Perspectives on stopping behavior : process analyses of stop-signal inhibition

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7 Neuro-stimulation of the subthalamic nucleus, but not the thalamus, facilitates response inhibition in patients with Parkinson's disease

Abstract

The present study adopts the neurophysiological perspective to explore the nature of inhibitory motor control vis-à-vis basal ganglia functioning. Two groups of patients who where treated with high-frequency deep brain stimulation (DBS) participated in this study. The members of one group had a neurostimulator implanted in the subthalamic nucleus (STN) to reduce the symptoms of advanced stages of Parkinson's disease (PD). In a second group of patients diagnosed with Parkinson's or Minor disease, the electrode targeted the ventral intermedius nucleus (Vim) of the thalamus to treat severe ('essential') tremor. Participants performed twice a stop-signal task and a go/nogo task - once with the neurostimulator turned on and once with the stimulator off during alternate runs in one session. Results indicated that DBS of the thalamus did not systematically affect task performance. In contrast, stimulation of the STN significantly facilitated response execution as well as inhibition processes. Findings are interpreted in terms of candidate neural circuits underlying inhibitory motor control.

7.1 Introduction

7.1.1 Anticipatory behavior

Anticipatory behavior requires the selection of relevant aspects from the stream of information impinging upon our senses, and the subsequent selection of appropriate actions. Originally, studies in human information processing have described selective attention either in terms of a bottleneck protecting limited-capacity central systems from overload (Broadbent, 1958), or as a resource that can be allocated to various processing systems (Kahneman, 1973). Theories on selective attention have been extended by Skinner and Yingling (1977), who presented physiological evidence that the selection of relevant channels might involve a thalamic gating mechanism. Skinner and Yingling hypothesized that selective (inter-modal) attention might be realized by a frontal mediated excitation of inhibitory neurons in the reticular nucleus (RN) of the thalamus, which exerts an inhibitory control over the underlying thalamic nuclei. Selective attention in the sensory domain has been associated with closing of irrelevant thalamic gates, leaving the relevant thalamo-cortical pathways open for information processing.

In order to shift attention to a new target, one has to 'disengage' attention from the present focus (Posner, 1995). Rather than the disengagement in perceptual aspects of attention, the present study focuses on the neural pathways that are involved in disengagement in

the motor domain. The interaction between the individual and the environment can call for a sudden change in the planned course of action, rephrasing inapt behavior into more appropriate current courses of actions that are related to new goals. In daily life, people are able to stop, interrupt, and change planned or ongoing actions rapidly. Stopping ongoing behavior is a first step that has to be taken when one reorients or switches towards new courses of action that are related to new goals. The ability to stop movement is therefore an important act of 'top-down' cognitive control (Logan, 1994).

7.1.2 The stop-signal paradigm

In laboratory settings, *the stop-signal paradigm* has been developed to investigate the covert cognitive processes that constitute inhibitory motor control. This paradigm was proposed by (Vince, 1948) and formalized by (Logan & Cowan, 1984). In the stop-signal paradigm the participant performs a task, usually a choice reaction time (RT) task requiring the discrimination of two visual stimuli, and a subsequent manual button-press response. This is referred to as the 'primary task', which consists of non-signal trials (i.e., trials without a stop signal). Additionally, a stop signal (usually a tone) is presented occasionally and unpredictably on a proportion of the trials, instructing the subject to inhibit his or her response in the primary task. These trials are called 'stop trials'. The interval between the presentation of the primary-task signal and the onset of the stop signal is under experimental control. If the stop signal is presented soon after the primary-task signal, it is quite easy for the subject to inhibit the response. Stopping becomes much more difficult, or even virtually impossible, if stop-signal delay increases.

Performance in the stop-signal task can be formulated in terms of a race between two sets of processes that run independently for completion (Logan & Cowan, 1984; Osman, Kornblum, & Meyer, 1986). One set of processes controls the execution of the primary choice RT task, starting with the presentation of the choice signal and racing toward the button-press response. The other set of processes is initiated by the stop signal and controls response inhibition. The process that finishes first wins the race; if the primary-task process wins the race the choice response is executed, but if the stopping process wins, the response is withheld. One of the merits of the race model is that it allows estimation of the covert or internal response to the stop signal or stop-signal reaction time (hereafter referred to as SSRT). Over the years, the race model has proven to fit stopping data from a variety of responses including speech (Ladefoged, Silverstein, & Papcun, 1973), typing (Logan, 1982), foot movements (De Jong, Coles, & Logan, 1995), and eye movements (Logan & Irwin, 2000; Hanes & Carpenter, 1999). In general, it turns out that healthy young adults are able to react to a stop signal, and stop whatever they are doing in about 200 ms., thus allowing close control over their actions.

7.1.3 Review of stop-signal studies

The stop task has proven to be an effective tool identifying slower than normal stopping latencies for groups of individuals that have been diagnosed with inhibitory deficits, such as ADHD (Jennings, van der Molen, Pelham, Brock, & Hoza, 1997; Oosterlaan & Sergeant, 1998; Schachar & Logan, 1990a; 1990b; Schachar, Mota, Logan, Tannock, & Klim, 2000; for

reviews of ADHD studies with the stop-signal paradigm see Nigg, 2001; Oosterlaan, Logan, & Sergeant, 1998). Although stopping latencies were longer in hyperactive children, there is no deficiency in detecting the stop signal (Schachar & Logan, 1990b). Schachar and Logan used a dual-task setting, instructing subjects to execute an overt response instead of an inhibitory response to the signal following another go signal. It was reported that hyperactive children detected the second signal as often as controls. Similarly, impulsive adults have been shown to have longer SSRTs than nonimpulsive adults (Logan, Schachar, & Tannock, 1997). Furthermore, like most - if not all - cognitive operations, stopping is subject to life-span changes, as indicated by longer stopping latencies in children (Bedard et al., 2002; Ridderinkhof, Band, & Logan, 1999; Van den Wildenberg & van der Molen, 2003a; Williams, Ponesse, Schachar, Logan, & Tannock, 1999) and limited evidence for age-related slowing of stopping across older adulthood (Kramer, Humphrey, Larish, Logan, & Strayer, 1994; Williams et al., 1999). Within the field of developmental psychology, the stop signal-paradigm has been used to identify separate developmental trends for simple inhibition (i.e., the abortion of all ongoing response activation) and more subtle manifestations of selective inhibitory control (Bedard et al., 2002). Finally, others reported the positive effects of methylphenidate (Tannock, Schachar, Carr, Chajczyk, & Logan, 1989) and the negative effects of alcohol op stopping latency (Mulvihill, Skilling, & Vogel-Sprott, 1987).

7.1.4 The nature of stopping

Over the years, the stop-signal paradigm has provided a highly informative stop-signal reaction time, representing the latency of the internally generated act of stopping. Although the application of the stop-signal procedure sheds light on stopping efficiency (e.g., it distinguishes between subgroups like ADHD children and controls) it does not provide a deeper understanding of the nature of inhibitory motor control. Like the go process, the stop process has an onset (the stop signal) leading to an (inhibitory) response. Several investigations have focused on experimental manipulation of processing stages in an attempt to identify the cognitive operations that constitute the go processes (Sanders, 1980; 1998; Sternberg 1969; for a review see Van der Molen, Bashore, Halliday, & Callaway, 1991). Recently, a similar technique has been applied to examine substages that make up stop-signal processing (Van den Wildenberg & van der Molen, 2003b). In his review article on stopping, Logan (1994) suggested three possible applications of the stop-signal paradigm that may broaden our understanding of the nature of stopping processes.

First, along with the suggestion of Logan (1994, p. 192), several investigators have focused on the experimental design of the stop task. They factorially combined stopping with other experimental manipulations that draw upon a form of inhibitory control to learn more about stopping from the possible interaction patterns. Logan (1981), for example, observed that stop latency is approximately equal for spatially compatible and incompatible responses (see also Logan and Irwin, 2000). Apparently, stopping does not interact with the ability to resolve the conflict between the prepotent compatible response and the spatially incompatible response (e.g., Kornblum, Hasbroucq, & Osman, 1990). Others combined stopping with the inhibition of responses to target stimuli flanked by task-irrelevant distracters assigned to the same or to the opposite response (Kramer et al., 1994; Ridderinkhof et al., 1999). These investigators found that responses to targets flanked by incompatible distracters were more difficult

to inhibit than responses to compatible displays. This pattern of results was interpreted to mean that stopping and the need to inhibit the (incorrect) response to incompatible flankers queue up, or compete for execution (cf. Ridderinkhof et al., 1999). A recent stop study indicated that stopping was less efficient when subjects were in a state of reduced response readiness (i.e., when awaiting the occurrence of a nogo signal in a series of go trials) compared to control trials during a series of consecutive go signals (Van den Wildenberg, van der Molen, & Logan, 2002).

Second, several investigators have used psychophysiological measures to focus on the temporal dynamics of response activation and response inhibition. De Jong was the first to bridge the gap between behavioral stop-signal studies and psychophysiological investigation (De Jong, Coles, Logan, & Gratton, 1990; De Jong et al., 1995). The lateralized readiness potential (LRP) in combination with electro-myographic (EMG) measures led De Jong and colleagues to propose two separate inhibitory mechanisms: a slower cortical mechanism capable of selective inhibition and a midbrain mechanism for fast simple stopping (De Jong et al., 1990; 1995; Van Boxtel, van der Molen, Jennings & Brunia, 2001). However, based on a review of psychophysiological data in the stop-signal literature, Band and van Boxtel (1999) formulated an alternative interpretation of the neural mechanisms involved in stopping. Their main point is that the inference of a stop mechanism operating downstream from the primary motor cortex is incorrect. Alternatively, Band and van Boxtel have suggested a model in which an integrated circuit of the prefrontal cortex and basal ganglia are candidate agents of response inhibition, whereas possible sites of inhibition are the thalamus and motor cortex (Brunia, 1999; cf. Goldberg 1985). In an extensive psychophysiological analysis of inhibitory motor control that included measures of brain activity, heart rate, muscle activity, response force, and respiratory cycle, the involvement of the prefrontal cortex in stopping has been indexed by a brain wave, called the N200, (Van Boxtel et al., 2001). The N200 is a negative ERP (event-related potential) that exhibits its maximum over the frontal cortex about 200-300 ms after the nogo signal in a go/nogo task (Eimer 1993; Jodo & Kayama, 1992; Kok, 1986; Naito & Matsumura, 1994; 1996; Pfefferbaum, Ford, Weller, & Kopell, 1985; Van Boxtel et al., 2001). There are several compelling arguments that support the view that the N200 reflects the activity of a central inhibition mechanism. These include the timing vis-à-vis behavioral measures of inhibition like stop-signal reaction time and the temporal relation between the N200 amplitude gain associated with declining response activation reflected by decreasing LRP amplitude (cf. Van Boxtel et al., 2001). A persuasive argument is that electrical stimulation of this frontal area during normal response activation suppresses the activity in the motor cortex and hampers the production of an overt response in monkeys (Sasaki, Gemba, & Tsujimoto, 1989). Brain imaging and microelectrode studies also have provided support for the frontal origin of the negative potential (Kawashima et al., 1996; Pliszka, Liotti, & Woldorff, 2000; Rubia et al., 2001; Sasaki & Gemba, 1986; Sasaki, Gemba, Nambu, & Matsuzaki, 1993). Another psychophysiological index of response inhibition is heart rate change. Successful inhibition is associated with heart-rate deceleration (Jennings, van der Molen, Brock, & Somsen, 1992).

Single-cell recordings in primates performing on a stop task provide a third approach towards a better understanding of the nature of inhibition. Hanes and colleagues recorded unit activity in the frontal eye fields during the countermanding of eye movements and identified neural signatures of visio-motor control (Hanes, Patterson, and Schall (1998); see Logan & Irwin (2000) for a behavioral study comparing inhibitory control of eye and hand movements).

Thus, psychophysiological data have complemented performance studies and so contributed to our understanding of the nature of stopping. A plausible mechanism by which the prefrontal cortex might exert response inhibition has been emphasized by Brunia (1999; Brunia & van Boxtel, 2001). Derived from Skinner and Yingling's (1977) neural network underlying perceptual anticipatory attention, Brunia proposed a thalamic gating model in which an integrated circuit involving the frontal cortex and forebrain exert behavioral inhibition through selective control over interconnections in the reticular nucleus (RN) of the thalamus. The thalamus has been proposed to be the site of response selection, operating as a relay station between input from the basal ganglia and cerebellum and output to the motor cortex. Important in this respect is the function of the RN. The RN takes up the total lateral aspect of the thalamus and has a local inhibitory influence upon the underlying thalamic relay nuclei. Excitation of the RN increases its inhibitory effect and decreases activity in the thalamo-cortical channel. A central role in stopping is accorded to the selective control of the RN by prefrontal brain areas - dubbed 'gating'.

Brunia (1997) suggested that a direct connection from the prefrontal cortex to the RN might be a possible route via which response inhibition could be realized. Given the anatomical constraints of this nucleus, it is difficult to present experimental evidence for that idea. Some years ago, he proposed another possible stop route, that is the excitatory pathway from the cortex to the STN (Brunia, personal communication). Activation of this pathway results in a blocking of thalamo-cortical output, which itself is considered a necessary condition for movement production. Although most neurophysiological investigations on inhibitory motor control focused on the involvement of frontal brain areas (see Band & van Boxtel, 1999 for a review), for practical reasons few experiments have directly investigated the role of the basal ganglia in inhibitory motor control. Recently techniques have been developed to intervene in basal ganglia functioning. Before explaining that, we will first present a brief overview of basal ganglia function.

7.1.5 Functional overview of basal ganglia connections

The basal ganglia are the principal subcortical component of a system of parallel circuits that links cortical output to the thalamus and back to the cerebral cortex. This enables modulation of motor output that ultimately is transmitted via the cortico-spinal system to the muscles (see Mink, 1996 for a review). The striatum (caudate and putamen) receives direct excitatory cortical inputs (see Figure 7.1). Two of the five dopamine receptor types: D-1 and D2 are present in the striatum, connecting to the so-called 'direct' and 'indirect' pathways, respectively. Although the synaptic actions of these dopamine receptors are different, the dopaminergic inputs to the two pathways give rise to the same effect – reducing inhibition of the thalamo-cortical neurons and thus facilitating movements initiated in the cortex. The striatum projects to the output nuclei – the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr) through two major projection systems.

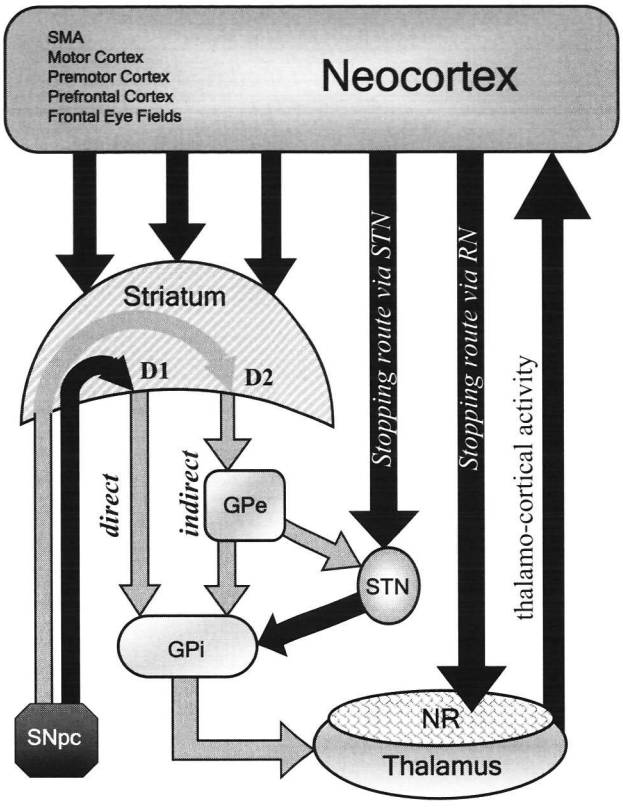

Figure 7.1: Schematic representation of excitatory (black) and inhibitory (gray) connections of the basal ganglia in a normal situation. D1 = dopamine d1 receptors; D2 = dopamine d2 receptors; GPe = external pallidum; GPi = internal pallidum; SMA = supplementary motor area; SNpc = substantia nigra pars compacta; STN = subthalamic nucleus; RN = reticular nucleus (modified after Alexander & Crutcher, 1990). Theoretically, two pathways might be involved in stopping behavior. The present study is aimed at the role of the pathway via the STN.

The direct pathway of the parallel basal ganglia-thalamocortical circuits connects the striatum directly to the GPi output nucleus. The indirect pathway passes first to the external pallidal segment (GPe), and from there to the STN. The output from the STN targets the GPi and is the only excitatory connection within the basal ganglia - all others are GABA-ergic and inhibitory. The GPi is the major output nucleus of the basal ganglia, targeting parts of the thalamus with inhibitory projections. Finally, these thalamic nuclei project to motor, premotor, supplementary motor, and possibly prefrontal cortex. The two efferent pathways have opposing effects on GPi activity, and thus on the thalamic target areas and downstream cortical activation levels. In summary, activation of the direct pathway disinhibits the thalamus, thereby increasing thalamo-cortical activity, whereas activation of the indirect pathway further inhibits

thalamo-cortical neurons. As a result, activation of the direct pathway facilitates movement, whereas activation of the indirect pathway inhibits movement.

There is mounting evidence suggesting that the STN can be regarded as another input station of the basal ganglia besides the striatum (Mink, 1996; Mink & Thach, 1993), because the STN receives direct cortical projections, especially from the frontal lobe (Hartmann-von Monakow, Akert, & Künzle, 1978). These anatomical relations made Brunia suggest that stopping of ongoing behavior might be realized via cortical excitation of the STN. In accordance with this idea Nambu, Tokuno, and Takada (2002) have called this connection the 'hyperdirect' pathway (see also, Mink, 1996; Nambu et al., 2000), via which inhibition of large areas of the thalamus and cerebral cortex could be realized.

In an extensive review of basal ganglia functions, Mink (1996) argues that the basal ganglia as such do not generate movement. Instead, voluntary limb movements are initiated by prefrontal, premotor, supplementary motor, and primary motor cortex, and the cerebellum. Premotor, supplementary motor, and primary motor cortex send a corollary excitatory signal to the STN. The STN projects in turn to the GPi in a widespread pattern and excites the GPi. The increased GPi activity causes inhibition of thalamocortical and brainstem motor mechanisms. Inhibitory striatal input to the GPi results in focally decreased activity in the GPi and a selectively disinhibition of the desired thalamocortical and brainstem MPGs. According to Mink: "the net result of basal ganglia activity during a voluntary movement is the braking of competing motor patterns and focused release of the brake from the selected voluntary movement pattern generators" (Mink, 1996, p. 414). Correspondingly, STN activity in primates has been related to the suppression of unwanted eye movements when fixation was required, linking STN functioning with the suppression of unwanted movements (Matsumura et al., 1992). The inability to inhibit competing motor programs results in slow movements, abnormal postures and involuntary muscle activity.

Supposing that the basal ganglia and the STN play a key role in inhibitory motor control, we studied stopping in a subset of patients diagnosed with Parkinson's disease (PD), a progressive neurological disease associated with basal ganglia disfuctioning. Modern techniques allow for a direct modulation of the STN, as we will explain later. First we give some more details of PD.

7.1.6 Parkinson's disease

Parkinson's disease (PD) is one of the most common movement disorders. Between 1 and 2 persons per 1000 are estimated to have Parkinsonism (Marttila, 1987). Because of the relatively late onset of the illness, the prevalence increases to 1 in 100 in populations older than 55 years of age. The four cardinal symptoms of the disease are (i) rigidity of the limbs, (ii) tremor of the limbs, often asymmetrical and more prominent in the hands, (iii) bradykinesia of the limbs and body involving difficulty initiating and slowness in movement, and (iv) postural instability resulting from impairment of righting or postural reflexes. Parkinsonism has been related to a dysfunction of the dopaminergic neuro-transmission in the basal ganglia (Jellinger, 1987). The symptoms of PD become apparent after degeneration of dopaminergic neurons in the substantia nigra (SNpc), a ventral midbrain region (Bernheimer, Birkmayer, Hornykiewicz, Jellinger, & Seitelberger, 1973).

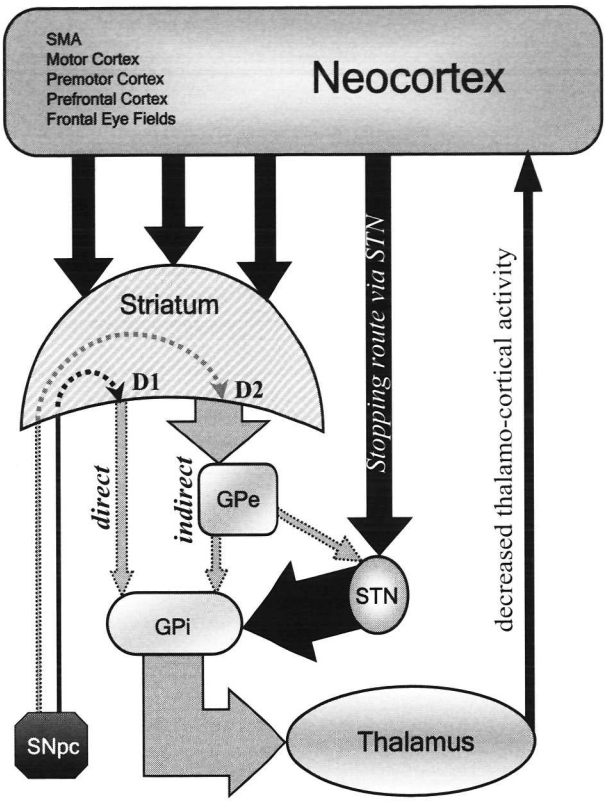

Figure 7.2: Schematic representation of excitatory (black) and inhibitory (gray) connections of the basal ganglia in Parkinson's disease. Degeneration of dopamine neurons in SNpc is associated with imbalance within the direct and indirect pathways, which in turn reduces thalamo-cortical activity.

Via the nigro-striatal pathway, the loss of pigmented cells in the substantia nigra parallels a loss of the neurotransmitter dopamine in the striatum. The effects of this reduction of available dopamine in the striatum are twofold. First, it is associated with overactivity in the indirect pathway – excessive inhibition of the GPe leads to disinhibition (i.e., increased activation) of the STN (see Figure 7.2). The net result of the hyperactive excitatory drive from the STN is an increased activity in the GPi. On the other hand, a lack of dopamine is associated with underactivity of the direct pathway – releasing the inhibition of the GPi. Thus, dopamine shortage in the striatum comes down to increased activity in one of the major output nuclei of the basal ganglia - the GPi -, which leads to increased inhibition of activity in the thalamo-cortical projections. Tonically active inhibitory output of the basal ganglia, acting as a 'brake' on motor pattern generators (MPG's) in the cerebral cortex and brainstem, is associated with hypokinetic aspects of Parkinsonism like the lack or slowness of movement.

7.1.7 Deep brain stimulation in Parkinson's disease and essential tremor

A recent direction for treating PD is provided by chronic high-frequency deep brain stimulation (DBS) of the GPi, and the STN through a surgically implanted electrode. DBS has also been applied in the ventral intermedius nucleus (Vim) of the thalamus to reduce symptoms of essential tremor. The implanted probe is connected to a wire run under the scalp and down the neck to the chest where it is attached to a battery-powered neurostimulator. When the electrode is turned on, a significant decrease in akinesia, rigidity, and tremor is achieved. The mechanism involved in DBS has not yet been resolved. A strong argument supporting the notion that high-frequency stimulation blocks or jams the output of the nucleus that is stimulated is provided by the observation that destruction of these targets consistently gives strongly similar effects (Ashby, Kim, Kumar, Lang, & Lozano, 2000; Benazzouz et al., 2002).

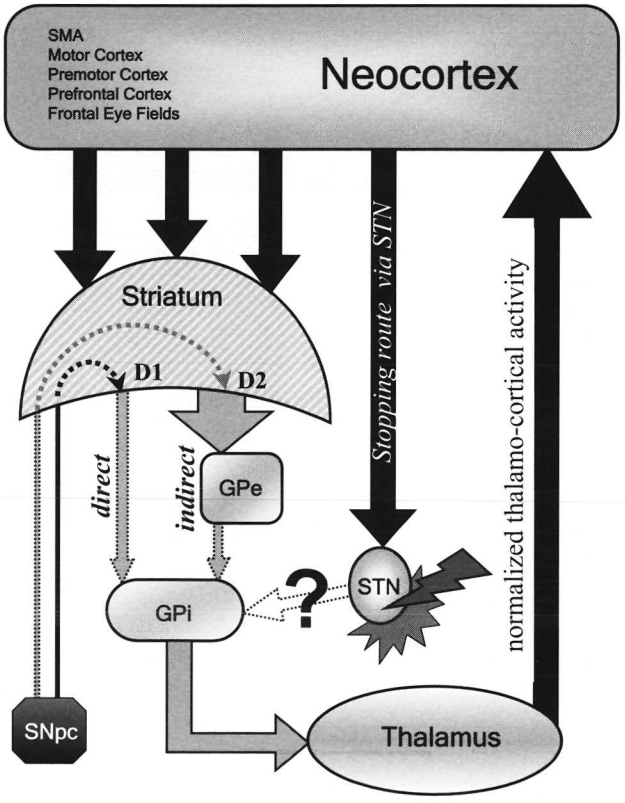

Figure 7.3: STN stimulation balances basal ganglia output and restores thalamo-cortical activity.

7.1.8 The present study

In the present study, we investigate the role of STN in response inhibition. Patients undergoing DBS in the basal ganglia provide us with the unique opportunity to explore the role of specific basal ganglia nuclei vis-à-vis stopping performance in the stop-signal paradigm. This study compares stopping performance of participants who have been treated with high-frequency DBS of the STN to reduce the symptoms of advanced stages of PD with patients who have been implanted with an electrode targeting the thalamus to reduce signs of essential tremor. According to the arguments outlined above, the STN is believed to play a key role in response inhibition. We expected a main between-subject effect of stimulation location on SSRT, in accordance with the prediction that the facilitating effects of stimulation on stopping is more pronounced in patients with STN stimulation than in patients with stimulation of the thalamus. Of particular interest in the current investigation is that the neurostimulator can be switched 'on' and 'off'. This affords a direct comparison of the effects of neuro-stimulation on stopping performance on a within-subject basis, with each patient providing his or her own baseline. According to the arguments outlined above, we predict that stimulation of the STN will facilitate stopping, indicated by shorter stopping latencies. Subjects are predicted to be better able to stop their manual response when the neurostimulator is turned on than when it is switched off.

7.2 Method

7.2.1 Participants

Two groups of patients treated with DBS, participated voluntarily in the experiment (see Table 7.1). One group of fourteen patients (7 females and 7 males, M = 60 years of age, SD = 6 years) has been diagnosed with Parkinson's disease (PD) and has been treated neurosurgically with a neurostimulator located in the STN. The other group consisted of eleven patients (2 females and 9 males, M = 62.3 years of age, SD = 13.3 years) with symptoms of essential tremor (ET) and have been implanted with a neurostimulator targeting the nucleus ventro-intermedius of the thalamus. Participants were tested individually, either visited at home or in a quiet room at the Academic Medical Center (AMC), Amsterdam.

Table 7.1: Number of participants, gender, mean age in years, and standard deviations (in parentheses) per group (Thalamus vs. STN targeted patients).

Group	*n*	female / male	Age
Thalamus	11	2 / 9	62.9 (12.1)
STN	14	7 / 7	60.0 (6)

7.2.2 Apparatus and signals

Stimuli were presented against the black background monitor of a laptop computer that was placed in front of the subject at a comfortable distance. The imperative signals were green left- and right-pointing arrows, consisting of a rectangle (2 cm x 1 cm) and a triangle (1.5 cm height x 2 cm base). The imperative stimulus was terminated by a button press or terminated if no response was given within 1000 ms after signal onset. Inter-stimulus intervals varied randomly but equiprobably from 1250 to 1750 ms in steps of 125 ms. During the inter-stimulus intervals, a white fixation point (3 x 3 mm) was shown in the center of the screen. Keyboard keys 'z' and '/' recorded left- and right-hand responses, respectively, from the onset of the target signal until the presentation of the next target signal.

7.2.3 Experimental tasks

Subjects performed on two experimental tasks; the stop task and the go/nogo task.

Stop task

During the stop tasks, subjects responded with the hand that was indicated by the direction of the arrow (e.g., if the arrow pointed to the left, they pressed the left button). The direction of the arrow was varied randomly within blocks of trials. On 30% of the trials, a stop signal was presented which instructed subjects to refrain from responding. Changing the color of the target arrow from green to red indicated the stop signal. Two separate tracking algorithms, one for each hand, compensated for possible between-hand differences in non-signal RT and dynamically adjusted stop-signal delay after every stop trial. After a successfully inhibited stop trial, stop-signal delay in the next stop-signal trial increased by 50 ms, whereas stop-signal delay was decreased by 50 ms in the next stop-signal trial if the subject was unable to stop. These tracking algorithms (Levitt, 1971) were used to reach about 50% successful inhibits, necessary for the estimation procedure of stop-signal reaction time, or SSRT (Logan et al., 1997). This tracking procedure compensated for differences in reaction time to primary-task signals (i.e., non-signal trials), either inter-individual (i.e., between subjects) as well as intra-individual (i.e., related to the stimulation condition).[1]

Go/nogo task

As in the stop task, arrow direction in the go/nogo tasks varied randomly and equiprobably. Two versions of the go/nogo task were administered. The left-hand version required subjects to respond with the left hand to arrows pointing to the left (go trials) but to refrain from responding to right-pointing arrows (nogo trial). In the right-hand version, the right-pointing arrow was designated as the go arrow, to be responded to by the right hand, whereas the arrow pointing to the left was designated a nogo signal.

[1] For matters of clarity, the term 'non-signal RTs' is reserved for RTs to primary-task signals within the stop-signal paradigm. 'Go-signal RTs' indicate RTs to go-signals in the go/nogo paradigm.

7.2.4 Procedure

Subjects were instructed to respond as quickly and accurately as possible to green go-arrows and to avoid errors of commission to nogo arrows in the go/nogo tasks. In the stopping tasks, subjects were told that the color of the green arrow would occasionally change to red, requiring them to refrain from pressing the response button. It was explained that stop-signal delay varied across trials so that on some trials stopping would be easy whereas on other trials stopping would be difficult.

The choice task without stop signals and the stop task were practiced initially in two consecutive blocks of 100 trials each. The stopping task was then administered in four blocks of 104 trials. After a separate practice block of 100 trials, the go/nogo tasks were presented in two blocks of 100 trials for the left and right hand, each. Half of the subjects started with the go/nogo task for the left hand, the other half started with the right-hand go/nogo task. Task order (stop task vs. go/nogo task) was counterbalanced across participants.

There were short intermissions between test blocks and an half-hour break halfway the test session, during which the neurostimulator was switched on or off. This procedure ensured that tremor had subsided after turning the stimulator on and off and that there was no rebound-exaggerated impairment after turning it off. Subjects were then again presented with the stop and go/nogo tasks. The order of stimulation conditions (on vs. off) was counterbalanced across subjects.

7.2.5 Data reduction and analysis

The first four trials of each block of trials were viewed as warm-up trials and were discarded from further analysis. Individual mean reaction times (RTs) of correct trials were calculated after the removal of outliers from the RT distribution (i.e., RTs > $M \pm 2.5\ SD$) on a subject-by-subject basis.

Stop-signal reaction times were estimated using the horse-race model (Logan & Cowan, 1984). Following the horse-race model's independence assumption, the RT distribution of the go process is the same whether or not a stop signal is presented. This implies that the left side of the distribution of RTs on non-signal trials, representing fast RTs, matches the distribution of RTs on stop trials that escape inhibition. The latency of the stop process can be estimated from the start and the finish of the stop process. The start of the stop process is under experimental control by the stop-signal delay, but the finish time has to be inferred from the observed non-signal RT distribution. If responses are not stopped on n% of the stop trials, the finish of the stop process is on average equal to the n-th percentile of the RT distribution on non-signal RTs. Finally, mean stop-signal delay is subtracted from this finish time to obtain an estimate of stop latency (for a detailed exposition see Logan, 1994).

7.3 Results

7.3.1 Go/nogo task

RTs to go signals in the go/nogo task (see Table 7.2) did not differ between left- and right-hand responses (479 ms vs. 478 ms, respectively), F (1, 23) < 1, p = .63. Therefore go RTs were averaged across left- and right-hand responses. There was no main effect of Group on go RT, indicating that responses to go signals did not differ between STN (496 ms) and thalamic patients (463 ms), F (1, 23) = 1.5, p = .23. In addition, Stimulation did not influence go RTs (482 ms in 'on' vs. 477 ms in 'off'), F < 1. Finally, a significant interaction between Stimulation and Group was absent also, F < 1. In sum, RTs obtained in the go/nogo task did not discriminate between Stimulation condition and Group.

Table 7.2: Mean reaction times on go-signals (Go RT), mean commission error percentages and standard deviations (in parentheses) and mean RT effect size per group (Thalamus vs. STN) and stimulation (on vs. off) in the go/nogo task.

	Stimulation				
	On		Off		
Stimulation Location	Go RT	Commission Error (in %)	Go RT	Commission Error (in %)	RT Effect size
Thalamus	464 (63)	4.6 (2.3)	463 (52)	5.3 (4.3)	-1
STN	491 (71)	3.6 (2.0)	501 (91)	2.9 (2.5)	10

The likelihood of committing a commission error to a nogo signal was equal across stimulation conditions, F < 1, (4.1% in both conditions), and did not differ between Group (3.3% ms in STN vs. 5% in thalamus patients), F (1, 23) < 3.1, p = .09. The interaction between Group and Stimulation did not approach significance, F (1, 23) < 1.3, p = .26.

7.3.2 Stop-signal task

Non-signal trials

Table 7.3 shows the mean reaction times (RT) on non-signal trials (i.e., trials without a stop signal). An overall ANOVA on non-signal RTs was conducted with within-subjects factor of Stimulation (on vs. off) and between-subjects factor of Group (STN vs. Thalamus targeted subjects). The main effect of stimulation on non-signal RT was not significant, F (1, 23) = 3.6, p = .07, the speed of non-signal responses was 621 ms in 'on' and 643 ms in 'off' conditions.

A main effect of Group was absent also, $F < 1$, $p = .54$; non-signal RT did not distinguish between STN patients (646 ms) and Thalamus patients (618 ms). The interaction between Stimulation and Group approached significance, $F(1, 23) = 3.2$, $p = .09$. Patients with an electrode in the STN displayed a decrease of 42 ms in non-signal RT as a result of stimulation, $F(1, 13) = 6.6$, $p = .02$. Stimulation did not significantly affect non-signal RTs in thalamus patients, $F < 1$.

There were less than 2% errors of omission. Choice errors were less than 3%. None of the main effects with respect to error rates were significant. When errors of choice and omission were taken together, the interaction between Stimulation and Group did not reach significance, $F(1, 23) = 3.9$, $p = .06$.

Table 7.3: Mean reaction times on non-signals (non-signal RT), error percentages and standard deviations (in parentheses) and mean RT effect sizes per group (STN vs. Thalamus) and stimulation (on vs. off).

	Stimulation				
	On		Off		RT
Group	Non-signal RT	Error (%)	Non-signal RT	Error (%)	Effect size
Thalamus	617 (91)	2.5 (2.1)	619 (92)	3.6 (2.3)	2
STN	625 (124)	4.2 (4)	667 (139)	3.5 (2.7)	42

Stop-signal trials

The stopping results are presented in Table 7.4. First of all, subjects were able to inhibit their responses about half of the times a stop signal instructed them to do so. The tracking algorithm resulted in an overall percentage of 49% correct inhibits which is very close to the anticipated 50%. The tracking algorithm worked very well in both stimulation conditions as the proportion of correct inhibits did not differ significantly between Stimulation conditions ($p = .13$), hands ($p = .76$) or Group ($p = .96$).

Second, as predicted by the horse-race model, responses on stop trials that escaped inhibition (signal-respond RT or SRRT) were significantly faster than responses on non-signal trials, $F(1, 23) = 115.5$, $p < .001$. The differences in RT between failed inhibits and responses on non-signal trials were about equal for STN patients (66 ms) and thalamus patients (63 ms), $F < 1$, and did not differ between Stimulation condition, $F < 1$ (62 ms in the 'on' condition vs. 63 ms in the 'off' condition).

Table 7.4: Mean proportion of failed inhibits (FI, in %), stop-signal delays (SS-delay), signal-respond reaction times (SRRT), stop-signal reaction times (SSRT), and standard deviations (in parentheses) per group (Thalamus vs. STN) and stimulation (on vs. off).

	Stimulation							
	On				Off			
Group	FI	SS-delay	SRRT	SSRT	FI	SS-delay	SRRT	SSRT
Thalamus	49.5	357 (112)	551 (92)	254 (36)	49.2	350 (119)	558 (83)	256 (49)
STN	50.0	369 (124)	564 (110)	246 (35)	48.1	371 (137)	596 (121)	281 (56)

SSRTs were estimated separately for each subject, each hand, and each Stimulation condition. An overall analysis of mean SSRTs yielded a significant main effect of Stimulation, F (1, 23) = 4.7, p = .04. Overall, stopping latencies were about 19 ms shorter with the stimulator turned on (250 vs. 269 in the 'off' condition). A main effect of Group on SSRT was absent, $F < 1$. Overall, SSRT did not differ between STN (263 ms) and thalamus patients (255 ms). Tests conducted in each group separately yielded a consistent pattern. SSRT improved significantly by an average of 35 ms with stimulation of the STN, F (1, 13) = 7.8, $p < .01$. In contrast, thalamus stimulation did not affect SSRT systematically (2 ms difference), F (1, 10) < 1, p = .83. However, when included in an omnibus ANOVA, the interaction between Stimulation and Group just failed to reach significance, F (1, 23) = 3.5, p = .07.

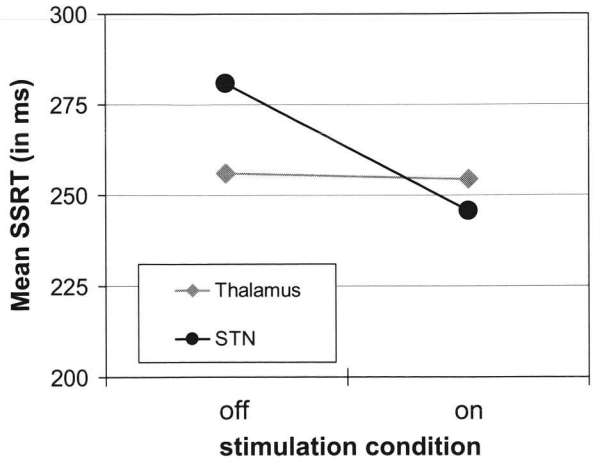

Figure 7.4: SSRT interaction between patient group and stimulation condition.

Shared versus unique effects of stimulation on stopping

Additional analyses of the STN data were conducted to investigate whether the improvement in stop speed with stimulation was independent of the observed stimulation-related improvement in the speed of response execution. To this end, an analysis of covariance (ANCOVA) was carried out on the effects of stimulation on SSRT with non-signal RTs obtained in the stop task as covariate. This correction for shared variance resulted in a largely attenuated effect of DBS on SSRT ($F < 1$), which suggests that DBS of the STN mediates both response execution and response inhibition.

In contrast, including go-signal RTs obtained in the go/nogo task as covariate yielded a residual effect of DBS on SSRT that approached significance, $F(1, 9) = 4.8$, $p = .056$. This outcome seems to suggest that the stimulation-related changes in SSRT can not be reduced to stimulation-related effects on the ability to execute a go response.

Finally, the Pearson correlation computed between the stimulation-related improvements in non-signal RT and SSRT was non-significant ($r = .42$; $p = .13$). This indicates that patients who displayed a relatively large increase in the speed of response execution with STN stimulation did not necessarily show a relatively large stimulation-related gain in the speed of stopping, which is in line with the suggestion of unique effects of STN stimulation on stopping.

7.4 Discussion

The current investigation was conducted to examine the role of the basal ganglia in the ability to countermand a manual motor response. A group of patients with DBS of the STN, and a group of patients with DBS of the thalamus performed a stop-signal task and a go/nogo task. The tasks were administered twice; once with neurostimulation of the target area ('on') and once without stimulation ('off'). Before embarking on a discussion concerning the main hypothesis of the present study, we first interpret performance in terms of the horse-race model.

7.4.1 Validation of the horse-race model

The pattern obtained from the RT and error measures, together with the observed inhibition ratios on stop trials indicate that all patients were quite able to execute simple finger responses according to task instructions despite their motor disabilities. The stopping data are in agreement with the predictions derived from the horse-race model that formulates behavior in the stop-signal task as a race between activating and inhibiting processes. In line with the race model, it was observed in all groups and all conditions that responses on stop trials that escape inhibition (i.e., signal-respond RTs) were executed significantly faster than average go-signal responses. Taken together, the overall stop-task performance observed in the current clinical setting attests to the robustness of the race model.

7.4.2 Response execution

In comparing performance of Parkinson's disease patients on non-signal trials obtained in the present study with performance of healthy elderly of about the same age, it should be noted that patients were slower in the execution of choice responses (632 ms on average vs. 538 ms for matched controls, data reported by Williams et al., 1999). This is in line with a variety of experimental paradigms showing that people with Parkinson's disease tend to have slower reactions than healthy adults of a similar age (Brown & Marsden, 1988; Rafal, Inhoff, Friedman, & Bernstein, 1987; Wascher et al., 1997). This is supported by evidence presented by transcranial magnetic stimulation studies showing that in Parkinson's disease, a longer time is needed for the motor cortex to reach the threshold necessary for eliciting an overt response (e.g., Pascual-Leone, Valls-Solé, Brasil-Neto, Cohen, & Hallet, 1994).

A recent psychophysiological study by Low and collaborators using LRP measures of motor preparation disentangled the slowing of motor processes observed in Parkinson's disease patients and slowing due to cognitive deficits arising before the motor system has been activated (Low, Miller, & Vierck, 2002). Motor processing of straightforward choice responses, like a single key press, was equivalent to that of an age-matched control group, whereas Parkinson's disease patients showed a deficit in motor processing speed when performing a relative complex response, like executing a sequence of button-press responses. Moreover, effects of manipulations of signal discriminability on RT indicated that premotor stages of processing are slowed too in Parkinson's disease.

It should be noted that the patients included in the present study were in advanced stages of their illness. This renders difficult any comparison of the present sample to that of Low et al. The present study was not designed to compare performance of patients diagnosed with Parkinson's disease directly with normal controls, but instead focused on the within-subject effects of DBS on the execution and subsequent inhibition of speeded motor responses. Within-subject measures of RT show a clear beneficial effect of STN stimulation on the execution of speeded choice responses - RTs were 42 ms faster on average when STN was stimulated compared to when it was not.

DBS of the STN has been reported to improve motor function in Parkinson's disease patients including akinesia, rigidity, tremor, dystonia, gait, freezing, and postural stability (Bergman, Wichmann, & DeLong, 1990; Limousin et al., 1995; Kumar et al., 1998; Rodrigues Oroz et al., 1998). Recent imaging studies have linked STN stimulation with enhanced movement-associated activation of supplementary motor area (SMA) (Ceballos-Bauman et al., 1999; Limousin et al., 1997).

Contrary to the decrease in choice RT observed in the STN group, no significant difference was detected between 'on' and 'off' conditions in thalamus-stimulated patients. Similar absence of thalamic effects of stimulation on RT has been reported previously (Flament et al., 2002). Flament and colleagues used auditory, visual, tactile, and proprioceptive stimuli as imperative signals to perform an elbow flexion and observed that reaction times were not different between on and off conditions.

Next to non-signal RTs obtained in the stop task, this current study included go RTs in a go/nogo task as yet another index of the ability to execute a motor response. In contrast to the observed speeding of non-signal RTs, DBS of the STN did not enhance the execution of responses to go-signals in the go/nogo task. For now, we do not have a ready explanation for

the apparent discrepancy between stimulation effects on non-signal RTs vs. go-signal RTs. In conclusion, the current results indicate that DBS speeded up the execution of choice responses in the STN group, but not in de Thalamus group.

7.4.3 Response inhibition

Like the pattern observed in the choice RT task, stopping latencies in the present study (264 ms) appear to be somewhat longer than the values obtained from healthy older adults (230 ms, results reported by Williams et al., 1999). Although the present design did not include a matched control group, the results suggest that response inhibition processes in patients diagnosed with Parkinson's Disease tend to be slower compared to stopping performance in normal controls, as reported by Kramer et al. (1994) and Williams et al. (1999). However, as stated above, our study was not designed to compare performance of patients with that of age-matched controls. Rather, we made a within-subjects comparison of stopping with stimulation versus stop performance with the stimulator off.

The major finding in the present study confirms the hypothesis that high-frequency stimulation of the STN facilitates the stopping of motor responses. The data provide three arguments supporting the notion that the improvement in SSRT with STN stimulation cannot be reduced to, or interpreted solely in terms of, the stimulation-related speeding of response-execution processes.

First, the tracking algorithm used in the stop-signal paradigm yielded stop latencies that were estimated independently of response execution processes. It was verified that the tracking algorithm worked well in the present sample - all patients in all stimulation conditions obtained response ratios very close to the intended 50%.

Second, the gains in the speed of go and stop processes associated with STN stimulation are unlikely to be due to one single speeding factor because the correlation between the improvements in choice RT and in SSRT was non-significant ($r = .42$; $p = .13$). Patients who displayed a relatively large reduction in the speed of response execution with STN stimulation did not necessarily show a large stimulation-related gain in the speed of stopping.

Third, the effects of STN stimulation still seem to stand when corrected for variance associated with the changes in the speed of go-response execution, as indicated by ANCOVA analysis. Taken together, the current results support the notion that the marked improvement in the speed of response inhibition associated with STN stimulation goes above and beyond the observed gain in the speed of response execution.

7.4.4 Mechanisms of DBS

The exact mechanism of action of neuro-stimulation on the targeted nuclei remains controversial. Stimulation may block transmission through the targeted structure, either by 'jamming' synaptic relays, or by means of activation of inhibitory interneurons. The hypothesis that DBS jams or blocks neural activity is supported by the highly similar clinical effects on behavior after lesioning the STN target (i.e., subthalamotomy) and animal studies (Ashby et al., 2000; Benazzouz et al., 2000). However, others have suggested that activity within the stimulated target might be increased. Dostrovski et al. (1999) recorded enhanced activity within the

stimulated thalamus when another electrode also in the thalamus was stimulating. Similarly, a recent study claims that there is no evidence that high frequency stimulation 'blocks' signal processing through the STN. Ashby and colleagues (2001) recorded frontal EEG activity while stimulating the STN. They concluded that high-frequency STN stimulation may excite low threshold neural elements, which can transmit impulses at frequencies greater than 100 Hz without blocking, and which may produce postsynaptic facilitation at the cortex (Ashby, 2001). Very recent PET recordings indicated increased blood-flow responses at the site of thalamic stimulation, as well as an enhanced flow in ipsilateral supplementary motor area, a region that receives afferents from the thalamus (Perlmutter et al., 2002). In conclusion, the exact mechanism of DBS still remains to be resolved, but the observation that STN stimulation enhances response execution as well as response inhibition does not contradict the notion that DBS stimulates the targeted site and downstream afferent projections. Also in the present experiment, the mechanism of DBS remains unclear, since we found both an amelioration of response execution and of response inhibition, while the two seem to be independent.

7.4.5 Neural mechanisms of stopping

One of the questions addressed in the present experiment concerns the nature of the processes that constitute the stopping of ongoing responses. Facilitation of stopping speed with STN stimulation confirms the view that the STN plays an important role in the motor circuit. Recent evidence from fMRI studies indicated that STN stimulation enhances movement-related activation in the supplementary motor area (SMA), the dorsolateral prefrontal cortex (DLPFC), and the anterior cingulate (Ceballos-Baumann et al., 1999; Limousin et al., 1997). However, recent neurophysiological investigation of patients diagnosed with Parkinson's disease suggested that the facilitation of movement-associated frontal activity is not necessarily associated with improvement in frontal executive functions (Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000). A study by Jahanshahi comparing 'on' versus 'off' states on cognitive functions showed ambiguous effects of DBS on various measures of executive function and working memory (Jahanshahi et al., 2000). Of particular interest is the observed impaired performance on the Stroop task with STN stimulation (see also Dujardin, Defebvre, Krystkowiak, Blond, & Destee, 2001). The Stroop task requires the suppression of the dominant response of reading the words in order to name the font color in which the color words are printed. Effective performance in the Stroop task requires a high level of conflict monitoring and response inhibition. Patients were non-significantly slower and made a greater number of self-corrected errors on the interference condition of the Stroop with stimulation of the STN even though color naming on the control Stroop tasks was significantly faster. This agrees with the decreased rCBF response in the rostral or 'cognitive' part of the anterior cingulate cortex (ACC) during the Stroop task, while task performance was impaired at the same time (Schroeder et al., 2002).

Thus, on the one hand STN simulation is associated with less-efficient executive functioning, indicated by impaired Stroop performance, but on the other hand the current study indicates that STN stimulation improves inhibitory control. This suggests a paradox. In support of the current models of fronto-striatal connectivity in Parkinson's disease, the effects of STN stimulation can be interpreted in terms of 'releasing the brake' over frontal cortical functioning, which could be associated with improvement of motor and cognitive function de-

pendent on these frontal areas. It has been suggested that the cognitive processes that benefit from DBS are not mediated by striatal processes, but are simply enhanced by facilitated cortical activation (e.g., Jahanshahi et al., 2000). On the other hand, Marsden and Obeso (1994) have proposed that disruption of basal ganglia outflow during STN stimulation impairs performance on tests requiring an alteration of behavior in novel contexts. It has been agued that performance on tasks that draw upon these executive functions, such as the Stroop task, may rely on the striatum, providing important information for subsequent cortical processing and hence are associated with sub-optimal functioning with STN stimulation (see Schroeder et al. (2002) for a similar interpretation). In spite of this, the claim that STN stimulation disrupts behavior in new and unexpected situations that require non-automated and flexible behavior seems to be at odds with the results obtained in the present study. Performance on the stop task demonstrated a clear stimulation-related facilitation of inhibitory motor control, indicated by a shortening of stop latency. Response inhibition in the stop-signal paradigm extends from perceptual processes (e.g., stop-signal detection) to response-related process like the actual interruption of ongoing movements (see Logan, 1994). The way around the paradox outlined above, could be that STN stimulation might have its main beneficial effects on the motor end of stop-signal processing.

List of abbreviations

DBS	:	Deep brain stimulation
ET	:	Essential tremor
GPi	:	Internal segment of the globus pallidus
GPe	:	External segment of the globus pallidus
PD	:	Parkinson's disease
RN	:	Reticular nucleus
RT	:	Reaction time
SNpc	:	Substantia nigra pars compacta
SNpr	:	Substantia nigra pars reticulata
STN	:	Subthalamic nucleus
Vim	:	Ventral intermedate nucleus of the thalamus