kelly and Strick 2004), matched by a gradient of dopamine input from the more motor-related nigrostriatal system to the more valence-related mesocorticolimbic system (HaberFudge and McFarland 2000).

The same pattern of graded organization has been confirmed in STN afferents, both for the cortical (Haynes and Haber 2013) and pallidal (Karachi and others 2005) inputs (ie the hyperdirect and indirect pathway, respectively), in a partially overlapping pattern that suggests both parallel processing and an integration of information (Figure 1B). Imaging studies have confirmed the existence of different STN subterritories in the human STN, indicating partly overlapping motor, associative and limbic regions along the longitudinal axis (Lambert and others 2012; Voon and others 2017). These parallel loops raise the possibility that the circuit function proposed for movements is relevant also for non-motor action control, and that cognitive and limbic information may be integrated into action control in the STN.

Anatomically, the STN is thus located at an intersection between the frontal cortex, which is related to cognitive control and decision making (Helfrich and Knight 2016) , and the basal ganglia, which is involved in habitual and goal-directed action control (Haber and Behrens 2014). Inhibitory control from the STN could therefore imply a switch between different modes of action control, in particular by inhibiting the default response in favor of a controlled response (Hikosaka and Isoda 2010).

Beyond the cortico-basal ganglia-thalamo-cortical loop outlined above, the basal ganglia and the STN also take part in subcortical circuits, involving areas such as the brainstem (AlexanderCrutcher and DeLong 1990; McHaffieStanfordSteinCoizet and Redgrave 2005). For example, the pedunculopontine nucleus (PPN) which is involved in motor and non-motor functions and also used as a target for DBS treatment of patients with Parkinson's disease (PienaarVernon and Winn 2016), is connected to the STN (HammondRouzaire-DuboisFegerJackson and Crossman 1983; Lambert and others 2012). The downstream effect of STN processing thus goes beyond feedback to the

cortex, and may involve integration of cortical and subcortical processes in action control (McHaffieStanfordSteinCoizet and Redgrave 2005).

Oscillatory dynamics in the STN

Neural communication in the cortico-basal ganglia loop is however not only characterized by anatomically defined networks but also by dynamic rhythmic activity in the local field potential of specific frequency bands (Figure 2). The most prominent rhythm of the STN is the beta rhythm (12-30 Hz), which has been particularly linked to sensorimotor functions and movement inhibition (Brittain and Brown 2014). Slower theta and delta rhythms in the STN (1-8 Hz, hereafter collectively described as theta) have been related to cognitive processes and conflict representation (Cavanagh and others 2011; Zavala and others 2014), while some reports link alpha rhythms (8-12 Hz) to emotional processing (Brucke and others 2007; Huebl and others 2011; Kuhn and others 2005). This distinction indicates that motor, cognitive and emotional functions of the STN may be related to separate spectral bands (AronHerzBrownForstmann and Zaghloul 2016; MarcegliaFumagalli and Priori 2011), but this outlined functional separation is far from absolute. Faster oscillations, i.e. gamma (60-90 Hz) and high-frequency oscillations (HFO, 200-500 Hz), are thought to be related to active neuronal processing, and are also observed in the STN (Alegre and others 2013; JenkinsonKuhn and Brown 2013; YangVanegasLungu and Zaghloul 2014). Moreover, oscillations in the STN can be transiently or persistently coupled to cortical oscillations through coherence or phase-amplitude coupling, which may allow for flexible and frequency-specific interactions between different cortical areas and the STN, possibly through the hyperdirect pathway (AronHerzBrownForstmann and Zaghloul 2016; YangVanegasLungu and Zaghloul 2014).

Pathophysiology of the STN and effects of DBS

Pathological activity in the basal ganglia loop can cause disturbances of action control that are characteristic not only of movement disorders (DeLong 1990) but neuropsychiatric disorders as well (Haber and Behrens 2014). Parkinson's disease is in

particular characterized by hypokinetic motor symptoms but may also involve nonmotor symptoms such as depression, apathy and cognitive dysfunction (Weintraub and Burn 2011). Obsessive compulsive disorder (OCD) is characterized by intrusive, repetitive thoughts and compulsive actions (Mallet and others 2008). Both diagnoses involve dysfunctions of action control.

In Parkinson's disease, the loss of dopamine neurons causes an imbalance between activation of the direct and indirect pathway, overexcitation of the STN and reduced movement (DeLong 1990). The hypokinetic Parkinsonian state is also characterized by an abnormally high synchronization of beta oscillations, which are observed at the neuronal and network level across the dorsal STN and motor cortex (BrittainSharott and Brown 2014; de Hemptinne and others 2013; LevyHutchisonLozano and Dostrovsky 2000; MoranBergmanIsrael and Bar-Gad 2008). The anti-kinetic effects of beta oscillatory activity are assumed to involve the rhythmic entrainment of neuronal firing and pro-kinetic high-frequency oscillations, which may reduce the information capacity of neuronal processing, and thereby interfere with the process of action selection (BrittainSharott and Brown 2014; YangVanegasLungu and Zaghloul 2014). Less is known about the pathophysiology in OCD, though studies indicate hyperconnectivity in associative-limbic cortico-basal ganglia pathways (Figee and others 2013), and increased theta synchronization both in prefrontal areas (Karadag and others 2003) and ventral STN neurons (Welter and others 2011). Thus, the pathophysiology of the two disorders share certain common features of cortico-basal ganglia hypersynchronization, although involve different frequencies and different parallel loops of the basal ganglia circuits.

In Parkinson's disease, circuit balance can be restored by pharmacological replacement of dopamine, or by DBS of the dorsal STN (Deuschl and others 2006; Limousin and others 1995), putatively by reducing the indirect pathway's inhibitory control of movements. Similarly, DBS of the ventral STN alleviates symptoms of heightened control in OCD (Mallet and others 2008). Conversely, STN DBS may also induce side effects related to lack of control, such as impulsivity and hypomania (FasanoDaniele and Albanese 2012; JahanshahiObesoBaunezAlegre and Krack 2015; KimJeon and Paek 2015; Mallet and others 2008) . The complex effects of DBS are not well understood, and cannot be sufficiently described as a functional inhibition of the STN, as was previously suggested

(Limousin and others 1995). Rather, DBS most likely modulates both local and widespread dynamic network activity and plasticity (Hamani and others 2017).

Action inhibition

While STN firing rate and beta synchrony are related to motor inhibition, action inhibition also involves executive control over pre-potent or habitual responses. Such habitual responses play an important role in many cognitive behaviors as well as motivational and emotional regulation. A considerable amount of evidence has shed light on how the STN is involved in various aspects of action inhibition, covering different diagnoses, different species and different methods (AronHerzBrownForstmann and Zaghloul 2016; JahanshahiObesoBaunezAlegre and Krack 2015; ZavalaZaghloul and Brown 2015). In brief, imaging and neurophysiology data suggest that the STN, during proactive and reactive action inhibition, receives controlling signals through dynamic connections with frontal cortical areas. Such communication involves increased local beta power and fronto-subthalamic beta coherence (Alegre and others 2013; Aron and Poldrack 2006; Benis and others 2014) (Figure 2 A&B). Frontal regions particularly involved in action inhibition are the right inferior frontal gyrus (rIFG) and pre-supplementary motor areas (pre-SMA) (AronHerzBrownForstmann and Zaghloul 2016). Different aspects of inhibition are also represented at the neuronal level (Bastin and others 2014; Benis and others 2016; Isoda and Hikosaka 2008) (Table 1). A causal role of the STN in stopping was recently demonstrated by optogenetic activation and inhibition of the STN in rats (Fife and others 2017).

Many decisions and actions may not involve an explicit motor movement, and one possibility is that the basal ganglia and STN may also play a role in controlling such non-motor actions. For example, the basal ganglia may participate in deciding which item to store in working memory (O'Reilly and Frank 2006). This possibility was recently confirmed as STN beta power and fronto-subthalamic beta coherence were found to decrease during memory encoding, but less for items that should be ignored, indicating a role of fronto-subthalamic beta oscillations in controlling cognitive actions such as memory encoding (ZavalaJang and Zaghloul 2017) (Figure 2C).

A switch or a break?

Inhibition of an action does not necessarily mean stopping all actions, but instead could mean slowing down to select the most appropriate action for the behavioral goals at hand. Consistent with this, the STN can facilitate switching from habitual to controlled behaviors (Hikosaka and Isoda 2010; Isoda and Hikosaka 2008; JahanshahiObesoBaunezAlegre and Krack 2015). Some neurons in the STN respond to behavioral switching rather than inhibition per se (Isoda and Hikosaka 2008; Pasquereau and Turner 2017), and STN DBS generally increases cognitive and behavioral flexibility (KrackHarizBaunezGuridi and Obeso 2010; Weintraub and Zaghloul 2013), though STN inactivation can also cause perseverative behavior in animal models (Baker and Ragozzino 2014; BaunezChristakouChudasamaForni and Robbins 2007; JahanshahiObesoBaunezAlegre and Krack 2015). A relevant point in this regard is that beta oscillations may have a broader role than merely inhibiting actions, and may instead promote the maintenance of the ongoing behavior and the status quo (Engel and Fries 2010; Jenkinson and Brown 2011). As such, a decrease in beta power may facilitate behavioral switching. The role of the STN and beta activity in action control may therefore extend beyond action inhibition to also involve control of behavioral switching, though the exact mechanisms are yet to be established.

From decision to action

A central purpose of action control is to optimize decisions that we make. This links the field of motor and action control to the field of decision making, where a solid framework of computational modeling based on drift diffusion models has been used to describe discrete choices, both at the behavioral and the neurophysiological level (Gold and Shadlen 2007; Ratcliff 1978). During a decision between two responses, the perceived evidence for each option is thought to gradually increase, and once the accumulated evidence reaches a certain threshold, that particular response is executed (Figure 3). A neural signature of this process has been found in cortical areas, where neuronal firing rates gradually increase according to the accumulated evidence for specific responses

(Brody and Hanks 2016; Gold and Shadlen 2007). But what decides when the evidence is sufficient and it is time to act?

Beyond motor control: Models of STN as a decision threshold

Two influential computational models (Bogacz and Gurney 2007; Frank 2006) point to the basal ganglia as a promising system for adjusting these thresholds. The models agree on their general prediction - evidence is accumulated in cortical areas, which then excite both the striatum and STN through outcome-specific channels. While the striatum conveys the option-specific signals to the GPI/SNR, the STN instead conveys a sum of the options widely to the GPI/SNR, effectively creating a "break" or "decision threshold". For an action to be executed, this threshold must be exceeded by an option-specific signal from the striatum, initiated by evidence that is sufficiently stronger than the alternative options. Thus, this model follows the same logic as the center-surround-model for movements outlined above.

According to these models, a difficult decision will lead to a slower response than an easy decision, because the alternative responses together will induce a stronger global activation of the STN and hence a higher decision threshold, reflecting the level of conflict (Frank 2006). However, the increased threshold implemented by the STN will ensure that the action is delayed until the best option is selected. These models therefore predict that the role of the STN in action control is to withhold a response during high-conflict decisions in order to improve accuracy (Bogacz and Gurney 2007; Frank 2006).

Evidence for conflict detection and decision thresholds in the STN

Experimental evidence confirms that the STN is involved in conflict representation during choice between multiple options (AronHerzBrownForstmann and Zaghloul 2016; ZavalaZaghloul and Brown 2015) (Figure 2B & 3B). Behaviorally, STN DBS in patients with Parkinson's disease has been shown to selectively impair accuracy in high-conflict choices, but not in low-conflict choices (Cavanagh and others 2011; FrankSamantaMoustafa and Sherman 2007). Decisions during high-conflict choices were made faster, indicating problems with slowing down the response in order to select the

best option. Consistent with this, DBS of the ventral STN in patients with OCD increase decisional impulsivity by reducing decision thresholds, and thereby shifts decision making towards a less cautious, more healthy style (Voon and others 2017).

Single unit activity in the STN has been found to increase during cognitive (Burbaud and others 2013; Zaghloul and others 2012) and sensorimotor (Zavala and others 2017; Zavala and others 2014) conflict (Figure 5 B&C), in line with increased action inhibition. While action inhibition involves increased power in STN beta band oscillations, conflict is instead associated with increased oscillatory power in the theta band, which is reported in the context of both sensorimotor (Zavala and others 2017; Zavala and others 2014), cognitive (Brittain and others 2012; Cavanagh and others 2011) and moral (Fumagalli and others 2011) conflict (Figure 2B & 3B). Increased STN theta activity co-occurs and is coherent with increased theta power in the medial prefrontal cortex (mPFC) (Zavala and others 2017; Zavala and others 2016; Zavala and others 2014). The conflict-induced cortico-subthalamic theta synchrony is not only related to conflicting responses (Zavala and others 2014), but also to difficulty related to sensory uncertainty, and the need to slow down the response until sufficient evidence has been accumulated (Zavala and others 2016).

A direct link between conflict-related PFC-STN theta activity and decision thresholds has been formally demonstrated in the context of drift diffusion models (Cavanagh and others 2011; Herz and others 2017; HerzZavalaBogacz and Brown 2016) (Figure 4). Increased medial PFC (mPFC) theta activity indicated increased decision thresholds on a trial-to-trial basis , but STN DBS reversed this relationship while accuracy dropped for high-conflict trials (Cavanagh and others 2011). The level of mPFC-STN theta coupling predicted adjustments of decision thresholds, while threshold-modulation by local theta power in the STN critically depended on level of cautiousness (HerzZavalaBogacz and Brown 2016). A recent study demonstrates that STN decision thresholds can be adjusted by instructed tradeoffs between speed and accuracy (Herz and others 2017), and further reveals that cue-induced beta oscillations are also related to the decision threshold. Interestingly, increased STN theta power, coupled to the mPFC, correlated with increased thresholds only after accuracy instructions. Conversely, decreased STN beta power, coupled to motor cortex, correlated with decreased thresholds when cued by the stimulus

itself regardless of instructions (Figure 4C). Thus, the frontal cortex can implement decision thresholds in the STN through theta or beta synchrony, which can be set both according to internal top-down cognitive control (for example, according to task instructions) or by external factors related to features of the task stimuli. The relationship between decision thresholds and STN oscillatory power is however more complex than a linear increase in STN theta power and mPFC-STN theta coherence with increased decision thresholds.

It remains to be determined how conflict-driven cortico-subthalamic theta oscillations interfere with inhibition-related beta oscillations and neuronal spiking in the STN to implement a decision threshold. No study has formally modelled the relation between neuronal spiking in the STN and decision thresholds, though uniform increases in firing rate related to conflict level have been reported (Zaghloul and others 2012). Notably, neuronal activity profiles reflecting evidence accumulation have also been found in the striatum in animal studies (Brody and Hanks 2016; Ding and Gold 2010), which further strengthen the possibility that the basal ganglia serves as a readout structure that transforms cortical evidence into actions. These findings strongly support the abovementioned models of the STN in action control, which extend the role of STN beyond motor control and into decision making and cognitive control.

Motivational and emotional processing in the STN

Beyond its involvement in actions and decisions, the STN is also involved in motivational and emotional functions (RossiGunduz and Okun 2015; Weintraub and Zaghloul 2013). This is anatomically supported by its connections to ventromedial prefrontal, orbitofrontal and anterior cingulate cortices and other limbic structures (AlexanderDeLong and Strick 1986; Haynes and Haber 2013; Lambert and others 2012; Voon and others 2017), and by the observation of occasional motivational and emotional effects of STN DBS (FasanoDaniele and Albanese 2012; KimJeon and Paek 2015; Mallet and others 2008). Motivational and emotional processing in the STN has been related to theta (Rosa and others 2013; Zenon and others 2016) and alpha power (Brucke and others 2007; Huebl and others 2011; Kuhn and others 2005), respectively. Neurons in the STN respond to features of reward, risk, outcome, arousal and emotional valence

(BreyssePelloux and Baunez 2015; LardeuxPaleressompoullePernaudCador and Baunez 2013; LardeuxPernaudPaleressompoulle and Baunez 2009; PearsonHickeyLadPlatt and Turner 2017; Rossi and others 2017) (Table 1).

While drift diffusion models for evidence accumulation are most commonly used in the context of perceptual decisions, a separate line of research has investigated decision making based on value-based choices and reinforcement learning. The former approach focuses on the dynamics of choice processes but assumes static decision values, while the latter focuses on the dynamics of experience but assumes a static choice process (Frank and others 2015). Frank and colleagues demonstrated that the drift diffusion model could describe choices during reinforcement learning with sequential sampling of reward values, involving dynamic adjustments of STN and mPFC activity corresponding to decision thresholds (Frank and others 2015). As the STN also is involved in processing of rewards and risks, it will be an interesting topic for future research to clarify how reward probability, valence and evidence-value of reinforcers are encoded in the fronto-subthalamic network.

Impulsivity

The role of cortical-subthalamic function in modulating decision thresholds has obvious implications for impulsivity, as lowered decision thresholds may increase impulsive actions, a phenomenon referred to as reflection impulsivity (Box 1). This perspective expands the view of STN in impulsivity beyond "motor impulsivity" (Voon and Dalley 2016) (Box 1) to be relevant also for "decisional impulsivity" (JahanshahiObesoBaunezAlegre and Krack 2015; Voon and others 2017; ZavalaZaghloul and Brown 2015) (Box 1), though this may be specific for the ventral part of the STN.

Box 1. Definitions of impulsivity.

"Motor impulsivity includes (i) waiting impulsivity or premature anticipatory responding prior to a cue predicting reward and (ii) response inhibition or stopping inhibition of a prepotent response. Decisional impulsivity includes (iii) delay and probabilistic discounting of reward and (iv) reflection impulsivity—the tendency to make rapid

decisions without adequate accumulation and consideration of the available evidence."
Citation from (Voon and Dalley 2016)

Dopamine has consistently been found to be important for impulsivity that is related to motivational drive, such as waiting impulsivity (Box 1) and delay discounting, i.e. the decline of perceived value for a delayed reward (Voon and Dalley 2016). Since the STN is involved in reward and risk processing (Table 1), it could also potentially be involved in more motivational aspects of impulsivity. Mixed results regarding the effects of STN modulation on delay discounting (JahanshahiObesoBaunezAlegre and Krack 2015; Voon and others 2017; WinstanleyBaunezTheobald and Robbins 2005) call for further investigation of the reward modulating effects of STN DBS, which may also have implications for mood regulation.

Thus, it is well established that the STN generally is involved in inhibiting actions, in particular in high-conflict situations, and that this can be described in the context of "decision thresholds" based on cortical input. Furthermore, rather than solely inhibiting actions, the STN may be involved in the balance between maintenance of the current action plan and behavioral flexibility. Pathologically high decision thresholds can cause problems for initiating or switching movements, behaviors or thoughts, and may induce hypokinetic symptoms, perseveration, compulsivity, obsessive thinking and possibly depression. In contrast, inactivation of the STN facilitates movements and flexibility, but may also lead to motor and decisional impulsivity, and potentially hypomania. The behavioral effects of how the STN may modulate decision thresholds seems dependent on dorsoventral topography. Obviously, the context of decision thresholds does not capture all aspects of any of the symptoms discussed here, but this perspective brings a unifying view which can generate hypotheses for future research.

Neuronal processing in the STN

The effect of STN on action control must ultimately be implemented by neuronal firing in the STN, yet current models often assume a uniform involvement of STN neurons. Here we summarize neuronal activity in the STN during specific tasks, which demonstrate a range of patterned activity (Table 1, Figure 5).

Neurons throughout the basal ganglia, including the STN, are active during movement, depending on the body part involved and the direction of movement (AlexanderCrutcher and DeLong 1990; Zavala and others 2017). STN neurons modulate their firing according to a range of task variables, such as different phases of movement and inhibition, preparation, conflict, switch, risk, elapsed time, reward and emotions, as summarized in (Table 1). General features of STN neuronal activity are comparable across diagnoses and species. A consistent finding is that some neurons respond to cues and pre-motor decisions, some to the movement itself, while yet others become active after the movement or outcome, and seem involved in postresponse evaluation. Most studies have demonstrated firing modulation that is eventually related through various factors to the motor response, possibly reflecting integration of different types of information towards action. However, firing modulation is also found in tasks where no movement (ZavalaJang and Zaghloul 2017), or even no nonmotor action (Eitan and others 2013; Espinosa-ParrillaBaunez and Apicella 2013; Sieger and others 2015), is executed. These findings generally confirm that various types of information are integrated in the STN to guide actions, but also that STN neuronal activity reflects cognitive and emotional outcomes in absence of motor actions.

Different task features are in many cases represented by distinct neuronal populations, such as separate populations for go or stop, for cue and movement, for different directions of movement, for different types of reward or valence, or for arousal (Table 1). However, the same neurons can respond to several different features, such as movement and reward (Espinosa-ParrillaBaunez and Apicella 2013), or to proactive and reactive stops dependent on task conditions (Isoda and Hikosaka 2008; Pasquereau and Turner 2017). This multimodal response could potentially be confounded by sub-optimal spike sorting, in which firing patterns reported as single neuron responses may in fact reflect firing from different neurons. It is likely, however, that the STN indeed does display such multimodal responses, as the prefrontal cortex, upstream to the STN, displays both mixed neuronal selectivity (Rigotti and others 2013) and firing patterns similar to the STN , (Hikosaka and Isoda 2010). A confusing but consistent finding is that most transient responses can result in both increases and decreases in firing rates, as is the case for both stop and movement responses (AlexanderCrutcher and DeLong 1990; Isoda and Hikosaka 2008; Pasquereau and Turner 2017).

The complexity of STN activity is well illustrated by a recent report of STN neuronal firing during response inhibition (Pasquereau and Turner 2017), which extends an earlier influential study (Isoda and Hikosaka 2008). This study demonstrated that the neurons within the STN respond to both proactive and reactive inhibition of movement, as well as to switches in the movement plan. The neuronal involvement is not straightforward; one functional cell type, the reactive "switch cells", had a defined topographical localization and did not overlap with another functional cell type, the "movement cells". However, the functional classes of proactive "Go" and "NoGo cells", which one could easily confuse with the reactive "switch-go" and "switch-stop" cells, were scattered across the entire STN. And both these populations overlapped with both the "switch-stop" and "switch-go" cell populations, but not with each other.

Given that different STN neurons behave differently, it is possible that different task-specific functional cell types can be characterized by specific connectivity and molecular properties. Though STN cells often are referred to as a uniform population, differential cell populations in the STN, in terms of transmitter type, connectivity and membrane receptor profile have later been reported (Arcos and others 2003; KitaChang and Kitai 1983; Levesque and Parent 2005; SatoParentLevesque and Parent 2000; TakadaNishihamaNishihama and Hattori 1988; Xiao and others 2015), suggesting the presence of sub-circuits within the STN. However, an in vitro study revealed that single neurons in the STN can function in as many as four stable states (Kass and Mintz 2006), suggesting that different recorded responses do not necessarily correspond to different defined cell types. Future research may clarify how these different properties align or overlap.

Integrative and parallel processing in the STN

Based on the above, it seems well established that different territories of the frontal cortex interact with the STN during different motor and non-motor task demands, that these inputs are anatomically arranged across the longitudinal axis of the STN according to information type, and that the frontal cortex and the STN can communicate via frequency-specific channels. But to what degree are different types of information

integrated towards one action versus being processed in parallel towards different outputs?

Though anatomical evidence indicates partially integrative afferents, it remains to be established how afferents from frontal and pallidal subregions monosynaptically connect and integrate on single STN neurons, and whether STN neurons are intrinsically connected, directly or via the GPe. This has been addressed by a recent functional connectivity study in rodents which confirms that motor and non-motor inputs partially integrate on to single neurons in the STN (Janssen and others 2017). Moreover, task-related studies (Table 1) demonstrate that different types of information, such as representations of movement and reward outcome (Espinosa-ParrillaBaunez and Apicella 2013), converge on to single neurons in the STN. Scattered localization of specific neuronal response profiles further confirms that information to some degree is integrated in the STN.

According to the global inhibition view, the major point of convergence is, however, not the STN, but the output nuclei SNR/GPI, which is thought to increase global inhibition of basal ganglia output in response to STN activation. Supporting evidence for this view is the causal effect of optogenetic activation of the STN on stopping (Fife and others 2017). Furthermore, recent studies have demonstrated an interesting interaction between sensorimotor and cognitive inhibition (Chiu and Egner 2015; Wessel and others 2016). On the other hand, the specific functional connectivity and pathophysiology involved in motor versus cognitive-limbic functions of the STN argues for somewhat distinct downstream routes of different STN sub-regions. It is possible that a "semi-global" signal may be computed by different modules of the STN, such as dorsoventral subregions or specific cell clusters, which would then differentially control specific types of actions.

It seems challenging to reconcile, however, the observed finely patterned but scattered response of different neurons in the STN with the possibility that a (semi)global STN activity exists as an inhibition signal. Various neuronal responses could certainly collectively participate in a (semi)global STN output; examining the average firing rate reported for the studies in Table 1 would be helpful to assess that possibility. Such a global summary of combined features of frontal and striatal processing would then indeed

be an informative signal reflecting overall conflict, as suggested by decision models of the STN. However, it appears likely that the information represented by the heterogeneous response is transmitted to downstream networks in a more specific way. Ensembles of specific functional STN cell types could form a uniform downstream signal even if they are not topographically clustered, either by specific anatomical wiring or dynamically by shared state or oscillatory coupling. Different hypothetical schemes for cortico-subthalamic processing is outlined in (Figure 6).

Interaction between rhythms and spikes

Rhythmic activity and coherence are both highly relevant for cortical-subthalamic function in action control. How this framework relates to neuron-specific and global firing rates, however, is an unresolved question in the field (NambuTachibana and Chiken 2015).

One possibility is that, regardless of whether the neuronal firing in the STN transmits a global or patterned signal, STN oscillations may represent global signals distinct from the neuronal firing, which may synchronize with downstream regions and in this way transmit information. Given the importance of synaptic transmembrane currents for shaping the local field potential (BuzsakiAnastassiou and Koch 2012), oscillatory field activity may reflect global input more directly than global spiking activity necessarily does.

A crucial point for how rhythms and spikes interact is, however, how neuronal firing is modulated by oscillatory activity. As Parkinsonism is characterized by beta band hypersynchrony across neurons and field-potentials in the STN and motor cortex, it has been hypothesized that this hypersynchrony leads to movement inhibition by compromising the processing capacity of STN neurons. This idea is consistent with the finding that oscillatory coupling decreases during a movement (Potter-Nerger and others 2017), potentially reflecting a release from oscillatory inhibition, and that oscillatory entrainment increases during conflict (Zavala and others 2017), in line with an increased action threshold. Beta entrainment of spiking, however , was not found to change during cognitive inhibition (ZavalaJang and Zaghloul 2017), although functional subtypes of the

neurons were differently entrained to the beta rhythm, suggesting an alignment between beta locking and task response. Interestingly, only cells with task-specific rate increase were beta locked (Zavala and others 2017; ZavalaJang and Zaghloul 2017), indicating that rhythmic entrainment may selectively control specific task-responsive populations.

Several studies have also reported theta modulation and entrainment of STN neurons at the same time as beta modulation (MoranBergmanIsrael and Bar-Gad 2008; Zavala and others 2017). The conflict-related entrainment mentioned above happened both at beta and theta frequency, and both for cue-cells and movement-cells (Zavala and others 2017). Even if it is unclear how each frequency specifically modulates neuronal firing, the finding that the same or co-localized cells were modulated by two rhythms, indicates a possible convergence point between theta-related conflict, beta-related stop and neuronal firing, although this needs further investigation.

Though broad evidence points to a link between movement inhibition and beta synchrony, and possibly also to conflict-dependent theta synchrony, this does not mean that all rhythmic modulation or entrainment is inhibiting. In the hippocampal system, neuronal phase coding relative to theta oscillations contributes to information coding (O'Keefe and Recce 1993), a principle that also is found in the ventral striatum (van der Meer and Redish 2011). Strong theta power in the local field potential does not necessarily reflect strong theta synchrony between neurons, but rather allows cell assemblies to decorrelate and facilitate information coding (Mizuseki and Buzsaki 2014). This is in line with the idea that Parkinsonian pathophysiology is related to hypersynchronized and maladaptive beta activity rather than beta oscillations per se. To further understand the role of spike-field interactions in the STN, there is a need to clarify how oscillations of different frequencies, levels, and scales interact. Taken together, however, cortico-subthalamic processing by specific rhythms may dynamically entrain or temporally bind specific populations of STN neurons, and by such mechanisms flexibly control how various types of information are linked and transmitted to downstream networks.

Conclusion

In this review, we have outlined the role of STN in motor and nonmotor action control. Behavioral, clinical, and physiological data, combined with computational modelling, converge in many ways towards a unified general understanding of STN function. Still, there are many unresolved questions regarding how different types of information is processed and integrated in the STN, how observed oscillatory and rate-based dynamics interact in this loop, and finally how the STN interacts with other structures in the basal ganglia, frontal cortex and potentially the brainstem to learn and perform optimal action control.

A focus that deserves attention is the converging evidence that different neurons exhibit differential responses within the STN. This evidence does not strictly align with the view that there is a global and uniform STN output. Given the rich and multidisciplinary reports on human STN function, it is surprising that there are relatively few studies from in vitro physiology work and from rodent models in which high-quality recordings and optogenetic circuit dissections during behavioral tasks could address many of the unresolved issues.

Though it is challenging to disentangle the increasing complexity of the circuits involved in action control, these questions offer a rich opportunity for investigating core features of behavioral control through multidisciplinary approaches and methods across clinical and experimental fields. Ultimately, better insight into these circuits may provide better understanding and treatment of disorders of action control, including but not limited to Parkinson's disease and OCD.

Declaration of conflicting interests

Funding

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Figure 1: Functional anatomy of the basal ganglia and the STN.

A) i: The basal ganglia pathways, highlighting both the STN and the striatum as input structures of the basal ganglia: the hyperdirect pathway (Cx-STN-GPI/SNR), the direct pathway (Cx-Str-GPI/SNR) and the indirect pathway (Cx-Str-GPe-GPI/SNR). Filled and empty arrows indicate excitatory glutamatergic (glu) and inhibitory GABAergic (GABA) projections, respectively. Abbreviations: Cerebral cortex (Cx); striatum (Str); subthalamic nucleus (STN); external segment of the globus pallidus (GPe); internal segment of the globus pallidus (GPI); substantia nigra pars reticulata (SNR); thalamus (Th). ii: Schematic diagram of the 'center-surround model' of basal ganglia activity; early activation of the hyperdirect pathway causes a broad inhibition, while subsequent activation of the direct pathway causes a specific activation of motor programs, antagonized by the indirect pathway. Republished with permission from (NambuTokuno and Takada 2002) and original figure.

B) Topographical organization of the projections from different regions of the frontal cortex to the STN, which partially overlap. Colored meshes represent dense projections from the cortical areas ventromedial prefrontal cortex / orbitofrontal cortex (vmPFC/OFC), anterior cingulate cortex (ACC), dorsal prefrontal cortex (DPFC), supplementary motor areas (SMA) and motor cortex (M1). Coronal view at i: anterior, ii: central and iii: posterior STN. Republished with permission from Society for Neuroscience, from (Haynes and Haber 2013); permission conveyed through Copyright Clearance Center, Inc.

Figure 2: Oscillatory dynamics in the STN during motor and non-motor inhibition, and conflict.

A) STN beta power decreases from onset of GO cue and during movement. If a STOP signals appears after the GO cue (ST(s) condition), beta power increases relative to the GO trials without STOP signal (GO(lm) condition).

B) STN oscillatory dynamics during sensorimotor decisions with low (i) and high (ii) conflict. Theta power increases only during high conflict trials, while perimotor beta power decreases similarly in both conditions.

C) STN oscillatory dynamics during non-motor memory decisions. Beta power decreases during memory encoding both in the lateral prefrontal cortex (PFC) (i) and the STN (ii), while theta power increases only in the lateral PFC. PFC-STN beta coherence (iii) decreases during encoding of target trials which are supposed to be encoded, but increases during distractor trials which are not supposed to be encoded.

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Figure 3: Evidence accumulation and decision thresholds

Schematic illustration of the evidence accumulation process, indicating how accumulated evidence increases over time towards the decision threshold for the correct decision. When the accumulated evidence reaches the decision threshold, a response is made. Upper panel displays high and low drift rate of the accumulated evidence. In this case, both conditions eventually accumulate the same level of evidence and therefore will have similar accuracy, but it takes longer time when the drift rate is low, as during a difficult task. Lower panel displays high and low decision thresholds. Drift rate is slower in the low-threshold condition, but since the decision threshold is lower, the response is made at the same time as the high-threshold condition, but with less accumulated evidence and therefore lower accuracy level.

Figure 4: Decision thresholds in the STN

A-B) Decision making during high and low conflict. In the moving dot task (A, left), participants are asked to indicate the overall direction of dot movement, which becomes gradually more coherent. Sensory information is sequentially sampled and integrated over time, as evidence for the correct response is accumulated. During high conflict trials in this study (A, right), some dots moved in the opposite direction of the overall

movement direction. STN theta power (B, i) and mPFC-STN theta coherence (B, ii) increased selectively in the high-conflict trials. In this task, increased STN theta power was related to increased decision thresholds in a drift diffusion model, and mPFC-STN theta coupling predicted threshold modulation (HerzZavalaBogacz and Brown 2016).

C) Decision making during instructed speed-accurracy tradeoffs. In this task, participants were instructed to be either fast or accurate in their responses, which should indicate the overall direction of moving dots with either high or low movement coherence. Increase in STN theta power predicted decision thresholds only after accuracy instructions (D, left). Decrease in STN beta during high dot moving coherence predicted decreased decision thresholds regardless of instructions (D, right).

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Figure 5: Neuronal activity in the STN during response inhibition, decisional conflict and reward.

A) Single neuron responses from a monkey performing an inhibitory control task which disentangles proactive Go-NoGo responses and reactive switch-responses: switch-go (stop-to-go) and switch-stop (go-to-stop). i) Response of two different cells to switch-go trials and switch-stop trials. ii) Response of two different cells to Go-trials and NoGo-trials in the Go-NoGo task. iii) Stop and Switch cells were separate populations during reactive trials, but each of these could be both Go and NoGo cells during proactive control trials.

B) STN population rate during associative decisions. Firing rate increases during high conflict trials relative to low conflict trials.

C) During a sensorimotor task, STN cell responses with increased firing rate aligned either to the cue ("Early cells") or to the response ("Late cells"). The cue-aligned cells increased in firing rate during high conflict trials relative to the low conflict trials.

D) STN neuronal responses following a "Go for Reward" cue for neurons that increased (red) or decreased (blue) in firing rate.

A) Reproduced with permission from (Pasquereau and Turner 2017), B) Republished with permission of Society for Neuroscience, from (Zaghloul and others 2012); permission conveyed through Copyright Clearance Center, Inc, C) Reproduced with permission from (Zavala and others 2017), D) Reproduced with permission from (Rossi and others 2017).

Figure 6: Action control in the STN

Simplified schematic of possible conceptual routes of information flow between the frontal cortex, STN and GPI/SNR, based on functional anatomical or dynamic connections. Color gradients represent topographical organization of functions from the blue "motor" part in the most posterior dorsolateral STN to the red "limbic" part in the most anterior ventromedial STN, with connected areas in the frontal cortex and SNR/GPI (Alexander and others 1990, Haynes and Haber 2013). Similar principles could be relevant for the striato-pallido-subthalamic (indirect) pathway, but the figure does not address how this input is integrated with cortical input in the STN. All of these schemes may be relevant, in parallel or depending on context.

a) Competing input model. Competing action plans reaching STN cause global excitation of GPI/SNR, conveying a "wait" signal to withhold response until the optimal action is selected by the striatum (Bogacz and Gurney 2007; Frank 2006).

b) Specific input model: Specific signal from the PFC to the STN (conveying for example "Stop" or "Conflict") causes global excitation of GPI/SNR (AronHerzBrownForstmann and Zaghloul 2016).

c) Parallel / spiral model: Parallel circuits in the basal ganglia loop process different types of information, though the inhibitory effect of STN on basal ganglia output may be similar regardless of information type (AlexanderDeLong and Strick 1986). Open and closed loops across the basal ganglia may allow information to

    spiral from ventral to dorsal loops (Haber 2003; Haynes and Haber 2013; Kelly and Strick 2004).

d) Integration model: Integration of information modalities to specific neurons across the STN (Espinosa-ParrillaBaunez and Apicella 2013; Janssen and others 2017). This is anatomically supported by nucleus-wide dendrites (SatoParentLevesque and Parent 2000), intranuclear axon collaterals (KitaChang and Kitai 1983), STN-Gpe interactions. STN neurons convey a specific but integrated (modular) signal to the GPI/SNR.

e) Dynamic model: The frontal cortex conveys different signals to the STN through directed oscillatory coupling. For example, a "conflict" signal from the mPFC can be transmitted through increased theta coherence, and a "go" signal from sensorimotor cortex can be transmitted through decreased beta coherence. In the STN, parts of the local processing by neurons and high-frequency oscillations can entrain to these rhythms, and the participating ensemble of neurons transmit a collective but patterned signal to the GPI/SNR. (AronHerzBrownForstmann and Zaghloul 2016; BrittainSharott and Brown 2014; Zavala and others 2017; ZavalaZaghloul and Brown 2015)

Table 1. Neuronal task responses in the STN.

Neuronal responses to executive, cognitive, motivational and emotional tasks, recorded in rats, monkeys or human patients with Parkinson's disease or OCD, from the last decade. Note the range of response types and functional cell types listed in the column "Feature of responsive firing". The column "Type of change and localization" illustrates that i) neuronal responses involve both increases and/or decreases in firing rate, ii) functional cell types can reflect separate and/or overlapping neuronal populations, and iii) these functional cell types can be topographically organized or scattered across the entire STN. Of note, some studies report single unit recording, others multiunit or background neuronal activity.
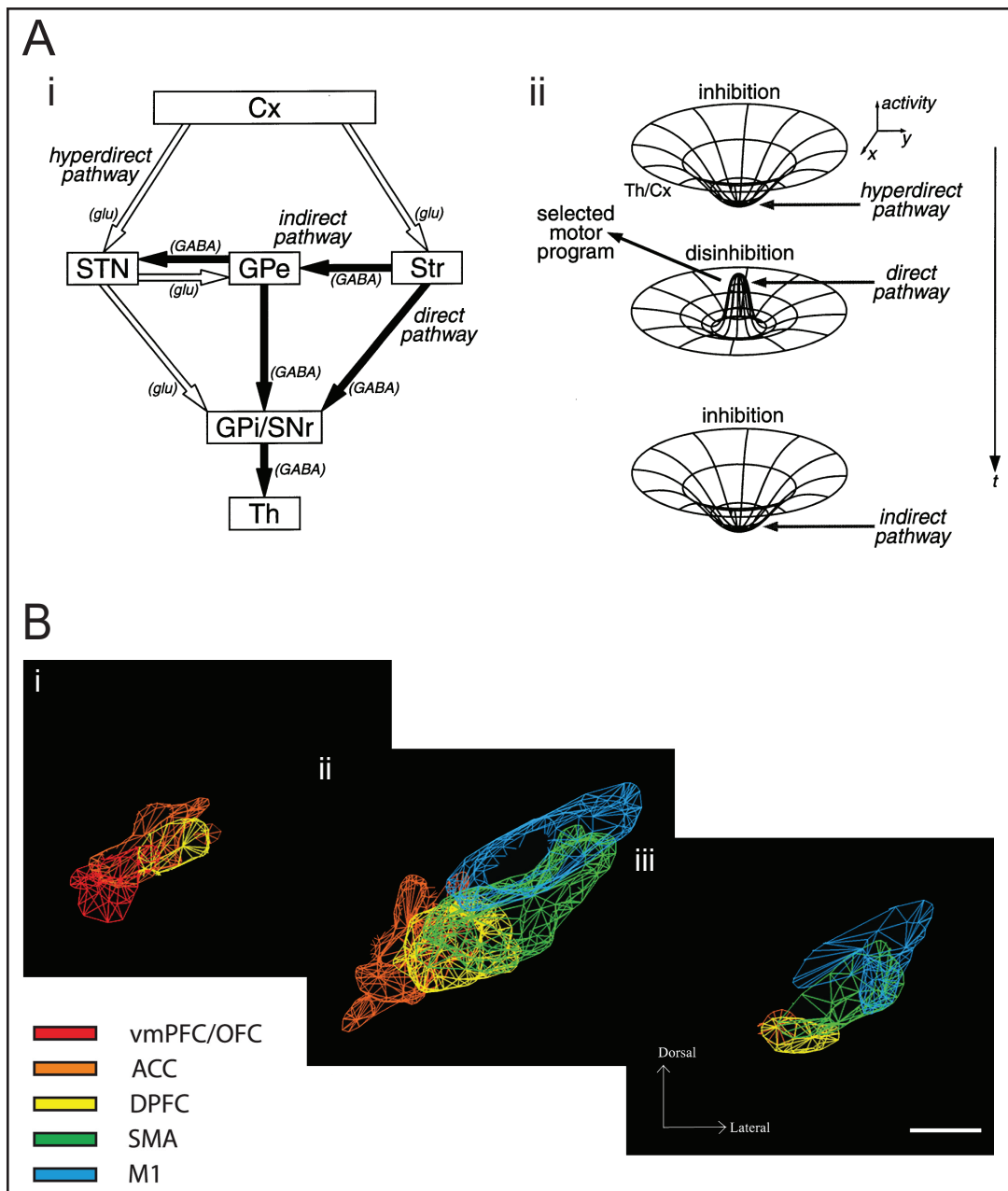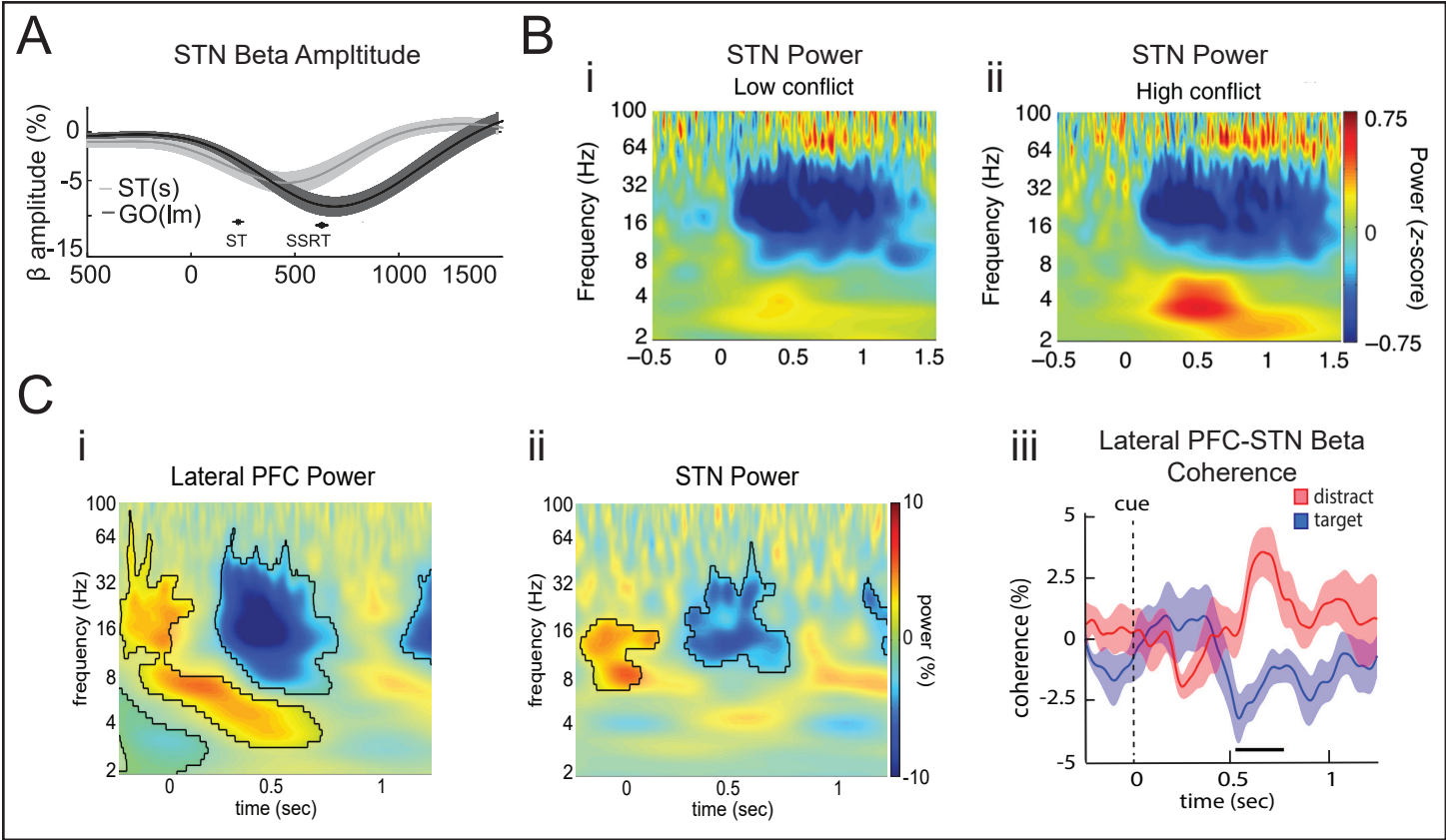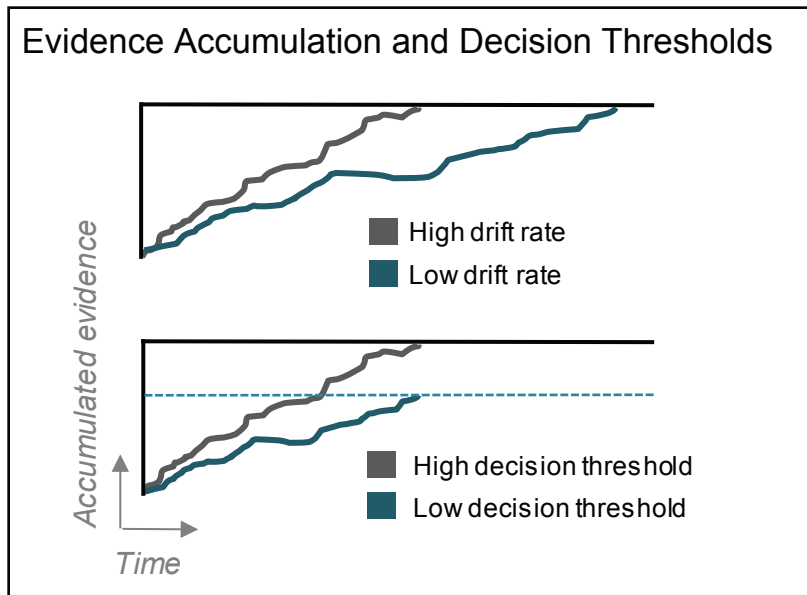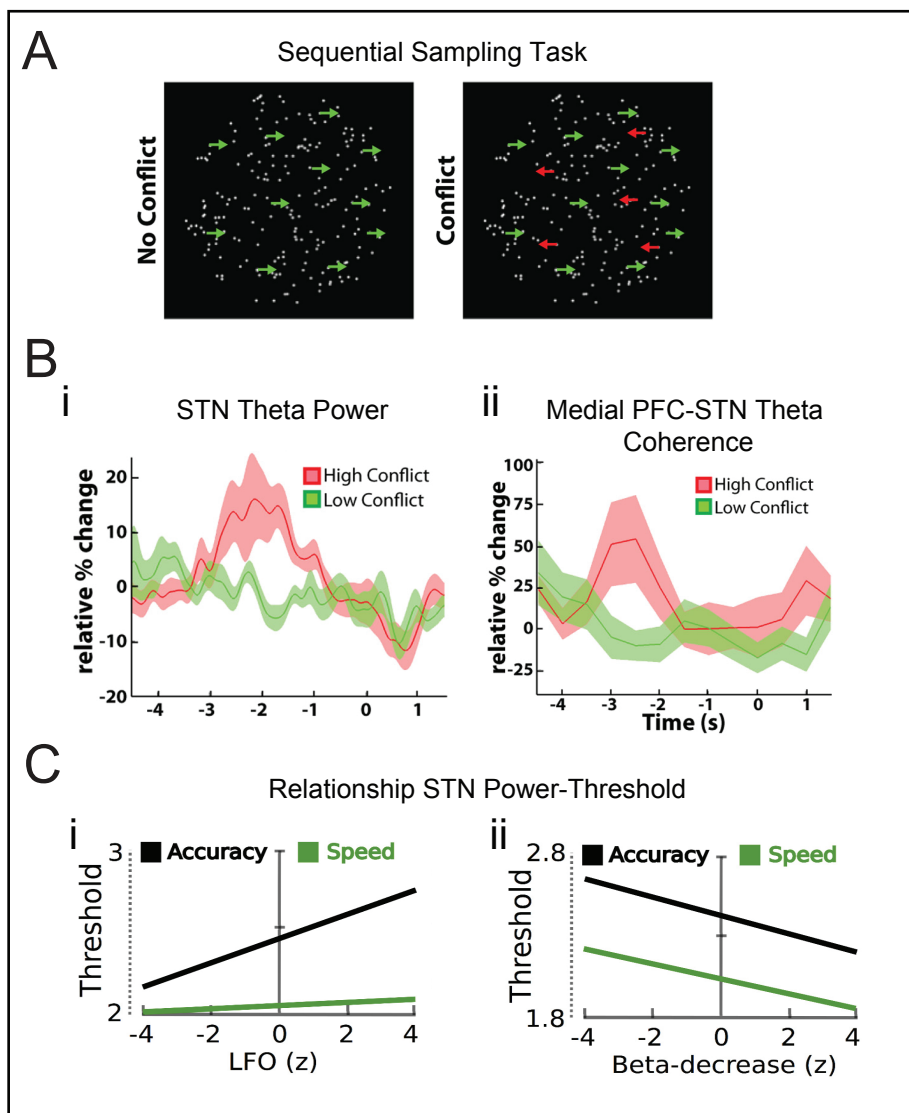
Figure 1.

Figure 2.

Figure 3.

Evidence Accumulation and Decision Thresholds

Figure 4.

A Sequential Sampling Task

B
i STN Theta Power
ii Medial PFC-STN Theta Coherence

C Relationship STN Power-Threshold
i
ii
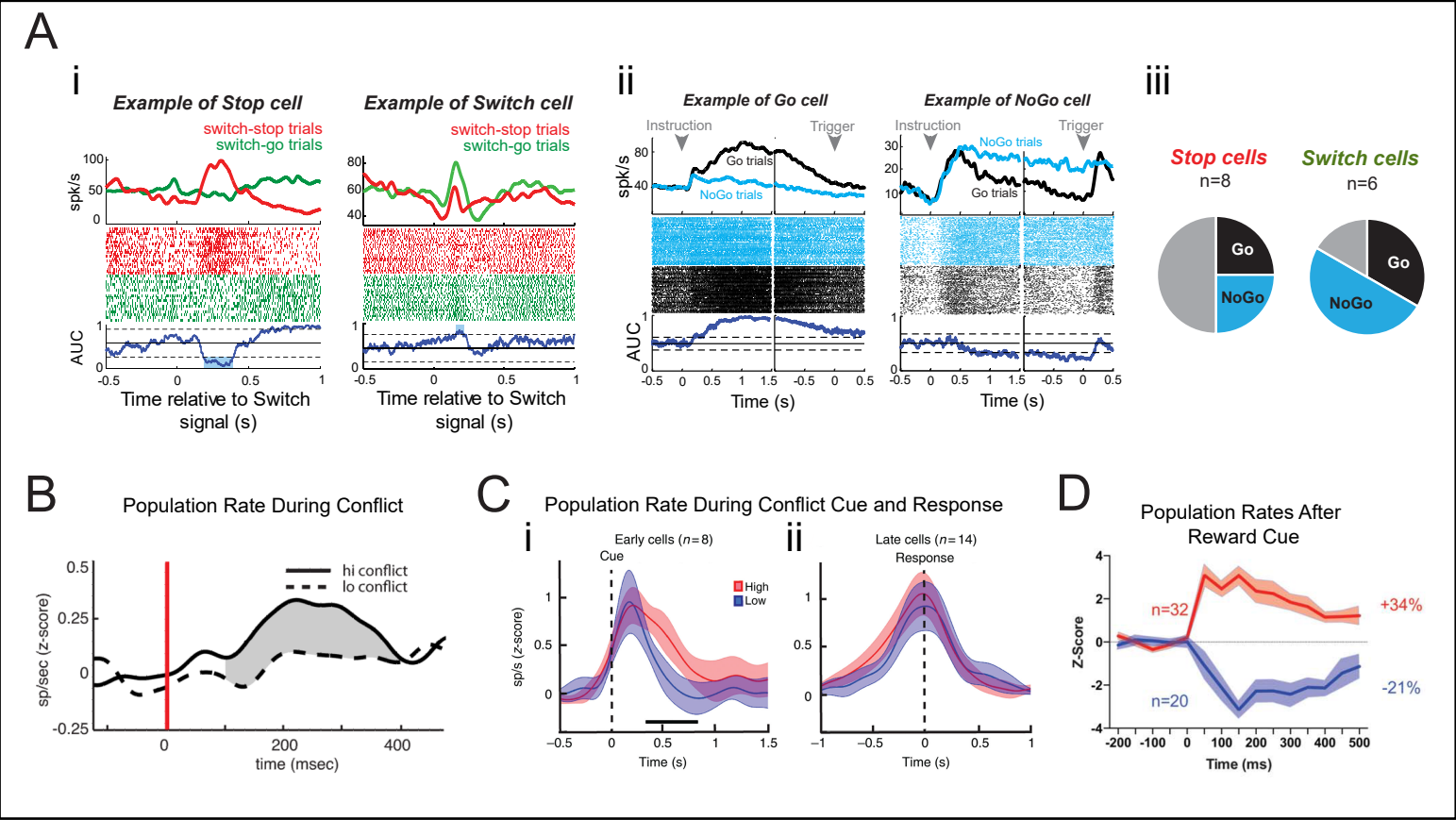
Figure 5.

Figure 6
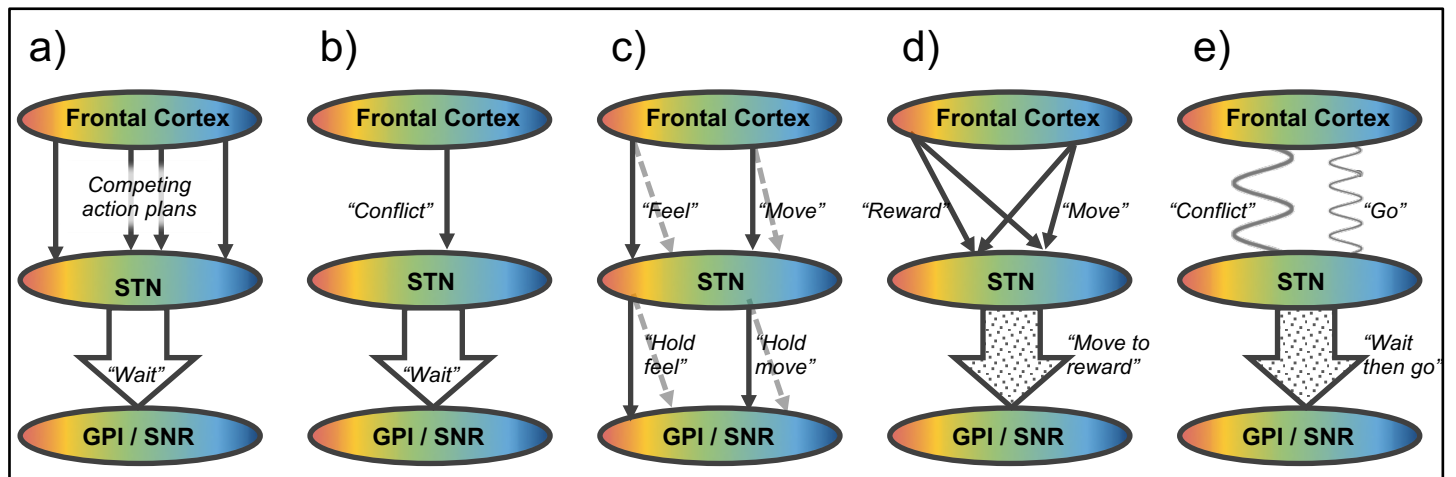
	Citation	Task	Feature of responsive firing	Type of change & localization
Response inhibition tasks	*Isoda 08* *(Monkey)*	Response inhibition: Switch / Go-NoGo	Switch cells, Go cells, NoGo cells (eye-movement).	Most ↑, some ↓ rate. Overlapping populations. Ventral STN.
	Schmidt 13 *(Rat)*	Response inhibition: SSRT	Response to stop-cue, regardless of actual stop.	Most ↑ rate. Successful stop depends on relative timing of inputs to SNr.
	Bastin 14 *(Human, OCD)*	Response inhibition: SSRT	Go cells, stop cells and error monitoring cells.	Most ↑ rate. Separate populations. Ventral STN.
	Benis 16 *(Human, PD)*	Response inhibition: SSRT	Go cells, stop cells.	Most ↑ rate. Separate populations. Dorsal STN.
	Pasquereau 17 *(Monkey)*	Response inhibition: SSRT and Go-NoGo	Switch cells, Go cells, NoGo cells.	Most ↑ rate. Distinct & overlapping populations. Switch cells: vm STN, others scattered.
Cognitive and conflict tasks	*Zaghloul 12* *(Human, PD)*	Value-based decision task (no feedback), conflict	Response to conflict, only in accurate choices.	↑ rate, relatively consistent across cells. Ventral STN.
	Burbaud 13 *(Human, OCD)*	Memory decision task, checks allowed	Response to cue, movement, decision, feedback and doubt/checking.	Most ↓, some ↑ rate, ↑ during checking. Multimodal responses, overlapping populations. Ventral STN.
	Zavala 17a *(Human, PD)*	Sensorimotor decision task, conflict	Cue cells: modulated by conflict. Move cells: directionally selective.	Most ↑, some ↓ rate. Higher rhythmic entrainment during conflict, across cell types. Cue cells: ventral STN.
	Zavala 17b *(Human, PD)*	Memory decision task (non-motor)	Response to memory encoding less to decision.	↑ and ↓ rate, overall ↓. Only ↓-cells were beta-locked. No localization.
Motivational tasks	*Lardeux 09* *(Rat)*	Instrumental task	Response to reward, dep on reward quality.	Specificl populations, some overlap. ↑ and ↓ rate.
	Lardeux 13 *(Rat)*	Instrumental task	Response to sucrose vs cocaine reward and future error.	Distinct populations.
	Breysse 15 *(Rat)*	Reward discrimination task	Response to positive / aversive reinforcers, execution and evaluation (missed rewards).	↑ rate at cue for preferred expected reward. Specialization reset when context changes. Distinct populations.
	Espinosa-Parilla 15 *(Monkey)*	Reward representation, different tasks	Response to task-related reward, reward expectancy and unexpected reward.	Most ↑, some ↓ rate. Overlapping populations respond to movement and reward.
	Rossi 17 *(Human, PD)*	Valence-based Go-NoGo task	Response to valence-info, more to reward than loss.	↑ and ↓ rate. Distinct populations, some multimodal. Little localization.
	Pearson 17 *(Human, PD)*	Risk decision task, self-paced (BART)	Response to risk, outcome, task context, elapsed time.	↑ and ↓ rate. Sparse response, overlapping population.
Emotional tasks	*Eitan 13* *(Human, PD)*	Auditory recognition of emotional stimuli	Response to emotional voices, correlated to recognition and arousal.	↑ RMS density, ↓ alpha band activity of neuronal responses. Right ventral STN.
	Sieger 15 *(Human, PD)*	Viewing of affective pictures	Response to emotional valence / arousal and eye-movement.	↑ and ↓ alpha band activity. Distinct populations in different locations.