Does unilateral basal ganglia activity functionally influence the contralateral side? What we can learn from STN stimulation in Parkinson’s disease patients.

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26 **Running head**: Contralateral STN activity with unilateral STN-HFS

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Abstract
In humans, the control of voluntary movement, in which the cortico-basal-ganglia circuitry participates, is mainly lateralised. However, several studies suggest that both the contralateral and ipsilateral basal ganglia (BG) systems are implicated during unilateral movement. Bilateral improvement of motor signs in Parkinson’s disease patients (PD) has been reported with unilateral lesion or high-frequency stimulation of the internal part of the globus pallidus (GPi) or the subthalamic nucleus (STN-HFS). To decipher the mechanisms of production of ipsilateral movements induced by the modulation of unilateral BG circuitry activity, we recorded left STN neuronal activity during right STN-HFS in PD patients operated for bilateral deep brain stimulation. Left STN single cells were recorded in the operating room during right STN-HFS while patients experienced, or did not experience, right stimulation-induced dyskinesias. Most of the left-side STN neurones (64%) associated with the presence of right dyskinesias were inhibited, with a significant decrease in burst and intraburst frequencies. In contrast, left STN neurons not associated with right dyskinesias were mainly activated (48%), with a predominant increase 4-5 ms after the stimulation pulse, and a decrease in oscillatory activity. This suggests that unilateral neuronal STN modulation is associated with changes in the activity of the contralateral STN. The fact that one-side of the BG system can influence the functioning of the other could explain the occurrence of bilateral dyskinesias and motor improvement observed in PD patients during unilateral STN-HFS, as a result of a bilateral disruption of the pathological activity in the cortico-subcortical circuitry.

Key words:
Subthalamic nucleus, deep brain stimulation, neuronal activity, dyskinesias, Parkinson’s disease.
Introduction

Neural control of movement is largely lateralised. However, there is evidence to suggest that both the contralateral and ipsilateral basal ganglia (BG) systems are implicated in the execution of a unilateral movement. In animals, the performance of a unilateral movement provokes bilateral single-unit activity changes in the striatum (input of the BG system), the external part of the globus pallidus (GPe), the subthalamic nucleus (STN) and the internal part of the globus pallidus (GPi, BG output nucleus) (Cheruel et al., 1996; Wannier et al., 2002).

By using functional brain imagery, in healthy volunteers, the performance of simple unilateral motor tasks has been shown to induce unilateral premotor (PM) and primary sensorimotor (PSM) cortical activation but a bilateral activation of the sensorimotor putamen and the GPi (Scholz et al., 2000; Lehericy et al., 2006; Kraft et al., 2007). In Parkinsonian (PD) patients, unilateral movement-related changes in the STN firing rate and oscillatory activity have been reported bilaterally (Williams et al., 2005; Alegre et al., 2005; Devos et al., 2006).

Conversely, unilateral lesion of the GPi or high-frequency stimulation (HFS) of the STN has been shown to induce a bilateral motor improvement in PD patients (Baron et al., 1996; Lang et al., 1997; Alberts et al., 2008; Walker et al., 2009). Unilateral GPi lesions can also lead to a bilateral decrease in levodopa-induced dyskinesias (Baron et al., 1996; Lang et al., 1997) whereas unilateral STN-HFS can induce bilateral dyskinesias, shown to be predictive of a good post-operative outcome (Houeto et al., 2003). Even though the BG may operate, at least partly, a bilateral control of movement in humans, little is known about how one-side of the BG circuitry influences the neuronal activity contralaterally (Lehericy et al., 2006; Kraft et al., 2007) and which BG circuits are involved. In rats, unilateral modulation of STN activity by pharmacological agents or lesion modulates neuronal activity in the contralateral STN (Mouroux et al., 1995; Castle et al., 2005). Two recent studies in PD patients reported an increase in the contralateral STN neuronal activity while stimulating the STN unilaterally
(Novak et al., 2009; Walker et al., 2011). In these experiments, however, 1) the recordings were multiunit activity (Novak et al., 2009), 2) the precise location of the recording and stimulation sites were not shown, 3) the motor behaviour changes were not assessed and 4) low (30 Hz) and high (160 Hz) stimulation frequencies produced similar effects on contralateral STN neuronal activity whereas the clinical effects are known to be opposite (Moro et al., 2002). This present study was undertaken to determine the quantitative and qualitative nature of the changes in neuronal activity of the contralateral STN in relation to the changes in motor behaviour induced by unilateral STN stimulation. Here we recorded single-unit left STN activity during right STN stimulation, in the presence or absence of right-side dyskinesias.
Materials and Methods

Patients

Seven patients with PD (6 F/1M, mean age: 59 ± 7 yrs) were operated for bilateral implantation of stimulating electrodes into the STN. PD patients included in this study had an advanced form of PD (Hoehn and Yahr “off” score ≥ 3; disease duration: 12 ± 4 yrs) (Hoehn and Yahr, 1967), a good response to the levodopa treatment before surgery (mean improvement in the motor parkinsonian disability-Unified Parkinson’s Disease Rating Scale part III: 70± 20%)(Fahn et al., 1987), with disabling levodopa-induced motor complications (UPDRS part IV: 10.4±6.9) in spite of optimal medical treatment (mean equivalent levodopa dosage: 700 ± 161 mg/day), absence of dementia (mean mini-mental status: 27.4 ± 3.1 [Cockrell and Folstein, 1988]; Mattis scale: 139.3 ± 4.9 [Mattis, 1988]), a normal brain MRI and absence of contra-indications to surgery (Welter et al., 2002). One year after surgery, the mean improvement in the motor parkinsonian disability with bilateral subthalamic stimulation was 47% ± 11%, with a 53% and 72% mean reduction in the antiparkinsonian drug treatment and levodopa-induced complications (UPDRS part IV), respectively. The protocol was supported by INSERM (RBM C06-02) and approved by the local ethics committee. All patients gave informed written consent.

Neurosurgical procedure

The surgery was performed as previously described (Bejjani et al., 2000; Maltete et al., 2007). Drug treatment was discontinued the evening before surgery. Subthalamic nuclei were preoperatively targeted by means of stereotactic MRI (Dormont et al., 2004). The implantation of bilateral stimulating electrodes (Medtronic, model 3389) was performed the day after using both preoperative anatomical and peri-operative electrophysiological targeting and clinical testing.
**Left subthalamic recordings during right-side electrical subthalamic stimulation**

Perioperative electrophysiological recordings were performed in awake but immobile patients, at rest. Three to 5 coaxial leads (a central tungsten recording microelectrode, diameter: 25 µm; impedance: 10 megOhm; and an external tube for macrostimulation; FHC, Instruments, Bowdoinham, ME, USA) were lowered stereotactically to 5 mm above the predetermined target, along 3-5 parallel trajectories using a microdrive (Medtronic, Minneapolis, USA). Four of the leads were arranged, at a distance of 2 mm, around a central lead positioned according to the stereotactic coordinates, thus allowing stimulation and recording from the central, anterior, posterior, medial and lateral parts of the STN. Signals were amplified (x10), filtered (300 Hz-3kHz), audio-monitored and digitally recorded using a Leadpoint system (Medtronic, Minneapolis, USA).

Extracellular single-unit neuronal activity of the left STN (Hutchison et al., 1998; Rodriguez-Oroz et al., 2001) was recorded 2 min before, during and after bipolar stimulation of the right STN (mean recording time: 432 ± 32 seconds; simulation parameters: 60 µs, 140 Hz, cathodal square pulses, 2 and 4 V), by using an external stimulator (Dual Screen model 3628, Medtronic, Minneapolis, USA) connected to the definitive electrode previously implanted (Figure 1a) (Walker et al., 2011). Left subthalamic recorded neurons were included if they were well isolated, stable and could be sampled for at least 60 seconds.

As passive movements may induce changes in the STN neuronal activity (Rodriguez-Oroz et al., 2001), we chose to record stimulation-induced dyskinesias to objectively assess the effect of the unilateral STN stimulation on the ipsilateral side of the body, instead of evaluating the clinical therapeutic effects (i.e. rigidity or akinesia). For this purpose, we used surface EMG recordings of both right and left leg muscles. This procedure also enabled us to precisely
evaluate the temporal relationship between stimulation-induced dyskinesias and the subthalamic neuronal activity changes.

Single unit anatomical localisation

During the electrophysiological procedure, control profile images were regularly obtained from right-left projections, with the short X-ray radiological device of the Leksell stereotactic frame, to check the electrode trajectories and depth. This device consists of x-ray-visible fiducial markers and a digital flat panel screen fixated to the stereotactic frame. Before starting the surgical procedure, the direction of the x-ray unit was adjusted in order to be perpendicular to the stereotactic frame to allow superimposition of the values of the right and left Z and Y scales. The trajectory of each recording electrode was precisely located with reference to the AC-PC reference system by identifying both the stereotactic frame and the AC-PC landmarks in the preoperative MRI. The X, Y, Z coordinates of each single unit recording were also precisely located within the AC-PC system. Then, its localisation within the STN was determined by using a digital 3D deformable basal ganglia histological atlas (Yelnik et al., 2007) which was adjusted to the individual brain geometry of each patient (Bardinet et al., 2009). Electrophysiological analysis of single unit recordings and their atlas-based localisation was performed independently and blindly by different experts (Figure 1a).

Off-line analysis

Neuronal recordings were exported offline as text files and analysed using the Spike 2 software suite (Version 5; Cambridge Electronic Device, Cambridge, UK). Spikes were discriminated from noise with no stimulus artifact removal method. The mean firing rate, mean interspike interval (ISI) and coefficient of variation were calculated for each neuron (Kaneoke and Vitek, 1996; Welter et al., 2011). Discharge pattern analysis was performed
using 2 methods. First, a discharge density histogram (Kaneoke and Vitek, 1996) was
corrected for each cell and the firing pattern was classified as regular, irregular or bursting.
Second, neuronal activity was sampled for each period and epochs of elevated discharge rate
were analysed for bursts using a Poisson surprise analysis (Legendy and Salcman, 1985),
carried out using a Spike 2 script (Degos et al., 2005). In this study, spike trains with \( S > 5 \)
were considered to be bursts (Steigerwald et al., 2008). The mean burst frequency, duration,
number of spikes per burst, intraburst frequency and interburst interval were calculated for
each neuron with burst discharges (Steigerwald et al., 2008). Investigation of neuronal
oscillations at the single-neuron level was performed as proposed by Muresan et al. (2008).
Briefly, this method consists of 5 steps: 1) the autocorrelogram histogram (ACH) was
computed, 2) the ACH was smoothed by using a Gaussian kernel, 3) the central peak was
removed, 4) a fast Fourier transform (FFT) was applied to compute the spectrum of the
peakless ACH, and 5) the oscillation score was calculated. The analysis was always made for
a chosen frequency band, whereby the two input variables \( f_{min} \) and \( f_{max} \), represent,
respectively, the lower and upper limit of the frequency band of interest (\( \theta \): 4-8 Hz, \( \alpha \): 8-12
Hz, \( \beta \) low: 12-20 Hz, \( \beta \) high: 20-35 Hz, \( \gamma \): >35 Hz). The oscillation score represents the ratio
of the magnitude of the oscillation frequency to the average magnitude of the spectrum (\( Os = \)
the highest magnitude in the band of interest-\( M_{peak} \)/the average magnitude of the spectrum-
\( M_{avg} \)). The average magnitude of the spectrum was computed by integrating the whole
frequency spectrum and taking its average where \( Magnitude (f) \) was the estimated magnitude
of frequency \( f \) in the FFT-computed spectrum. The average spectrum was reduced by removal
of the central peak from the ACH. Finally, the estimated oscillation frequency \( f_{osc} \) was taken
as the frequency the highest magnitude \( M_{peak} \) in the band of interest. The strength of the
oscillation was given by the oscillation score \( Os \). Oscillations were considered to be
significant for \( Os > 10 \) and signal to noise ratio (\( snr \)) >5 (Muresan et al., 2008).
Statistical analyses

Results are given as mean ± SD. Modifications of the neuronal activity of the left STN (frequency of discharge, characteristic of the bursts, peak frequencies of the oscillatory activity) during right STN stimulation were studied using the nonparametric Wilcoxon Rank test. In order to examine the modifications of the pattern of discharge and oscillatory activities in the various frequency bands, Bowker’s Test of Symmetry was used. Statistical analysis was carried out using the Statview® software suite.

Comparisons between neurons associated with the occurrence of leg stimulation-induced dyskinesias versus neurons recorded without were performed using the non parametric Mann-Whitney test. Statistical significance was accepted at p< 0.05. No Bonferroni correction was applied.
Results

A total of 36 single cells were recorded in the left STN before, during and after STN-HFS of the right STN (Figure 1): 35 with 2 V stimulation current, 19 with 2 and 4 V stimulation and one with 4 V stimulation. During the 2 V stimulation of the right STN, 14 neurons were recorded in the left STN while dyskinesias occurred in the right leg, and 21 neurons were recorded in the left STN without stimulation-induced dyskinesias (Figure 1a).

Changes in neuronal activity of the left STN during right leg dyskinesias induced by right STN stimulation (2V)

When right leg dyskinesias were induced by right STN stimulation, firing rate and bursting activity of the left STN neurons were significantly modified (Figure 2). This was not the case in the absence of stimulation-induced dyskinesias (Figure 2). Changes are detailed below. On average, left STN neuronal activity was not significantly modified by right STN-HFS at 2 V (Table 1).

Mean discharge rate

When right STN-HFS induced right leg dyskinesias, an inhibition was observed in 64% of left STN neurons recorded with a significant decrease in their mean firing rate (Table 2, Figure 2a). This decrease in the left-side neuronal activity occurred 76 ± 34 ms following the start of the right STN stimulation (Figure 3a, left) and the PSTH showed a permanent inhibition of neuronal activity with no time-locked residual neuronal activity (Figure 3a, right).

Conversely, when no dyskinesias occurred, no significant change in the mean firing rate was observed but there was an inhibition in 24% of left STN neurons and an activation for 48% (Table 2, Figure 2a-3b). When the neuron was activated in the absence of stimulation-induced dyskinesias, the PSTH was differentially affected with an excitation peaking 4-5 ms after the
stimulation pulse (Figure 3b). In 3 left STN neurons, a very short latency response (<2 ms) was observed with 2-V right STN stimulation (dyskinesia neurons: n=2, no-dyskinesia neurons: n=1, Figure 4).

The mean, median, mode and SD interspike interval and the mean coefficient of variation of the 35 left STN neurons recorded during 2 V right STN-HFS were not significantly modified during right STN-HFS (Table 1). No significant difference in these neuronal activity characteristics was found in neurons recorded both with or without stimulation-induced dyskinesias (data not shown).

Bursting activity

Preceding right STN stimulation, about half of the left STN neurons exhibited a burst type pattern of activity (Figure 4a, Table 1). Right STN-HFS (2 V) induced significant changes in the distribution of the discharge pattern, with 10 cells switching their firing pattern (p<0.02, Figure 4a). The change in discharge pattern was not significantly different between the two groups of neurons, i.e. those recorded in the presence of dyskinesias vs without dyskinesias (29% of changes in both, not shown).

When right STN-HFS induced right leg dyskinesias, the mean burst frequency (not shown), intraburst frequency and interburst interval of the left STN neurons significantly decreased (p<0.05, Figure 2b-c). Conversely, no significant change was observed for left STN neurons recorded when stimulation failed to induce dyskinesias (Figure 2b-c).

Oscillatory activity

Before stimulation, about half of the neurons exhibited oscillatory activity, mainly in the beta frequency band (12-35 Hz, Figure 4b). Right STN-HFS (2 V) induced a significant decrease in the proportion of left STN neurons with oscillations (P < 10^{-4}, Figure 4b), with a significant
decrease in the beta band frequency (not shown). This decrease was only significant for left STN neurons recorded in the absence of right leg stimulation-induced dyskinesias (57% before vs 19% during STN-HFS, $P < 0.003$, Figure 5). No significant change in oscillatory activity was found for left STN neurons recorded while right leg stimulation-induced dyskinesias occurred (36% before and during STN-HFS).

Changes in neuronal activity of the left STN during stimulation of the right STN as a function of stimulation intensity.

Increasing the stimulation current did not significantly modify the mean discharge rate of the 19 neurons recorded in the left STN, with either the 2 or 4-V stimulation ($49.8 \pm 21.4$ Hz before vs $46.3 \pm 24.5$ Hz with 2-V stimulation vs $44.6 \pm 22.2$ Hz with 4-V stimulation, $P = 0.52$). However, during 4-V right STN stimulation, about half of the left STN neurons were activated while one third were inhibited ($P < 0.001$, Table 2). In 5 neurons recorded with both intensities, a very short latency response ($< 2$ ms) was observed when the stimulation was increased to 4 V (Figures 3c-6).

An increase in right STN-HFS from 2 to 4 V led to 4/19 cells changing their discharge pattern when recorded in both conditions, 2 cells switched from a regular to an irregular pattern, one from a regular to a burst-type and one from a burst-type to a regular one (not shown). The increase from 2 to 4-V stimulation did not significantly modify the effects of right STN-HFS on left STN burst characteristics (not shown) and oscillatory activity (47% before vs 16% during 2 V STN-HFS vs 20% during 4 V STN-HFS, $P = 0.06$, not shown). Increasing stimulation current induced an increase in the occurrence of dyskinesias with 12/20 neurons recorded during stimulation-induced dyskinesias (Table 2, $P < 0.05$). Among the 12 neurons recorded with 4-V induced-dyskinesias, 6 were previously recorded during 2-V stimulation in
the absence of induced-dyskinesias. In these 6 neurons, no significant change was observed,
with however a tendency for fewer spikes per burst (17.6 ± 5.4 vs 14.5 ± 4, $P=0.15$).
Discussion

In this study, we showed that ipsilateral dyskinesias induced by unilateral STN-HFS were associated with significant changes in contralateral STN neuronal activity, with a decrease in the firing rate and bursting activity, but no significant change in oscillatory activity. We also found that an increase in stimulation current induced a short latency activation of neuronal firing. These results are consistent with the hypothesis that the complex changes provoked by unilateral STN-HFS stimulation involve the BG thalamocortical networks bilaterally.

Technical considerations

Several lines of evidence suggest that these results are robust. 1) The recording microelectrodes were localised within the STN as attested by the neuronal activity recorded which was similar to that previously reported in PD patients (Hutchison et al., 1998; Rodriguez-Oroz et al., 2001; Steigerwald et al., 2008). 2) The location of recorded STN single cells and stimulating electrodes were precisely determined by using a validated 3D histological deformable basal ganglia atlas (Yelnik et al., 2007; Bardinet et al., 2009). 3) It is unlikely that the stimulation artefact could have masked the response of left STN neurons to right STN stimulation: the artefact was short (1 ms), the time-locked excitatory response observed in PD patients was maximal 4 to 6 ms after the stimulation pulse and very short latency responses (<2 ms) could be detected (Figure 3 and 7) (Walker et al., 2011). Although a possible role of stimulation artefact in the decrease in oscillatory activity observed during STN stimulation cannot be totally excluded, the fact that these changes were not observed for all neuronal activity recordings is not in accordance with this hypothesis. Lastly, a possible role of dyskinesias in the neuronal activity changes observed during stimulation-induced dyskinesias cannot be completely ruled out, the fact that these changes occurred before the emergence of dyskinesias (<100 ms) argue against this explanation (Figure 3). In addition,
decrease in neuronal activity was also observed in some neurons in the absence of stimulation-induced dyskinesias (Table 2).

Ipsilateral STN stimulation-induced dyskinesias are related to complex changes of neuronal activity in the contralateral STN

In STN neurons recorded while contralateral dyskinesias occurred, the main effect was a decrease in the firing rate and bursting activity (Figure 2), with no significant change in the oscillatory activity. This result is in line with the report of an inhibition in neuronal activity of the STN, the GPi and the SNr when levodopa-induced dyskinesias (LID) occur in PD patients and animals rendered parkinsonian (Filion and Tremblay, 1991; Lozano et al., 2000; Boraud et al., 2001; Stefani et al., 2002; Alonso-Frech et al., 2006). Conversely, this result seems to be in contradiction with the increase in glutamatergic transmission observed in the STN, the EP (rat GPi) and the forelimb motor cortex in PD patients and parkinsonian rats when STN-HFS induces dyskinesias (Boulet et al., 2006; Quintana et al., 2010), that leads, in theory, to an increase in neuronal activity. However, when increasing the intensity of stimulation from 2 to 4 V, we observed an increase in ipsilateral dyskinesias with an increase in the number of activated neurons (Table 2). This suggests that the neuronal firing rate in the STN is probably not per se the determinant of the occurrence of dyskinesias but that the pattern and level of oscillatory activity may be of greater importance. The reduction in the STN bursting activity observed when STN-HFS induced dyskinesias is in line with this hypothesis (Figure 2) and has also been reported in GPi neurons (one of the STN outputs) of parkinsonian monkeys during LID (Filion and Tremblay, 1991; Boraud et al., 2001). The persistence of oscillatory activity in STN neurons during STN-HFS induced dyskinesias, with even a tendency to have more oscillatory activity (36 vs 19%), is also in line with this hypothesis, and was previously reported during LID, with, in some reports, an increase in low (4-10 Hz) and high frequency
band oscillatory activity (Lozano et al., 2000; Stefani et al., 2002; Meissner et al., 2005; Alonso-Frech et al., 2006). Finally, these data suggest that dyskinesias induced by STN-HFS are probably mainly related to the pattern of neuronal activity and oscillatory activity, and less to the firing rate (Obeso et al., 2000), with a complex combination of these three parameters (Boraud et al., 2001).

Unilateral subthalamic high frequency stimulation modulates contralateral subthalamic neuronal activity

In our patients, unilateral STN-HFS provokes inhibitory and excitatory responses of the contralateral STN neurons with changes in bursting and oscillatory activity (in particular a decrease in the beta band oscillations, Figure 5). An increased STN firing rate provoked by a contralateral STN-HFS has been recently reported in PD patients (Novak et al., 2009; Walker et al., 2011) and may result from an increased excitatory input and/or a decreased inhibitory input to the STN. Anatomical and functional studies suggest that the STN receives inhibitory GABAergic inputs from the ipsilateral but also the contralateral GPe (Castle et al., 2005), and excitatory glutamatergic inputs from the ipsilateral premotor and motor cortices (Nambu et al., 2002), but also (in rats) from the ipsilateral and contralateral Pf-Th (Mouroux et al., 1995; Castle et al., 2005). The STN projects excitatory inputs in turn to both Pf-Th (internal circuitry between the two Pf-Th and the two STN) (Castle et al., 2005).

Unilateral STN-HFS has been shown to induce an antidromic ipsilateral GPe activation in animals (Sato et al., 2000; Hashimoto et al., 2003) and also a short latency (2.5 ms) ipsilateral activation of neurons of the deep motor cortex, in both PD patients and parkinsonian rats (Baker et al., 2002; Li et al., 2007; Gradinaru et al., 2009). These two antidromic activations could have opposite effects on the contralateral STN neuronal activity with 1) for the former a decrease in both ipsilateral (Welter et al., 2004; Degos et al., 2005)
and contralateral STN firing rate (our results), and 2) for the latter, an increase in both
ipsilateral (Gradinaru, 2009) and contralateral STN firing rate (Walker et al., 2011), via an
activation of the contralateral motor cortex via the corpus callosum. The latency of 5-6 ms of
the main excitatory response, previously reported (Walker et al., 2011) and observed in our
patients, is consistent with this hypothesis. This excitatory response could also result from an
orthodromic activation of both the ipsilateral and contralateral Pf-Th induced by unilateral
STN-HFS (Castle et al., 2005), as previously reported in the ipsilateral output efferent
structures, such as the GPi or the SNr, in both PD patients and animals rendered parkinsonian
(Maurice et al., 2003; McIntyre et al., 2004; Galati et al., 2006; Maltete et al., 2007). The very
short excitatory response observed in a few neurons could result from an activation of fibres
passing through or near the stimulated STN and connected to the contralateral one (Walker,
2011). Finally, it appears that the composite effect of these neuronal firing changes is not
clearly established, but the complex time-locked responses (activation-inhibition-activation-
inhibition) of the contralateral STN neurons during unilateral STN-HFS probably result from
these different antidromic and orthodromic effects. This complex change could also lead to
the decrease in the bursting activity of the contralateral STN during unilateral STN-HFS with
a more regular discharge pattern, as also previously reported in the ipsilateral output
structures (Maltete et al., 2007).

Here we also found that unilateral STN-HFS reduced oscillatory activity in the
contralateral STN, mainly in the beta frequency band. In patients and animal models of PD,
an increase in the beta band oscillatory activity has been identified as a pathophysiological
hallmark of the disease and related to the akinesia induced by dopaminergic denervation
(Brown et al., 2001), but also as a predictive factor of symptomatic improvement provoked by
STN-HFS (Zaidel et al., 2010). In both normal and parkinsonian animals, STN-HFS has been
shown to produce a significant decrease in beta band oscillations in the ipsilateral STN
(Meissner et al., 2005; Gradinaru et al., 2009), but also in the ipsilateral cortex by activation of intracortical inhibitory neurons (Li et al., 2007; Gradinaru et al., 2009; Deniau et al., 2010). Given the known cortical organisation, we would expect that this cortical effect could be transmitted to the contralateral motor cortex with a disruption of the abnormal corticosubthalamic oscillation on the other side and a reduction in beta oscillations in the contralateral STN.

In conclusion, our results demonstrate that unilateral STN-HFS changes the contralateral STN activity in relation to the occurrence of ipsilateral dyskinesias. The fact that one-side of the BG influences the functioning of the contralateral BG system may explain the bilateral dyskinesias and motor improvement observed in some PD patients with unilateral STN-HFS (Houeto et al, 2003; Alberts et al., 2008). This bilateral effect could also play a role in the behavioural improvement induced by unilateral STN-HFS observed in some patients with a supposed corticobasal dysfunction such as patients with obsessive-compulsive disorders (Mallet et al., 2008). Finally, these motor and behavioural clinical effects provoked by unilateral STN-HFS are probably related to a bilateral disruption of the pathological activity in the cortico-subcortical circuitry.
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Conflict of Interest: The authors have no conflict of interest to declare.
Figure captions

Figure 1. Neuronal recordings in the left STN during right STN-HFS stimulation.
(a) Localisation of the recorded STN neurons and stimulating electrodes by means of the three-dimensional (3D) digitised distortable basal ganglia atlas. The motor part of the STN is represented in green, the associative part in pink and the limbic part in yellow in a 3D posterior view of both sides. In the left panel, each sphere represents an individual neuron (orange for STN neurons recorded during stimulation-induced dyskinesias and blue for STN neurons recorded when no dyskinesias occurred). In the right panel, pink and black cylinders represent the contacts used as anode and cathode, respectively. Middle panel: localisation of both recorded neurons (white spheres) and stimulating site (bipolar stimulation, blue contact: anode, red contact: cathode) in an individual patient. (b) Example of a left subthalamic neuron recorded before (left) and during (right) high frequency stimulation in the right STN (130 Hz, 60 μs, 4 V).

Figure 2. Subthalamic neuronal activity as a function of stimulation-induced dyskinesias in PD patients. (a,b,c) Mean firing rate, intraburst frequency and interburst interval before (Off), during (On) and after (Off) unilateral STN-HFS (130 Hz, 60 μs, 2 V). STN neurons recorded without (DSK−, white spheres) and with stimulation-induced dyskinesias (DSK+, black spheres) during STN-HFS with a 2 V (n=35) and 4 V (n=20) stimulation current. Asterisks indicate significant differences (P<0.05) between before and during STN-HFS.

Figure 3. Effects of low (2 V) and high (4 V) intensity right STN-HFS stimulation (130 Hz) on left STN neuronal activity in 2 individual neurons.
Left post-stimulation time histograms (PSTHs) represent left STN neuronal activity recorded 400 ms before and after 2 V STN-HFS. Right PSTHs represent neuronal activity during the 7
ms following the stimulus pulse histograms before (left: white) and during STN-HFS (right: 2V, grey; 4 V; black). (a) Left STN neuron recorded during right stimulation-induced dyskinesias with a significant reduction in its neuronal discharge rate at both 2 and 4 V stimulation intensities. Note that the decrease in neuronal activity occurred in the first 100 ms after the stimulation was activated (b) Left STN neuron recorded while no stimulation-induced dyskinesias occurred with a significant increase in its neuronal discharge rate at both 2 and 4 V stimulation intensities. Note that the increase in neuronal activity was time-locked with a 4-6 ms response.

Figure 4. Distribution of discharge pattern and oscillatory activity in left STN neurons recorded during right high frequency STN stimulation. (a) Relative distribution of the discharge pattern of the 35 left STN neurons. The left-hand column show results before right STN-HFS and the right-hand column during 2 V right STN-HFS. The right-hand column represents pooled data of the modification of the three subpopulations of discharge pattern (irregular, regular and burst) in each left STN neuron induced by right STN-HFS. The first step (bottom section) shows the modification of the firing pattern of cells discharging in burst-type before stimulation; the second step (middle section) shows the modification of the firing pattern of cells discharging regularly before stimulation; and the third step (top section) shows the modification of the firing pattern of cells discharging randomly before stimulation. (b) Relative proportion of the 35 left STN neurons showing none, one or more than one period of significant oscillatory activity before (left bar) and during 2 V right STN-HFS (right bar).

Figure 5. Raster display (left) and power spectrum (right) of a left STN neuron during right STN-HFS stimulation. This individual STN neuron was recorded (a) before, (b) during
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Figure 6. Individual left STN neuron with a short-latency response induced by contralateral 4 V STN-HFS stimulation. (a) Single-unit neuronal activity aligned to the onset of the contralateral stimulus (top trace), showing consecutive occurrences of the same neuron in the condition where the discharge follows the contralateral STN-HFS. Asterisk represents the stimulation pulses and (√) marks the action potentials from this individual neuron. Bottom trace: raw neuronal recordings showing residual neuronal activity during contralateral STN-HFS. (b) Post-stimulus raster display (top) and time histogram (bottom) of the response of this individual neuron during 120 s of contralateral 4 V-STN-HFS. Note the presence of a complex neuronal response with 2 excitation phases 1-2 and 5-6 ms after the stimulation pulse.
References


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parafascicular projection to the subthalamic nucleus and evidence for ipsi- and


Table 1. Effects of 2 V right subthalamic high-frequency (140 Hz) stimulation on the neuronal activity of 35 left subthalamic neurons

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>With STN stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (Hz)</td>
<td>46.3 ± 18.4</td>
<td>43.2 ± 20.8</td>
</tr>
<tr>
<td>Interspike interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ms)</td>
<td>27.5 ± 15.4</td>
<td>29.2 ± 20.0</td>
</tr>
<tr>
<td>Median (ms)</td>
<td>15.8 ± 8.5</td>
<td>16.3 ± 7.4</td>
</tr>
<tr>
<td>Mode (ms)</td>
<td>6.4 ± 4.8</td>
<td>6.3 ± 4.6</td>
</tr>
<tr>
<td>SD</td>
<td>34.3 ± 26.5</td>
<td>36.0 ± 33.3</td>
</tr>
<tr>
<td>Coefficient of variation</td>
<td>1.17 ± 0.35</td>
<td>1.16 ± 0.26</td>
</tr>
<tr>
<td>Burst-type activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean bursting index (Sm)</td>
<td>5.9 ± 1.7</td>
<td>5.8 ± 1.8</td>
</tr>
<tr>
<td>Burst frequency (Hz)</td>
<td>0.83 ± 0.55</td>
<td>0.84 ± 0.57</td>
</tr>
<tr>
<td>Number of spikes per bursts</td>
<td>15.5 ± 5.5</td>
<td>13.8 ± 4.6</td>
</tr>
<tr>
<td>Intraburst frequency (Hz)</td>
<td>87.8 ± 32.7</td>
<td>85.0 ± 33.4</td>
</tr>
<tr>
<td>Interburst interval (sec)</td>
<td>1.29 ± 0.87</td>
<td>1.23 ± 0.76</td>
</tr>
</tbody>
</table>

Values are means ± SD; * p<0.05 when compared to pre-stimulation values (Wilcoxon rank-tests)
Table 2. Effects of right 2V and 4V high frequency STN stimulation on left STN neuronal activity as a function of stimulation-induced dyskinesias.

<table>
<thead>
<tr>
<th>140-Hz stimulation</th>
<th>Dyskinesias</th>
<th>No dyskinesias</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 V (n=35)</td>
<td>n=14</td>
<td>n=21</td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td>2</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>No change</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4 V (n=20)</td>
<td>n=12</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td>5</td>
<td>6</td>
<td>0.58</td>
</tr>
<tr>
<td>No change</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

P: comparison between neurons recorded during stimulation-induced dyskinesias and neurons recorded in the absence of dyskinesias (Fisher’s Exact test).