

# **Clinical and neurophysiological assessment of DBS frequency**

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I, André Zacharia, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

# Abstract

Deep brain stimulation is a surgical treatment for patients with advanced Parkinson's disease whose symptoms have become challenging to control with available drug therapy. It involves implanting electrodes bilaterally into the subthalamic nuclei and then connecting them to a stimulator placed under the skin in the thoracic area. Several stimulation parameters can be adjusted to produce the best clinical effect, namely: frequency, pulse width, and voltage. After several years of DBS, many patients develop postural instability, gait, and speech disorders. Those problems have been attributed to disease progression. Nevertheless, recent studies have shown that they might improve using a lower frequency of stimulation than the one commonly used.

We have decided to conduct this thesis to try to understand better the role of the DBS frequency. We looked at the effect of 80Hz vs. 130Hz. We have performed four studies exploring different domains. Fifteen patients were randomized in a cross-over trial to receive 3 weeks of stimulation at 80 Hz and 130 Hz. Study 1 was dedicated to assessing the motor outcome, which showed that: a) overall clinical scores were unchanged and stable throughout the trial, b) proximal and complex movements were slightly improved at 80Hz, but more distal movements were improved at 130 Hz. Study 2 analyzed the cognitive aspects and showed an improvement of 80 Hz on phonetic fluency but not on semantic fluency. Study 3: looked at the neurophysiological aspects: various paradigms assessed cortical excitability by transcranial magnetic stimulation (TMS): short intracortical inhibition ended up being more physiological at 130Hz. Study 4 was performed to compare saccades and antisaccades' performances at 80 and 130Hz, respectively. 21 patients and 16 matched healthy controls (HC) were enrolled: saccades were facilitated at 80Hz instead of 130Hz; however, more errors were seen.

# Impact statement

Deep brain stimulation (DBS) is a neurosurgical technique that has allowed to treat more than hundreds of thousands of patients worldwide. Its efficacy in improving the quality of life of patients with Parkinson's disease is largely demonstrated. It has been made possible thanks to high-frequency electrical stimulation (produced by a battery located under the skin at the thoracic level) delivered to two electrodes, the latter being implanted in a specific brain's target: the subthalamic nucleus (STN). This technique is currently undergoing a significant transformation with new technological advancements (i.e., directional stimulation, low pulse width, close-loop stimulation) and new surgical indications under investigation, such as obsessive compulsive disorder.

While not wholly integrated into the clinical routine, new technology's appearance has raised questions on whether the current treatment is optimally set. Indeed, there is room to improve some symptoms that are not satisfactorily addressed with the current state of the art, particularly for gait disorders (i.e., freezing of gait) and speech difficulties. Next to these unmet needs, a comprehensive understanding of DBS's effects on the brain is lacking. Besides, numerous parameters are available to personalize the stimulation to a given patient (i.e., pulse width, frequency of stimulation). Those parameters have not been studied extensively; in particular, the frequency of stimulation is usually set at 130Hz. However, there is a lack of knowledge on the effect of lower frequency of stimulation such as 80Hz on the motor and cognitive outcomes and its effect on the brain physiology measured by transcranial magnetic stimulation (TMS).

Therefore, this thesis aims to fill those gaps by comparing two different frequencies of stimulation currently used in the clinical routine: 80Hz and 130Hz. The aims were a) to objectivate a potential differential impact on the motor, cognitive, and eye movements and b) to assess a potential difference in the cortical excitabil-

ity as measured by transcranial magnetic stimulation. Our results showed that both frequencies led to similar results from a motor point of view, but subtle movements (finger tapping) were slightly improved at 130Hz; the cognitive measures confirmed the advantage of 80Hz, while the opposite was true for eye movements. Finally, TMS revealed that 130Hz is normalizing brain excitability better than 80Hz.

Consequently, changing the stimulation frequency may affect specific outcomes differently without losing the stimulation's benefit from the motor perspective. This allows clinicians involved in adapting DBS parameters to modify the frequency of stimulation. Besides, our results are pointing out that a given frequency may be stimulating better given neuronal networks. This opens avenues for new research on a) trying to disentangle which networks would benefit most from a particular frequency and b) adapting the frequency of stimulation to a specific context. These new research avenues have the potential to improve treatment efficiency and bring a more personalized treatment based on an objective physiopathological understanding.

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# Publications

*Effect of Low versus High Frequency Subthalamic Deep Brain Stimulation on Speech Intelligibility and Verbal Fluency in Parkinson's Disease: A Double-Blind Study.* Grover T, Georgiev D, Kalliola R, Mahlkecht P, **Zacharia A**, Candelario J, Hyam J, Zrinzo L, Hariz M, Foltynie T, Limousin P, Jahanshahi M, Tripoliti E. J Parkinsons Dis. 2019;9(1):141-151.

*Impact of Subthalamic Deep Brain Stimulation Frequency on Upper Limb Motor Function in Parkinson's Disease.* Momin S, Mahlkecht P, Georgiev D, Foltynie T, Zrinzo L, Hariz M, **Zacharia A**, Limousin P. J Parkinsons Dis. 2018;8(2):267-271. doi: 10.3233/JPD-171150.

*Bilateral Deep Brain Stimulation of the Globus Pallidus Pars Interna in a Patient with Variant Ataxia-Telangiectasia.* Georgiev D, Mehta D, **Zacharia A**, Vinke RS, Milabo C, Candelario J, Tripoliti E, Hyam JA, Zrinzo L, Hariz M, O'Riordan S, Foltynie T, Limousin P. Mov Disord Clin Pract. 2016 Jan 21;3(4):405-408.

*Pyramidal tract activation due to subthalamic deep brain stimulation in Parkinson's disease.* Mahlkecht P, Akram H, Georgiev D, Tripoliti E, Candelario J, **Zacharia A**, Zrinzo L, Hyam J, Hariz M, Foltynie T, Rothwell JC, Limousin P. Mov Disord. 2017 Aug;32(8):1174-1182.

*Varying time-course of effects of high frequency stimulation of sub-regions of the globus pallidus in patients with parkinson's disease.* Angeli A, Akram H, **Zacharia A**, Limousin P, Hariz M, Zrinzo L, Foltynie T. Parkinsonism Relat Disord. 2015 Jun;21(6):597-602.

*Effects of deep brain stimulation frequency on initiation and suppression of eye movements and cognitive control* **André Zacharia**, Diego Kaski, Walid Bouthour, Viswal Dayal, Matthieu Bereau, Philipp Mahlkecht, Dejan Georgiev, Julie Péron, Johnathan Hyam, Ludvic Zrinzo, Tom Foltynie, Marjan Jahanshahi, John Rothwell, Patricia Limousin (Submitted)

*Effects of deep brain stimulation frequency on cortical excitability* **André Zacharia** , Damien Benis, Philipp Mählknecht, Dejan Georgiev, Matteo Ciocca, Tom Foltynie, Marjan Jahanshahi, John Rothwell, Patricia Limousin (in preparation)

*Bilateral Globus Pallidus internus deep brain stimulation provides long term dyskinesia relief in Parkinson's disease* **André Zacharia** , Philipp Mählknecht, Isabel Sastre, Marjan Jahanshahi, Ludvic Zrinzo , Tom Foltynie, Dejan Georgiev and Patricia Limousin (in preparation)

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## Chapter 1

# Introductory Material

### 1.1 Rationale

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a very effective surgical treatment of advanced Parkinson's disease (PD) for patients with major fluctuations of their neurological state in particular on cardinal symptoms such as rigidity, bradykinesia, tremor, dyskinesias and quality of life. Bilateral high frequency (130–185 Hz) STN-DBS has been performed for 25 years (Pollak *et al.*, 1992; Limousin *et al.*, 1995). The initial settings used were based on two facts: the symptoms' response to high frequency  $> 50\text{Hz}$ , and the fact the first electrical stimulator used were the implantable Itrel I and II generator where the maximum frequency available was respectively 130Hz and 180Hz (Benabid *et al.*, 1991; Limousin *et al.*, 1995). Substantial experience has been acquired in the assessment of settings (voltages  $\geq 3\text{ V}$  frequencies  $\geq 130\text{ Hz}$  with a combination of the narrowest pulse width) that produce the best clinical results (Moro *et al.*, 2002; Weaver *et al.*, 2012a; Williams *et al.*, 2010; Deuschl *et al.*, 2006). However, there has not been a lot emphasis so far on studying the role of the frequency stimulation and there is emerging evidence that the commonly used frequencies (130-185 Hz) may not represent the best form of treatment for all patients. There is controversy, for example, about whether stimulation at high frequency can worsen postural instability and gait, or lead to adverse effects on speech intelligibility (Bakker *et al.*, 2004; Gentil *et al.*, 2003; Pinto *et al.*, 2005; Tripoliti *et al.*, 2011). In some patients, pre-

liminary data suggest a better effect on gait with low frequency (60Hz) than high frequency stimulation if the parameters were set to have the same energy equivalence (Moreau *et al.*, 2008). A recent study examined the acute and chronic effect of 80Hz stimulation (Ricchi *et al.*, 2012). Gait and particularly freezing of gait were improved acutely.

DBS, despite having a major effect at high frequency of stimulation on cardinal motor symptoms, may have negative effects on other functions such as: impulsivity, verbal fluency, visual saccades or emotion recognition.

We are already using low frequency of stimulation in our clinical routine as an alternative treatment in PD patients suffering from speech or gait problems. Empirically, many of these patients have better results regarding these two symptoms without losing benefit of the treatment against bradykinesia. Some of our patients also reports having a benefit from 80Hz frequency on more complex motor task with more cognitive load.

This latter observation is particularly intriguing. STN is in the heart of striato frontal circuitry model for motor and cognitive task; it inhibits the cortex ( via its excitatory action on GPi,). Different cognitive tasks are modulated differently by STN-DBS: Simple reaction time improved after STN-DBS (Brown *et al.*, 1999), but the (mRT) go-no-go test , semantic and phonemic fluency were associated with a lower frontal activation (Hershey *et al.*, 2004; Ballanger *et al.*, 2009; Parsons *et al.*, 2006).

The goal of this work is to analyse the role of the frequency of stimulation by comparing the impact of high versus low frequency STN-DBS on the motor, oculomotor, and associative fronto-striatal loop. Our hypothesis is that high frequency stimulation interferes with some remaining physiological activities in those loops and lead to worsening of those functions in comparison to low frequency.

In order to introduce how frequency of stimulation modify PD symptoms I will first describe shortly the neuro-anatomical loops linked to the STN and its anatomy. I will then describe: how DBS treatment has started, and how previous treatment had made possible the advent of DBS. I will, then, present a review of the literature

on the respective efficacy of different frequencies. I will, finally, summarise the hypothetical mechanisms on how this technique actually works.

## 1.2 Motor Loop

The motor loop can be analysed from the anatomical or functional perspective.

From the anatomical perspective, this loop is a network connecting cortical structures such as prefrontal cortex, supplementary motor area (SMA) and motor area to subcortical structures such as the striatum and the STN. Then the Globus pallidus Internus (GPi) and the Substantia nigra pars reticulata (SNr) projects to the thalamus, (Ventrolateral nuclei: VLo, VApc, VAmc, and centromedian nucleus) to the Pedunculo pontine nucleus (PPN) and to the superior colliculus (SC) in the brainstem (Alexander & Crutcher, 1990). The thalamus projects back to the cortex. The detail of the connections can be seen on figure 1.1.

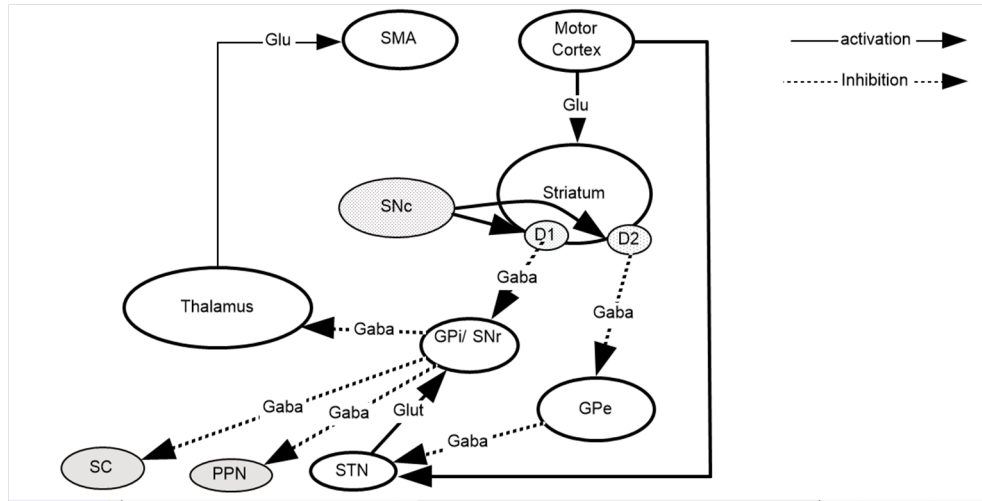
An important part of the loop is the Substantia nigra pars compacta (SNc) containing dopamine. This nucleus is linked bidirectionally to the striatum. Its role is to modulate the cortico striatal loop.

From the functional perspective, three main pathways are depicted classically as follow: the direct, the indirect and the hyperdirect pathway. The direct pathway links directly the striatum to the GPi while the indirect goes through the Globus pallidus externus (GPe) before reaching the GPi (DeLong, 1990; Albin *et al.*, 1989).

Two main Dopamine receptors are involved in the motor loop (D1 and D2). D2 activates the direct pathway and D1 activates the indirect one. According to the model, the direct pathway facilitates the movement while the indirect one inhibits it. The subtle balance of the two will adjust the action. (Kim & Hikosaka, 2015)

Substantia nigra is one of the major basal ganglia part degenerating in PD (68 % of the lateral tier at the onset of the disease) (Fearnley & Lees, 1991). Consequently, dopamine synthesis decreases. As a result, the direct pathway become deficient leading to a poverty of movement, hence bradykinesia. Interestingly this model has been recently replicated by an optogenetic experiment in the transgenic

mice (Kravitz *et al.*, 2010). Their striatum has been infected selectively either to D1 or D2 thanks to an adenovirus. Optical stimulation of D1 receptor has led to bradykinesia and freezing while the opposite was true when stimulating D2 receptor. Another optogenetic study tried to monitor the effect of stimulating the direct or the indirect pathway (Cui *et al.*, 2013) by recording the neural activity of specific cell type. One important result of this study shows that the self-paced move toward the contralateral side was associated with co-activation of both direct and indirect pathway within 500ms before the movement. Moreover, both pathways were silent when no movement were produced by the mice. This raise the question if activating both pathways will, for example, inhibit unwanted program and promote wanted program. The STN-DBS technique implies stimulating the STN which is the heart of the system as described in more details later on.



**Figure 1.1:** Basal ganglia diagram showing relationship between the central role of STN and the motor loop. SC: superior colliculus , PPN: pedunculopontine nucleus, SNc: Substantia Nigra compacta, SNr: Substantia Nigra reticulata

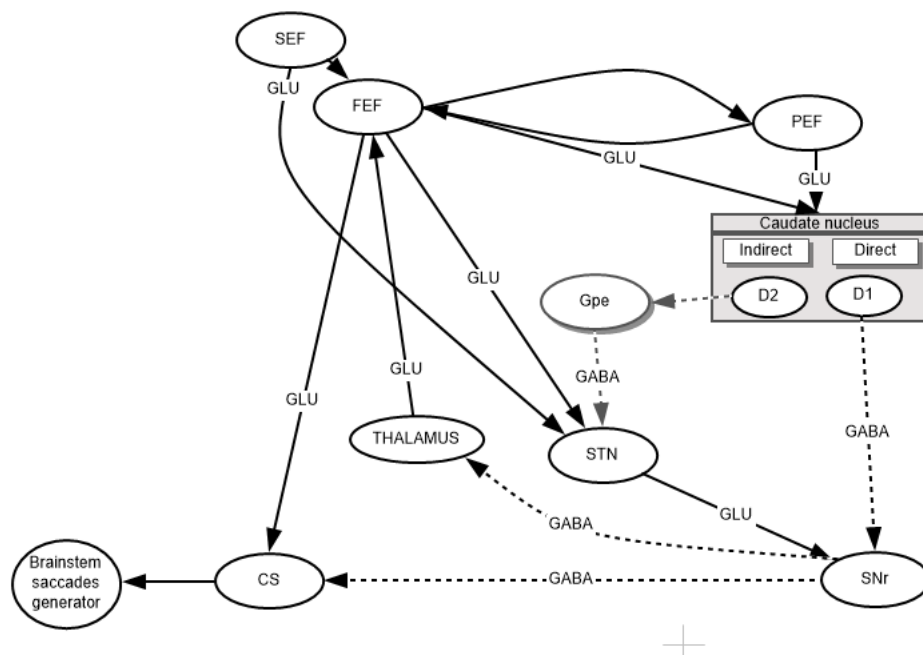
### 1.3 Oculomotor loop

The function of the oculomotor loop is to control the eye movement. The anatomical structures involved in the oculomotor loop include the frontal eye field (FEF) , the supplementary eye field (SEF) and the parietal eye field (Pierrot-Deseilligny *et al.*, 2004). The latter projects to the caudate nucleus (towards its central and lateral parts of the head and body (Çırak *et al.*, 2020)) which is linked to the SNr

(Parthasarathy *et al.*, 1992). The SNr projects to the ventral anterior and mediodorsal nuclei of the thalamus and to the superior colliculus (Çırak *et al.*, 2020). The thalamus closes the loop by reaching the FEF and prefrontal cortex. Direct and indirect pathways have been described linking the caudate nucleus directly or indirectly to the SNr. The D1 direct pathway facilitates saccades while the D2 indirect pathway is inhibiting it through its action on the GPe (Smith & Parent, 1986; Nakano *et al.*, 2000). Dopamine depletion seen in PD should therefore leads to an overactivity of the indirect pathway: saccade inhibition.

The superior colliculus, via the medial longitudinal fasciculus, is linked to the oculomotor nerves (abducens, oculomotor and trochlear nerve). All these structures represent the basic frame allowing the eye movement. It is classical to separate functionally: the frontal part of the system to the volitional saccades; the parietal part to the reflexive saccades (Leigh & Kennard, 2004). The saccades is made possible by removing the brake coming from the SNr when the loop is activated.

Many authors demonstrates a direct link between the FEF, SEF and prefrontal association cortices and the STN (Huerta *et al.*, 1986; Huerta & Kaas, 1990) in the monkey. Visuo-oculomotor neurons are part of the Ventral STN (Matsumura *et al.*, 1992). As for the motor loop, two pathways can be depicted. The first one being between FEF, caudate and SNr and the second one being between FEF and the STN as shown from figure 1.2



**Figure 1.2:** Basal ganglia diagram showing relationship between the central role of STN and the oculomotor loop. FEF: Frontal eye field, SEF: Supplementary eye field, SNr: Substantia Nigra reticulata

The impaired visual exploration has been postulated as one of the component in Parkinson's disease which could impair gait ability and is associated also with cognitive decline (Archibald *et al.*, 2013).

The antiparkinsonian drugs do not improve saccadic movement or can even impair them. (Vermersch *et al.*, 1994; Michell *et al.*, 2006; Hood *et al.*, 2007; Crevits *et al.*, 1999).

## 1.4 Associative loop

The associative loops in basal ganglia (dorso lateral circuits and lateral orbitofrontal circuits) are also related to the STN. The direct pathway in the associative loop is classically depicted as follow. The dorsolateral prefrontal cortex (DLPFC) is linked to the dorsolateral head of the caudate nucleus. Then the caudate projects GABAergic projections to the globus pallidus and the rostral part of the SNr. The latter inhibits the thalamus (ventral anterior and dorsal medial thalamic nucleus) which is linked to dorsolateral prefrontal cortex (Parent & Hazrati, 1995). The lateral orbitofrontal cortex is also linked to the dorsolateral part of the head of the

caudate nucleus, and, then, to the dorsomedial part of the GPi and the SNr. In both cases, the indirect pathway includes the ventromedial STN.

Both Stroop test and verbal fluency are tightly linked to the DLPFC (Frith *et al.*, 1991; Milham *et al.*, 2002) as demonstrated by imaging studies. PET imaging studies (while patients involved on these task) have confirmed the STN (its ventromedial aspects) being linked to several associative cortices in STN DBS patients (Schroeder *et al.*, 2002a, 2003). Stroop task, (Schroeder *et al.*, 2002a), showed a decreased right hemisphere activity for the right anterior cingulate cortex and the right ventral striatum. The verbal fluency revealed a decrease in the activity of the right orbitofrontal cortex, the left temporal gyrus and the left inferior fronto-insular cortex (Schroeder *et al.*, 2003). Interestingly, while the motor scores in those patients are improved according to several studies (Limousin *et al.*, 1995; Krack *et al.*, 2003), both cognitive scores were decreased in DBS patients (Jahanshahi *et al.*, 2000; Okun *et al.*, 2009).

## 1.5 Subthalamic nucleus

### 1.5.1 STN's anatomy

The STN is a small nucleus found between the thalamus and the mesencephalon described first by Luys (Parent, 2002). Its volume varies according to different studies but is thought to be around 106-158mm<sup>3</sup>. Its size is around 3 / 6 / 12 mm in respectively coronal, sagittal and axial plan (Massey *et al.*, 2012; Yelnik, 2002). It is surrounded by white matter fibres tracts: the pallidothalamic tract, the cerebellothalamic tract (CT), the medial lemniscus, and the internal capsule. The pallidothalamic tract runs from the GPi and is divided in two bundles - ventrally: the ansa lenticularis, dorsally: the lenticularis fasciculus. These bundles are then converging dorsally to become the fasciculus thalamicus (connecting the thalamus). Part of the fibres emerging from the ansa lenticularis are connected, ventrally, to the PPN. The cerebello thalamic tract runs from the dentate and fastigial nucleus in the cerebellum and runs through and dorso-lateral to the red nucleus. It passes medially to the STN but more ventrally compared to the ansa lenticularis and connects the VIM

in the thalamus. As a consequence, the STN's dorsomedial aspect is formed from the lenticularis fasciculus and the ansa lenticularis and more ventrally by the cerebello thalamic tract. The medial lemniscus carry sensation's informations from the periphery and runs medially and posteriorly to the STN. The lateral aspects of the STN is formed by the internal capsule. The Zona Incerta is a grey matter structure dorso medial to the STN and separated from it by the lenticular fasciculus (Hamani *et al.*, 2004; Galloway *et al.*, 2008)

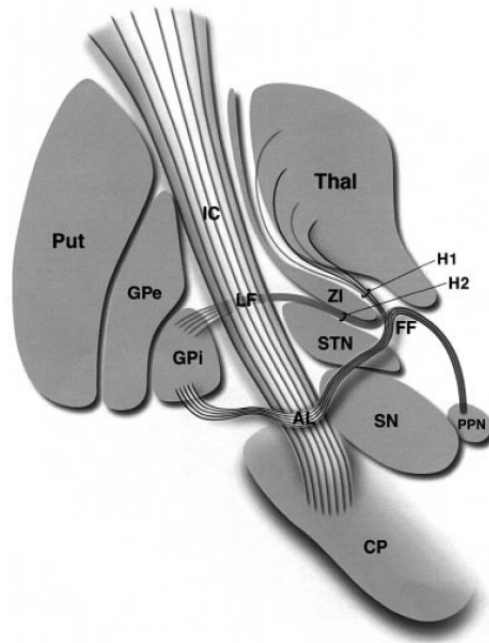
The Forel fields have been described in the nineteenth century. This nomenclature describes mainly the pallidothalamic fibres. According to Galloway *et al.* (Galloway *et al.*, 2008), H field corresponds to the part where the ansa lenticularis and fasciculus lenticularis are together dorsally to the STN and to the dorsal final part of the cerebello thalamic tract before entering the thalamus. The Forel field H2 corresponds to the fasciculus lenticularis and H1 the fasciculus thalamicus. One can see the different structures surrounding the STN on figure 1.3.

These structures are important for DBS adjustments because of their proximity with the STN. The current spreading from the electrode can affect these structures and lead either to favourable effects or to side effects.

Stimulating the CT can alter speech (Tripoliti *et al.*, 2008) while stimulating the Forel field stimulation can be effective for alleviating PD symptoms (Voges *et al.*, 2002) but can also impair speech. Stimulating the internal capsule leads to the so-called capsular effect which can be often seen with muscle twitches or contractions (Ashby *et al.*, 1999; Tommasi *et al.*, 2008).

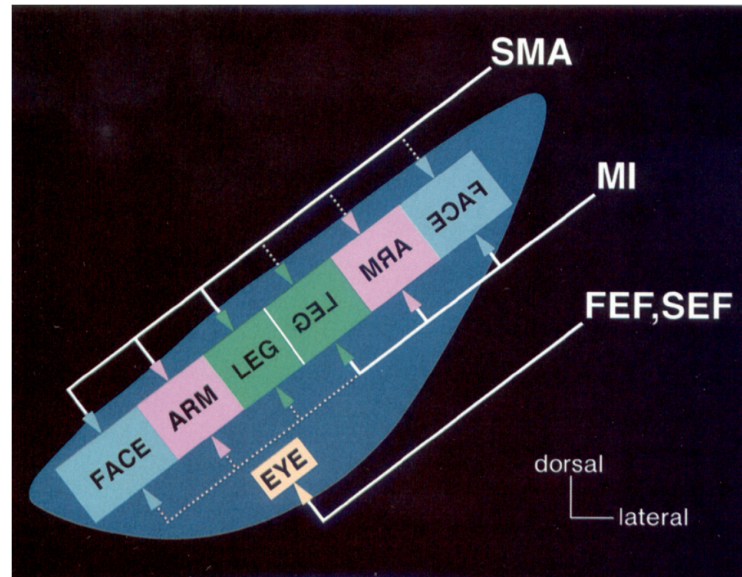
### 1.5.2 STN's partition

The STN is a crossroads for all three cortico-striatal loops and the second most important link to basal ganglia from the cortex (Lambert *et al.*, 2012). Studies using anterograde tracer in the monkey revealed STN's projections. It was found that: the lateral and the central part of the STN is tightly linked to the pallidum and form the motor part of the STN, the medial part of the STN is more linked to the ventro-rostral part of the globus pallidus, and the subcommissural part of the pallidum and the substantia innominata (Smith *et al.*, 1990). Part of the STN projects also to the



**Figure 1.3:** STN's region anatomy, "Representation of the major anatomical structures and fibre tracts associated with the subthalamic nucleus. AL = ansa lenticularis; CP = cerebral peduncle; FF = Fields of Forel; GPe = Globus pallidus externus; GPi = globus pallidus internus; H1 = H1 Field of Forel (thalamic fasciculus); IC = internal capsule; LF = lenticular fasciculus (H2); PPN = pedunculopontine nucleus; Put = putamen; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus; ZI = zona incerta.", (Hamani *et al.*, 2004)

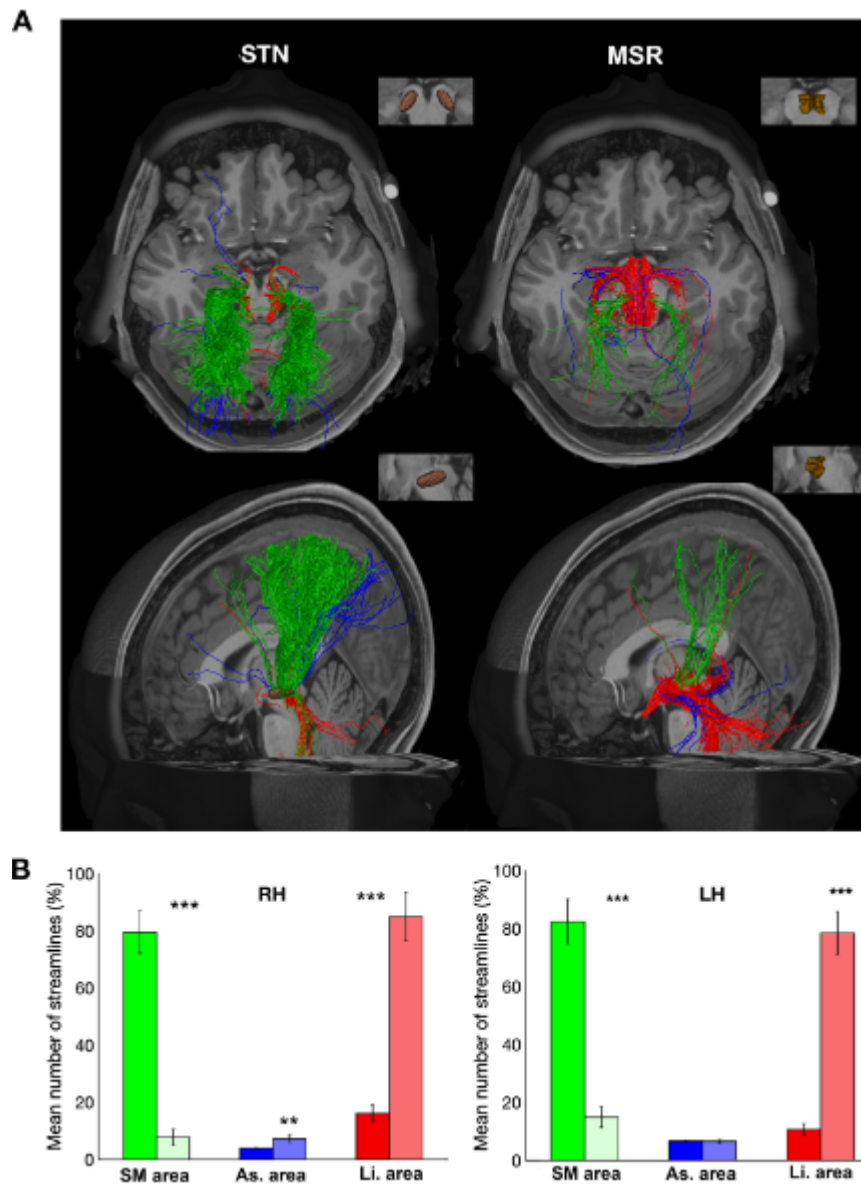
midbrain, namely: the Substantia nigra, the PPN, and the periaqueductal area. The STN's anatomy is roughly segregated into three parts that are functionally intermingled: the motor part (dorsolateral aspects) is the larger STN's part (The primary motor cortex ends up to the dorsolateral aspect of the STN); the associative and oculomotor part (ventromedial aspects); and the limbic part (tip aspects) which projects to ventral tegmental area (Parent & Hazrati, 1995). The STN's dorsolateral part of has a somatotopic representation of the leg arm and face see figure 1.4 (Nambu *et al.*, 1996).



**Figure 1.4:** STN's Somatotopy according to Nambu *et al.* (Nambu *et al.*, 1996)

The STN receives afferences from the pallidum (pallido-subthalamic tract). Interestingly, a study looking at axonal tracers injected in GPe demonstrated that the limbic GPe was linked to both the accumbens nucleus and medioventral and anterior STN, while associative and sensorimotor GPe was linked to central and dorsolateral part of the STN (Karachi *et al.*, 2005). Therefore the pallidosubthalamic tract has a functional partition, which was also confirmed in the hyperdirect pathway (see below) (Haynes & Haber, 2013)

The hyperdirect pathway links the cortex directly to the STN. This has been demonstrated in the monkeys for the motor loop (Nambu *et al.*, 2002) and confirmed: in this study, monkeys were injected with anterograde tracer from the prefrontal areas. In this study, the number of fibers linking the prefrontal cortices directly to the STN has respected a rostro-caudal topography of the motor, limbic and associative cortices (Temiz *et al.*, 2020). In humans: this topographical organization was partly replicated in a study using the whole brain probabilistic tractography: projections within the STN were organized so that the postero-lateral STN was strongly linked to the motor cortices; while the STN's medial tip was more linked to the limbic cortices. However, the associative cortices were poorly represented in the STN, see figure 1.5.

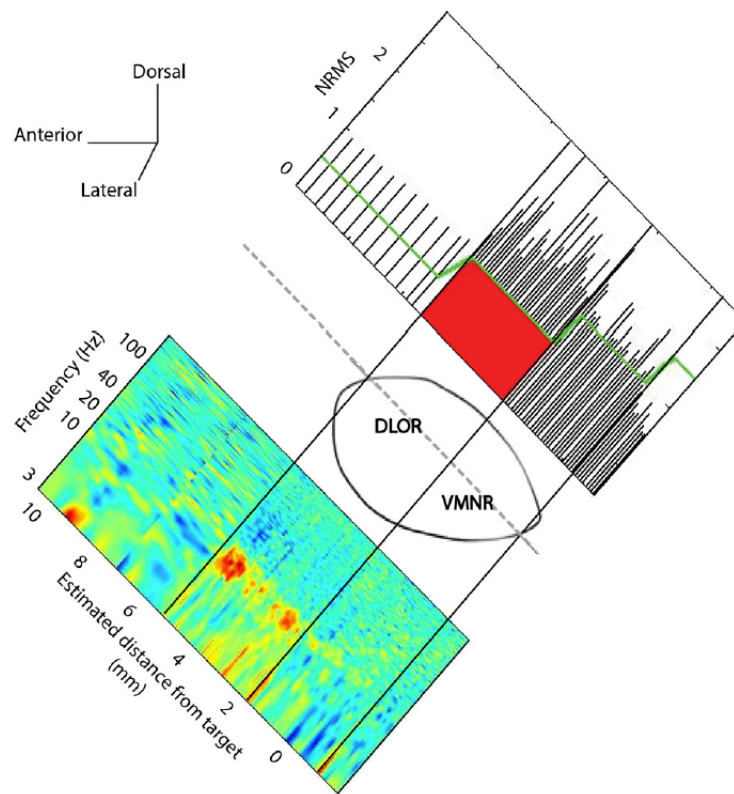


**Figure 1.5:** Hyperdirect pathway: "Fig. 3 3D views of streamlines connecting the overall cortex with the STN and MSR (medial subthalamic region). a 3D horizontal view (upper line) and sagittal view (lower line) of the overall sensorimotor (in green), associative (in blue), and limbic (in red) cortical streamlines connected to the STN (left) and the MSR (right). The STN and the MSR masks are illustrated. Note that the STN received mostly from sensorimotor cortical projections whereas the MSR receives mainly from limbic cortical projections. b Histogram showing the total mean number of streamlines, expressed as percentage (%), connecting the cortical areas (sensorimotor, associative, or limbic) to the STN (dark bars) or MSR (bright bars): the mean streamline numbers were averaged over 30 subjects. The error bars represent standard deviations.  $**p \leq 0.01$ ;  $***p \leq 0.001$ " (Temiz et al., 2020)

This has strengthened the idea of important direct connections between the

prefrontal cortices and the STN (bypassing the pallidal structures). This raises the question of whether the motor effect of STN-DBS is linked to a retrograde modulation of the cortical areas heavily represented in the hyperdirect pathway, while the associative and limbic pathways are less represented, consequently less modulated.

Most of the STN neurophysiology comes from direct in situ measurement of local neuronal discharge either in the monkey or DBS patients. Numerous studies tend to confirm the presence of so-called  $\beta$  oscillations (12-30Hz band) that is supposedly linked to bradykinesia (Brown *et al.*, 2001; Kühn *et al.*, 2004; Weinberger *et al.*, 2006). The Microrecording technique demonstrates that the motor part of the STN is mostly represented in dorsolateral aspects of the STN (Zaidel *et al.*, 2010; Rodriguez-Oroz *et al.*, 2001). Also, this technique enables to determine the borders of different bands in the STN. One can see from figure 1.6 that the dorsolateral part of the STN correlates with the presence of the beta band, which disappears when the more ventromedial part of the STN is reached (Eitan *et al.*, 2015). Many authors believe that high frequency of stimulation could override the pathological signal in the basal ganglia-cortical loop, especially the  $\beta$  band, correlating with the favourable effect of DBS (Zaidel *et al.*, 2010).



**Figure 1.6:** Power band spectrum: "The parasagittal plane of the STN (atlas of Schaltenbrand and Wahren, 1977) is represented at laterality of 12 mm with respect to the AC-PC line. Normalized root mean square (NRMS) was computed on the Micro-electrode recording (MER) to delineate the STN boundaries (upper image). The x-axis the estimated distance of MER from the STN target as defined on the pre-operative MRI image. Power spectral density was computed at each MER site, and a spectrogram visualizing the change of oscillatory activity with location before and within the STN is presented (lower image)". (Eitan *et al.*, 2015)

The associative part of the STN (on ventro-medial aspect) is more related to emotional processes. Voices' emotional content and concomitant STN neuronal activity were compared by Eitan *et al.* They have found a larger neuronal response on the right STN's ventromedial part (Eitan *et al.*, 2015). Indeed the spiking activity increased more in the ventromedial part compared to the dorsolateral part of the STN. Consequently, this study tends to confirm that different band might be involved differently: beta band being more involved in the dorsal (but not ventral) part as a signature of parkinsonian state; gamma band: more involved as a physiological band in emotional process in the ventral part of the STN.

### 1.5.3 STN's network interactions

The interaction between STN and its neighbourhood can be divided between interaction with the cortex and its local interactions as summarized by Hammond et al (Hammond *et al.*, 2007).

#### 1.5.3.1 Cortical interaction

Williams et al described, in 2002, coherence over  $\beta$  range mostly (8-30Hz) with the cortical midline (Williams *et al.*, 2002). They have also demonstrated coherence for different range of frequencies on other cortical parts and in the GPi. These authors posited that frequencies  $\leq 30$  Hz coming from motor cortices where leading the basal ganglia while the basal ganglia's response frequency towards the cortex was around 70-85Hz. Importantly, as the strongest coherence was on the midline, this confirmed earlier studies showing the SMA (being in the midline) as an important output cortical target for cortico-subcortical loop. Nevertheless, this study paved the way only for the motor loop, while other cortico-subcortical loop where not assessed. Interestingly, only the more caudal contact showed coherence between the STN and the cortex while other contacts failed to do so. Consequently, it may be that the interaction between more rostral contact and the cortex communicate on a different frequency. Interestingly this synchronization appears as more important when a patient is involved in the no-go part of the go-no go task.

#### 1.5.3.2 Local interaction

Some  $\beta$  synchronization is found in STN's surrounding structures, such as in the GPe, SNr, and GPi. The  $\beta$  band is quite broad as defined by researchers involved in local field potential recording. It is not clear whether the full range of this band is involved in the parkinsonian state or just a part of it. (Hammond *et al.*, 2007)

Different loops within the basal ganglia do not synchronize the same way. This could be due to the fact that cellular components and the voltage-gated channels are different, leading to different resting states, hence different electrochemical properties. Therefore an intrinsic particular resonance frequency could apply to different loops (Hammond *et al.*, 2007). This is illustrated by Fogelson et al. (Fogelson *et al.*,

2006). In this study, a coherence analysis has been done to compare macroelectrode recording to the scalp EEG recording. A partial coherence technique was used in order to compare many brain regions, for example, Cz-Fz scalp recording to subthalamic area recording on the one hand and P3-Pz to the subthalamic area on the other hand. The analysis revealed that it exists a partial coherence that is different for a given brain area. The upper beta band was more coherent at the midline (as stated by Williams et al. (Williams *et al.*, 2002)) compared to other areas, especially frontal and parietal areas.

### 1.5.4 $\beta$ band bradykinesia and tremor

#### 1.5.4.1 $\beta$ band and Bradykinesia

$\beta$  oversynchronization is designated a potential culprit leading to bradykinesia and rigidity. Local field potentials show an excessive *beta* synchronization that is related to off states in monkeys and patients. which is breakable in patients, MPTP monkeys, and 6-OHDA rats (Rivlin-Etzion *et al.*, 2006) when giving Levodopa or high frequency DBS (mirrored by a concomitant clinical improvement) (Hammond *et al.*, 2007).

#### 1.5.4.2 $\beta$ band and Tremor

The parkinsonian tremor physiopathology differs in many aspects as compared to bradykinesia and rigidity. Firstly, the anatomical pathway involved is the cerebellothalamic pathway. The latter is not directly involved in the classical basal ganglia loop. This has been highlighted by several authors, among others Timmermann et al. (Timmermann *et al.*, 2003). In this study, non-invasive magnetoencephalographic recordings in six PD patients revealed a coherence between several cortical areas and contralateral cerebellum at the single tremor frequency and its double. Additionally, a spectra coherence was found at the double of the resting tremor between the thalamus and the cerebellum at around 20Hz. Altogether this study confirmed an abnormal coupling between the cerebellum, the diencephalon, and many cortical areas but at a low frequency. Secondly, so-called tremor cells have been described in the STN. These cells could be directly linked to tremor supposedly by

two different routes: as a result of peripheral input or as a result of cortical input (for discussion see (Deuschl *et al.*, 2000)). Tremor is not correlated to the dopaminergic deficit (Deuschl *et al.*, 2000). Consequently particular frequency oversynchronization on a particular anatomical location will lead, for example, to tremor and will respond to different DBS targeting and frequencies of stimulation. The clinical routine shows that patients with tremor could be worsened on a lower frequency than 130 Hz. It may be that DBS on particular anatomical location drives the neurons differently either by silencing them, as explained later, or by enhancing some others pathways able to overcome the pathological process.

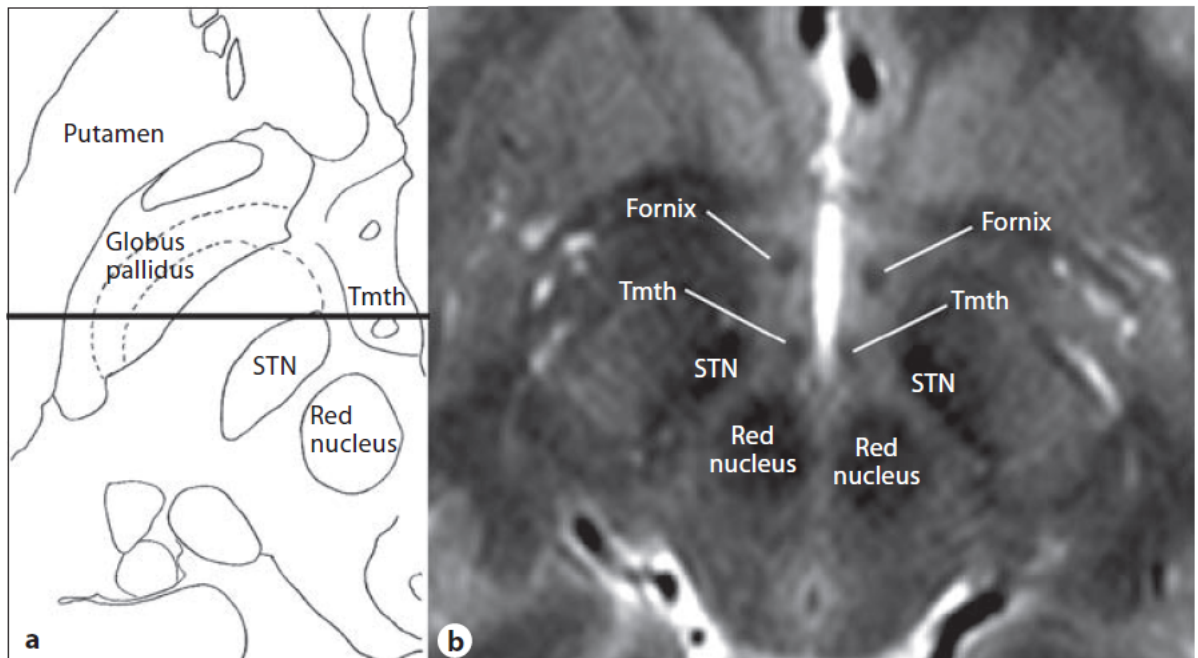
Gamma band power increases during a cognitive task in the STN, especially during the verbal fluency task. This was concluded by Anzak *et al.*: verbal fluency (semantic or letter fluency) performances depend on the power of a specific band in the STN. While both tasks needed an increase in the gamma band, some additional desynchronization in the beta band was only seen for semantic fluency. If 130 Hz is overriding any activity in the STN, then this subtle balance cannot be reached. Poor verbal fluency could then be correlated to a too high frequency inhibiting too much the STN, while 80Hz could leave this subtle balance to appear instead.

Altogether, these arguments express the fact that different cortico-subcortical loops may have different pathological or physiological resonance frequency when dealing with particular task such as go-no-go task (increase in the beta band for no-go (Hammond *et al.*, 2007; Kühn *et al.*, 2004)) or verbal fluency (increase in the  $\gamma$  band (Anzak *et al.*, 2011)) when involved in the generation of a particular symptom (tremor or bradykinesia). Therefore stimulating these loops with different frequencies could lead to different effects.

### 1.5.5 STN surgical targeting

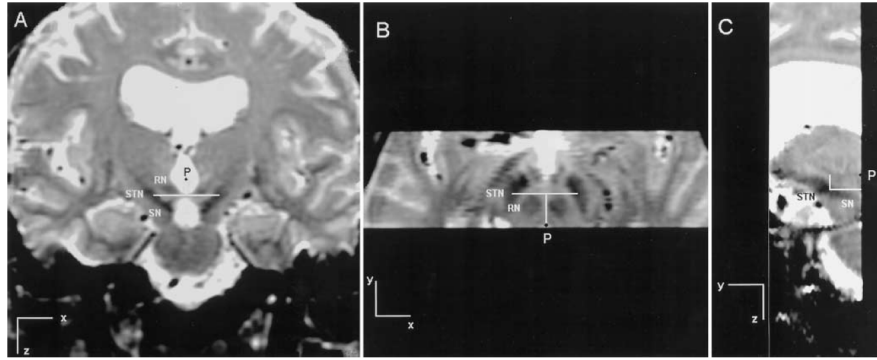
Targeting correctly the STN is very important; it allows to generate a maximal benefit if the electrode is well placed or leads, otherwise, to adverse effects (Wodarg *et al.*, 2012). STN can be delineated thanks to its high Iron load on T2 weighted imaging (Dormont *et al.*, 2004). The usual coordinates for the STN depend on an imaginary line joining the anterior commissure (AC) to the posterior commissure

(PC): the AC-PC line. The middle of this line is the mid-commissural points from where are calculated the Cartesian coordinates. The STN's centre is to be found 4mm ventrally, 12mm laterally, and -3mm posteriorly to this point. These coordinates have been confirmed by a retrospective study based on 76 patients see (Starr *et al.*, 2002). Some anatomical landmarks are also used to confirm a STN location. The anterior limit of the STN on an axial view is attributed to the mamillothalamic tract. The latter borders the interpeduncular cisterna, as one can see from figure 1.7.



**Figure 1.7:** STN anatomical relationship, Tmth: mamillothalamic tract (Caire *et al.*, 2011)  
The anterior border of the red nuclei is considered to be the STN's centre.

An imaginary line is drawn at the level where red nuclei are at their maximal diameter. This line goes through the middle of the STN.



**Figure 1.8:** Anatomical relationship between the red nucleus and the STN (Bejjani *et al.*, 2000)

The surgical approach performed in our centre follows the MRI-verified approach. This technique, instead of relying on neurophysiology, relies on the proper check of the lead position while the patient is still asleep in the operation theatre and wearing the Leksell frame (Martínez-Fernández *et al.*, 2011). Technical accuracy of this technique (Hyam *et al.*, 2015), as well as its long term benefit, have been confirmed (Aviles-Olmos *et al.*, 2014).

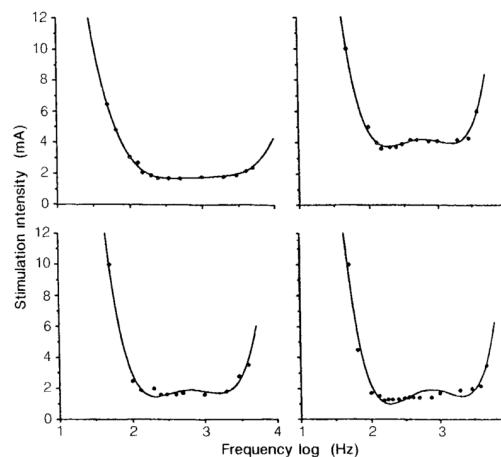
## 1.6 STN-DBS frequency effect

### 1.6.1 Historical aspects

The subthalamic nucleus (STN) is a surgical target for the treatment of Parkinson's disease. The first STN lesioning experiments were done in the MPTP monkey in the early 1990s (Bergman *et al.*, 1990; Aziz *et al.*, 1991). These experiments were the proof of concept that a lesion in the STN can alleviate all main parkinsonian symptoms such as akinesia, tremor, and rigidity. This was a very impressive result. Authors mentioned, for example, that apomorphine treatment could be discontinued. The downside was, nevertheless, the expected appearance of hemiballismus. These symptoms disappeared in one monkey after two weeks but remitted in the second. The reason for targeting STN derived from the basal ganglia functional anatomy model (Albin *et al.*, 1989). It was believed that in Parkinson's disease, the STN is over-active, which in turn inhibits thalamus activity. Despite a striking effect on the main symptoms in the monkey, the appearance of involuntary movement

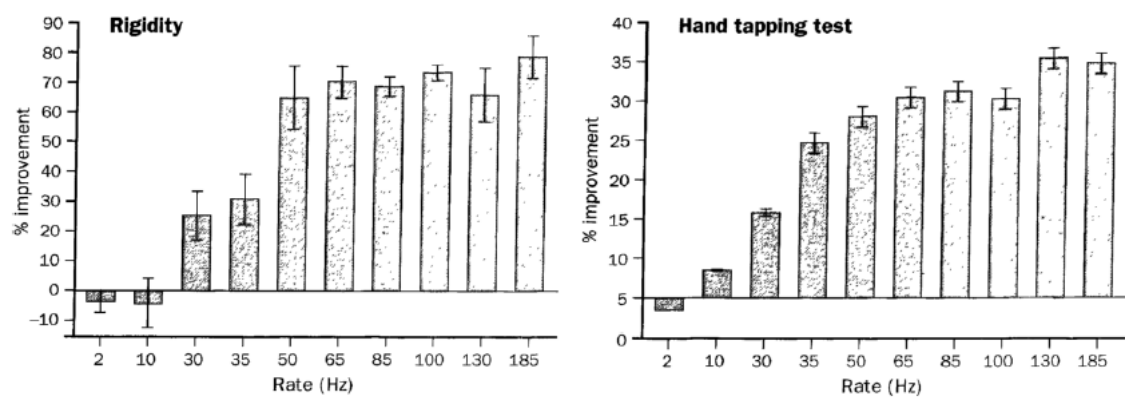
(dyskinesias) hampered the feasibility of STN lesion as an intervention in humans.

While the lesioning experiment was ongoing in the monkey, it was known that high frequency stimulation can stop tremor. This knowledge came from previous work in neurophysiology (Albe-Fessard *et al.*, 1963) and from thalamotomies in the VIM for tremor. The latter was targeted thanks to specific electrophysiological signatures and to the fact that the tremor ceases after electrical stimulation at a frequency of 60 Hz, 0.2mA, during 1second (Ohye *et al.*, 1982). Interestingly, Bechtereva had already successful experience in therapeutical electrical stimulation in USSR since 1975. In this case, 24-40 electrodes were inserted into 4-6 bundles in specific targets such as the thalamus with particular settings (bipolar square pulses at 10V, 50Hz during 3 seconds, 30-40 trains in a trial, one trial every 1 minute during 3-5 seconds) applied once a week to the patients either as inpatients or outpatients. In 1991, Siegfried and Blond and Benabid *et al.* published that frequency-dependent effect could alter tremor in patients with DBS in the nucleus VIM of the thalamus (Benabid *et al.*, 1991; Blond & Siegfried, 1991). Both essential and parkinsonian tremor were improved. The DBS effect was noticeable from 60Hz onwards, followed by a plateau effect between 150 Hz and 1000Hz and then a loss of efficacy at higher frequencies (see figure: 1.9 ).



**Figure 1.9:** Effect of frequency on tremor in VIM on four different patients (Benabid *et al.*, 1991). These curves show the relationship between electrical stimulation frequency and intensity necessary to abolish tremor in four individual patients. In each four patients, a plateau effect was noticed on the VIM stimulation for frequencies between 60Hz and 1000Hz with no necessity for further amplitude increase to improve the tremor.

In 1993, an attempt to modulate the STN with an electrode was tried in the monkey by using a high frequency of stimulation (Benazzouz *et al.*, 1993). Both rigidity and bradykinesia were improved acutely when switching on the 100-130 Hz frequency, with an after effect lasting up to 40 minutes after switching the stimulation off. This was then reproduced in the STN in humans (Pollak *et al.*, 1992; Limousin *et al.*, 1995). In the latter study, 3 patients were assessed thoroughly regarding STN-DBS effect on bradykinesia and rigidity during the procedure and reassessed 8 months later. One of the patients benefited from an external stimulator allowing the investigation of the frequency effect from 30Hz to 2000 Hz. Indeed a plateau effect was shown from 100 Hz onwards, especially on rigidity. Both motor scores and activity daily living were improved at 3 months (58%-88%). Later on, bigger randomized control studies and observational studies have confirmed a long and sustained term effect on the cardinal symptoms as well as on the quality of life and Levodopa reduction (Weaver *et al.*, 2012a; Deuschl *et al.*, 2006; Williams *et al.*, 2010; Aviles-Olmos *et al.*, 2014).



**Figure 1.10:** Effect of Frequency on rigidity and bradykinesia in STN "Mean and standard SE derived from studying 4 subthalamic electrodes in three patients" (Limousin *et al.*, 1995)

### 1.6.2 Very low frequency

The literature on very low frequency (10-30Hz) generally reports no benefits for PD and side effects. In the first studies done by Benabid *et al.*, very low frequency, but not high frequency, increased tremor when stimulating VIM, see 1.9 (Benabid

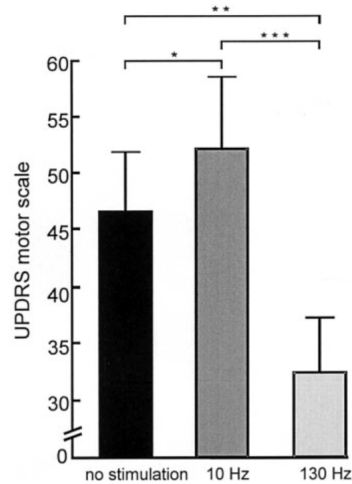
*et al.*, 1991). The same was true for STN. Timmermann *et al.* lowered frequency (4 frequencies were compared randomly: 5, 10, 20, 45) in 7 patients without adjusting any other parameter. This revealed that 10Hz stimulation worsened PD symptoms compared to both no stimulation and therapeutic 130Hz frequency. In this study, 20 and 45Hz did not show any benefits. This finding was also reported in another study by Wojtecki *et al.*; 12 patients were assessed with verbal fluency in three conditions: no stimulation, 10Hz stimulation, and 130Hz stimulation. No other adjustment was made apart from changing frequency. The verbal fluency performance was improved compared to high frequency and no stimulation. The explanation behind the fact that very low frequency can worsen PD symptoms could be related to the intrinsic oscillatory frequency cortico-subcortical loop.

In 2001, Rizzone *et al.* included 10 patients in a study to investigate the best settings regarding pulse width, frequency of stimulation, and voltage for the best clinical outcome on the worst side of the patients. 20 conditions were assessed, mixing four different pulse widths (60, 120, 210, 450  $\mu$ s) and five stimulation frequencies (10, 50, 90, 130, 170 Hz). In this study, no combination of settings reached a clinical efficacy below 50Hz. Reducing the pulse width to 60 $\mu$ s allowed the therapeutic window to be increased but at the cost of the need to increase the stimulus intensity to reach a clinical effect. The combination of the lowest pulse width and 90Hz stimulation led to the greatest therapeutic window. Decreasing the frequency gave the opportunity to increase even further the stimulus intensity before reaching side effects. Interestingly, the side effects manifested were different according to the frequency used, hence more paresthesias, muscle contractions, and dyskinesias with frequencies  $\geq$  of 90Hz, whereas there were more myoclonic jerks and tremor at 50 or 10Hz.

Wojtecki has shown that very low frequency could have an opposite effect on verbal fluency compared to high frequency (Wojtecki *et al.*, 2006). In this study, no voltage compensation was applied when decreasing frequency. Patients experienced a better verbal fluency aptitude, but the motor symptoms worsened dramatically by 25 points on the UPDRS scale compared to 50 and 100Hz frequency. This

has, nevertheless, raised the question of whether a somewhat lower frequency of stimulation could help better particular tasks.

The explanation behind the fact that very low frequency can worsen PD symptoms could be related to the intrinsic oscillatory frequency cortico-subcortical loop.



**Figure 1.11:** The 10 Hz frequency effect worsened UPDRSs cores compared to both high frequency stimulation and no stimulation (Timmermann *et al.*, 2004)

Some contradictory results were found by Chen *et al.* in two consecutive studies on the effect of 20Hz frequency and behavioral measures. (Chen *et al.*, 2011, 2013). In the first study, 20Hz stimulation did slow down the grip force. The authors argued that this result was in line with the fact that this frequency would synchronize the STN the same way as the beta oversynchronization. In the latter study, the performance of patients depended on the baseline off stimulation performance. The authors reported a beneficial effect of grip force and rising slope for 10Hz (but not 20Hz) frequency and 130Hz frequency.

### 1.6.3 Low frequency

We posit that a somewhat lower frequency of stimulation may help better particular symptoms such as gait or speech. It is nevertheless disputed as studies done on this specific question are scarce and report contradictory results. In 2008, Moreau *et al.* (Moreau *et al.*, 2008) studied the acute effect of 60Hz in 13 patients. This study reported an acute effect of 60Hz on freezing of gait (double-blinded rating). The primary endpoint was the number of steps during the Stand-Walk-Sit test over

7 meters. Indeed the number of steps 41(31-67) vs. 32 (26-48) and the number of freezing episodes 3 (2.5-3.5) vs. 0.75 (1-2.5) were reduced on 60Hz. Those results were achieved after a voltage adaptation in order to keep the same energy equivalence. Indeed, those patients who tried on a non-adapted voltage had poorer results.

Brozova et al. reported an open-label follow-up on twelve subjects in 2009 in a letter to the editor in *Neurology* 2009. Three of the 12 subjects did not managed to be switched to 60Hz despite a slight increase in the voltage (around 1.3 volts). The authors also noticed that some patients might improve gait at 60Hz but at the cost of losing the benefit of the therapy from the rigidity bradykinesia and tremor point of view (Brozova *et al.*, 2009).

In 2011, Ricci et al. studied the effect of 80Hz stimulation on gait in eleven patients. The main outcome was the stand-Walk-Sit test. In this study, the voltage was adapted in order to keep the same energy equivalence (Koss *et al.*, 2005). An acute effect was then measured after 3 hours of stimulation and a chronic effect assessed after 1, 5, and 15 months. 8 out of 11 patients could be switched to 80Hz for 15 months with either better response on gait compared to previous setting or unchanged status for 3 of them. The stand-Walk-Sit test showed that the number of steps (24 at baseline steps vs. 21 at 80 Hz) to complete the test was reduced acutely but not anymore at the various other time points (Ricchi *et al.*, 2012).

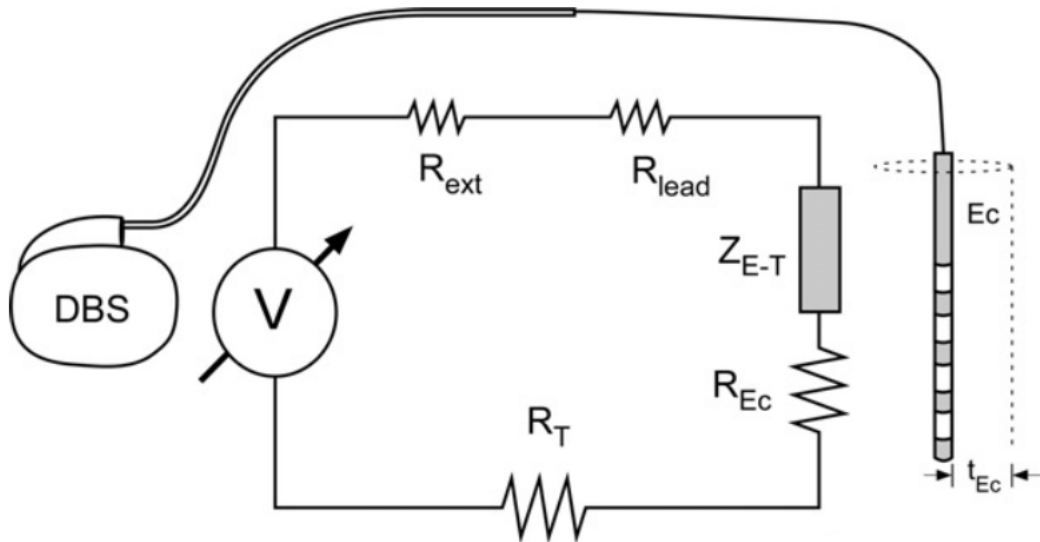
In 2014, a Japanese group assessed whether the contact of an electrode would change the outcome of a given frequency (Khoo *et al.*, 2014). In this study, 60Hz and 130Hz were assessed. Interestingly, more ventral contact was more prone to give clinical motor improvement compared to dorsolateral ones. The global UPDRS scores were improved at 60Hz as well as the axial and akinesia subscores. The gait was also improved on the 10-meter walk test, which was quicker achieved and with fewer steps.

#### 1.6.4 Electrical aspects

The Medtronic ® electrode 3389 contains four cylindrical electrodes 1.27mm in diameter and 1.5mm in height separated from each other from 0.5mm. Hence be-

cause of the STN oblique position with respect to the vertical line around  $40^\circ$ , it is believed that around 3 electrodes are actually in the STN while the last one is usually in the SNr but this depends on the surgical technique.

The DBS efficacy depends on many factors. Electrode's positions and parameters used are among the most important. Hence many studies including subthalamotomy demonstrated the best clinical outcome when the STN and its closest neighbourhood are involved either in the "tomy" or the stimulation such as the FF and ZI (Voges *et al.*, 2002). This is certainly an achievable goal thanks to the current diffusion from one electrode. It is admitted that the current spreading follows the Ohm's law. This encompass the wire resistance, the lead resistance, the electrode-tissue interface and the electrode thickness an encapsulation. One can see from figure 1.12 the model as drawn by Brocker et al (Brocker & Grill, 2013). Therefore, for an usual impedance, when applying 3V, the current could spread up to 3mm distance. The latter does not follow a linear relationship so that a higher voltage (for example 9V) will produce a current spreading up to 5.1mm.

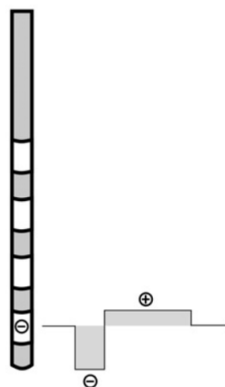


**Figure 1.12:** Voltage constant circuits.  $R_{ext}$ : Extension wire resistance,  $R_{lead}$ : Lead wire resistance,  $R_T$ : Tissue resistance,  $R_{Ec}$ : Encapsulation resistance,  $Z_{E-T}$ : Electrode tissue interface resistance (Brocker & Grill, 2013)

The way the current spreads through the tissue depends on many factors, among other the actual neural element present near the tip of the electrode. The tissue conductivity is anisotropic and inhomogeneous. Also, the Medtronic DBS contact is around  $6\text{mm}^2$ . The smaller the surface the smaller is the electrode's capacitance. The polarization time is then shorter, allowing a smaller amount of current delivered. Of note, one has to remember that the transmembrane potential is around  $-70\text{mV}$ . A cathodic stimulation brings a more negative polarization outside the cell making the transmembrane potential being less negative. In this state the membrane is depolarized allowing some ionic channel to be excited and some potential actions to be generated. In the STN, the cathodic stimulation is much more powerful in exciting neural stimulation compared to anodic stimulation. The latter produces more hyperpolarization in the STN. The cathodic stimulation provokes a current flows in its neighbourhood while the flanking regions become anodal to satisfy the current's conservation law (Brocker & Grill, 2013).

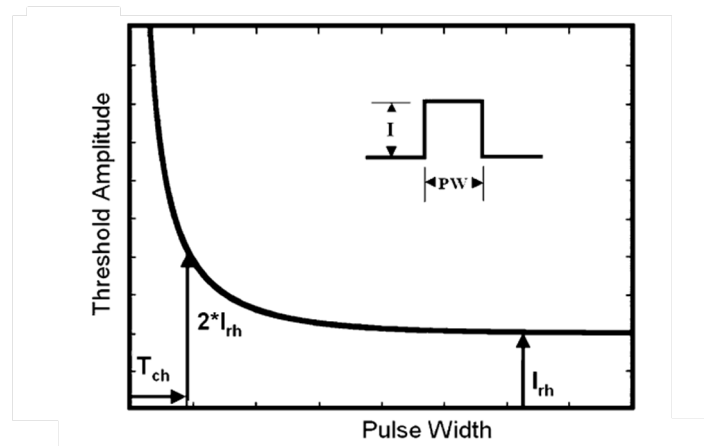
In order to preserve the tissue and the electrode the charge applied to the tissue is balanced. An axon activated by the electrode can produce electrical potential both orthodromically or antidromically.

The actual current waveform is asymmetrical and biphasic. This allows to avoid to charge the electrode too much and select axons we would like to stimulate. see fig 1.13



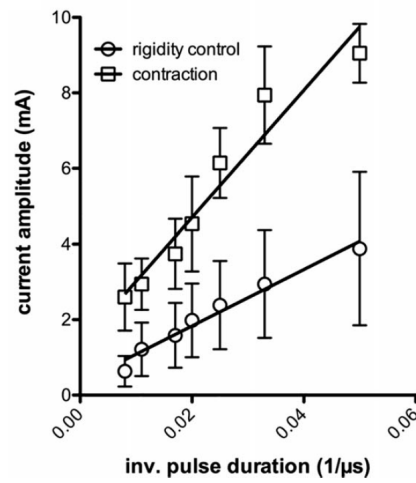
**Figure 1.13:** Monopolar cathodic waveform as described by Brocker et al (Brocker & Grill, 2013). This kind of current delivery allows to avoid to bring too much charges on the electrode that could lead to damage the electrode and the tissue.

Indeed the DBS system is to be considered as a closed electrical circuit. The current flows from the battery to the electrode through the tissue and back to the battery. The current application to neural elements follow certain rules. The so-called strength-duration curve describes how a neural element would be excitable. The rheobase is the minimal current at an infinite time stimulation able to provoke a cellular excitation. The chronaxie is the excitation time needed to reach twice the rheobase (Kuncel & Grill, 2004) as one can see from figure 1.14.



**Figure 1.14:** Strength duration curve according to (Kuncel & Grill, 2004)

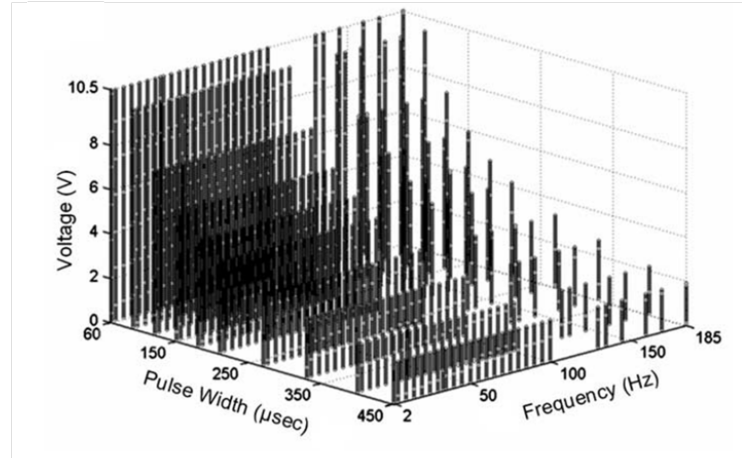
A recent study came back on the importance of the pulse width and emphasizes that different pulse widths could activate different neural populations. A shorter pulse width is able to increase the therapeutic window hence the difference between the appearance of a beneficial effect and a side effect (Reich *et al.*, 2015). This is illustrated on figure 1.15



**Figure 1.15:** Effect of Pulse width on therapeutic window according to Reich et al (Reich *et al.*, 2015) "Linearised strength–duration curves for rigidity control and muscle contractions."

It has been calculated that the charge density prone to provoke tissue damage is around  $30 \mu\text{C}/\text{cm}$  (Kuncel & Grill, 2004). This density depends on the surface of the electrode which is  $0.06 \text{ cm}^2$ . This give an important number of combination parameters available for the clinician to adjust the patient as one can see from fig: 1.16.

From this principle, the shortest pulse width is used hence  $60 \mu\text{s}$ . This can be important as it is possible that certain neural element may be excitable at higher pulse width. This then could excite different cell population leading to different clinical effect.



**Figure 1.16:** Voltage adjustment according to frequency and pulse width (Kuncel & Grill, 2004)

Numerous hypothesis on the effect of STN-DBS has been raised. The hypothesis is based upon many experiences showing that high frequency stimulation trains may either enhance or suppress axons activity. The most reported hypothesis in the current literature are summarized here.

### 1.6.5 Hypothesis on effect of STN-DBS frequency

Most established hypothesis have been summarized by McIntyre et al (McIntyre *et al.*, 2004)

#### 1.6.5.1 The inhibition hypothesis

The abnormal oscillatory activity in the thalamocortical circuits in PD may be reduced by STN high frequency of stimulation. Two ways of inhibition have been postulated namely the depolarization blockade hypothesis and the suppression of somatic neural activity.

**I Depolarization blockade hypothesis.** From of functional point of view, the inhibition effect hypothesis of the STN seems the most accurate as stimulating high frequency and subthalamotomy lead to similar benefit in the monkey (Bergman *et al.*, 1994; Benazzouz *et al.*, 1993). From the neurophysiology point of view, Feng et al studied (Feng *et al.*, 2014) the effect of high frequency of stimulation and axonal block generation. In their study, hippocampal neurons in the rats where stimulated with biphasic high frequency pulse at 50, 100

or 200Hz. The pulse duration was 0.1ms per phase. The length of a train was 1 minute. Some of the trains of stimulation were modified by changing the interstimulus interval. Gaps of 20 or 100ms were introduced in the train of stimulation every 2 seconds. Interestingly in this study, the pattern of stimulation may have generated different type of axonal block duration. Short train of high frequency of stimulation have induced large spikes activity. From this study, it seems that high frequency of stimulation may increase the refractory time period which induce the axonal block. The overall recovery time was similar between all the frequencies tested (50, 100, 200 Hz). This study is in agreement with Beurrier et al (Beurrier *et al.*, 2001) who showed transient blockade of possible calcium channel which causes according to this study a depression of STN neurons.

- II **Synaptic depression** Urbano et al in 2002 (Urbano *et al.*, 2002) spoke in synaptic depression's favour. It was hypothesized that DBS stimulation provokes a depletion in pre-synaptic cleft which interfere then with efferent output.

### 1.6.5.2 Activation hypothesis

**The activation hypothesis:** This hypothesis claims that high frequency of stimulation activates inhibitory axons afferent to the STN. One as to consider retrograde activation from the STN towards the GPe; which in turn release more GABA and then in turn inhibits more the GPi. In this case, the GPi exerts a less important inhibition on the thalamus improving bradykinesia. We report here three studies in monkeys. Hashimoto in 2003 demonstrates a change in the irregular firing pattern in GPe and GPi to a regular pattern higher frequency pattern corresponding to the frequency applied to the STN (Hashimoto *et al.*, 2003). Anderson et al demonstrated also an excitation effect on the GPi as high frequency stimulation excited GABAergic stimulation mirrored by a decrease in the thalamic activity (Anderson *et al.*, 2003). Garcia et al tried to record cells directly in the rats STN by a patch clamp method in hydroxydopamine treated rats (Garcia *et al.*, 2003). The mode of

stimulation was quite similar to the one used in clinical setting. In this configuration the STN shows a spontaneous mode of discharge with a frequency between 2-20Hz. They applied an extracellular stimulation at 10 Hz and between 80-180Hz. With 10 Hz, they were able to see spikes with the same frequency as the stimulations. With higher frequency a modification of the type of spiking was seen. Firstly the spontaneous spiking disappeared to be replaced by a new type of firing pattern STN activity called by the authors: "recurrent bursts". This was typically true with frequencies beyond 100 Hz while with 80 Hz the STN cell followed the stimuli. An important amount of cells were not able to follow the stimuli as the frequency raised. The mean frequency of spikes inside a burst was in the  $\gamma$  range (64-84 Hz). It can be that the abnormal oscillatory activity in the thalamocortical circuits in PD may be reduced and replaced by STN high frequency of stimulation.

#### 1.6.5.3 Jamming effect

**Electrical effect of DBS** The high frequency of stimulation act roughly on a radius of 3 mm depending of the intensity (see Boraudet al 1996). One has to remember the size of the STN in the human brain in average about 5 mm in radius (Yelnik *et al.*, 2007). In the Medtronic® system each electrode is 1.27 mm in diameter and the electrode spacing is 1.5 mm. DBS may mask pathological oscillation acting as jamming.

## 1.7 Effect of frequency of stimulation on other anatomical structures

Interestingly, DBS' s high frequency effect was demonstrated not only in VIM and STN but also in the GPi. A very good clinical effect was achieved when stimulating the motor part with high frequency (ventroposterolateral) of the GPi in 1994 in 3 patients with PD (Siegfried & Lippitz, 1994). The effect was then replicated in numerous studies on GPi. Nevertheless, these studies did not assess methodically the frequency effect. It is known, today, that, not only frequency of stimulation can drastically change the effect of the treatment, but also that other anatomical

structures need to be modulated differently in order provide a maximal effect. For example, the PPN needs to be stimulated at a lower frequency. A first study found that 15 to 25 Hz brought some benefit especially on freezing of gait in PD (Ferraye *et al.*, 2010). A somewhat higher frequency of stimulation was found as effective in another study in which essentially subjective measures (UPDRS II) were found to be improved at 50-70Hz and 60 $\mu$ s. The same was true in trials aimed at improving cognition in dementia when stimulating the nucleus basalis of Meynert. In these studies a rather low frequency was used: 20Hz. It is thought that a very low frequency of stimulation can stimulate rather than inhibit acetylcholine cells (Kuhn *et al.*, 2015; Freund *et al.*, 2009; Gratwicke *et al.*, 2013).

## 1.8 Aims of the studies

The main goal of this thesis is to measure how the DBS frequency modulate different loops and if they respond differently to 130Hz and 80Hz.

Therefore, we have planned four studies. The first study is focussing on clinical measurement and behavioural outcomes; the second is focussing on cognitive assessment and its variation according to DBS frequency, the third study aims at measuring the cortical excitability with transcranial magnetic stimulation, finally the fourth study will focus on the oculomotor loop in order to assess how eye-movement are modulated by DBS frequency.

The aims of these exploratory studies are to measure prospectively both the clinical and the cognitive/neurophysiological effects of 80Hz versus 130Hz STN DBS, in order to provide more definitive evidence that stimulation at different frequencies improves or worsens particular constellations of parkinsonian deficits. The aim is to provide a rationale for future treatment of individual patients with particular frequencies of DBS.

Clinical state, repetitive motor tasks, selected cognitive tasks have been recorded and we will try to assess how these relate to cortical excitability using transcortical stimulation. A final, study is measuring eye movement (saccades, latencies, and errors in anti-saccades)

## Chapter 2

# General Method

### 2.1 Subjects

Patients were selected during routine consultations in the movement disorders clinics at the National Hospital of Neurology and Neurosurgery. The inclusion criteria were STN-DBS for 6 months or more in patients with diagnosis of Parkinson's disease. All the patients gave informed consent for the present study according to the Helsinki declaration; it was approved by the local ethical committee. We have recruited 16 patients in our study between September 2013 and December 2014. Participants' details are summarized in table 2.1.

	n	mean(SD)
Patients	15	
Male:Female	10:5	
Worst side Right:Left	2:13	
Right:Left handed	13:2	
Age (years)		63,3(6,6)
Time Since DBS (years)		4,45(3,93)
Disease Duration (years)		15,47(5,15)
MMSE		28.87 (1,3)
UPDRS On medication		17,93(5,51)
UPDRS Off medication		23,87(6,95)
Voltage Left Side		2,73(0,71)
Voltage Right Side		2,68(0.66)

**Table 2.1: Baseline data.** SD: Standard Deviation, MMSE: Mini mental state

### 2.1.1 Inclusion criteria

Participants were adult males and females diagnosed according to the UK Parkinson's disease brain bank criteria. All had had bilateral STN-DBS implants (model 3389; Medtronic, Minneapolis Minn) for at least 6 months to ensure good local healing and avoid the frequently seen "implantation effect". Patients were also receiving anti-Parkinsonian medication.

### 2.1.2 Exclusion criteria

A patient was excluded if under the age of 18, unable to give informed consent, pregnant, is unable to stand and walk independently when off treatment, demented as assessed by Mini Mental State Examination (MMSE) < 24, or had a contraindication to TMS because of the presence of metallic objects in the head other than implanted electrodes.

## 2.2 Conditions

Patients were assessed clinically and electrophysiologically on four separate days (See Figure 2.1). Clinical testing was performed using the UPDRS part III. The side of disease onset and handedness were noted. Details of electrophysiological assessments are given in subsequent chapters.

### 2.2.1 Procedure

Participants were first assessed at baseline with their chronic stimulation frequency on 130 Hz and on their usual anti parkinsonian medication. An attempt to switch the stimulation frequency to 80 Hz together with an adjustment of the voltage was made (see figure 2.1).

After 1 hour of stimulation at 80 Hz, if the patient tolerated it, he was qualified for the randomization.

Following randomisation the patients were assigned to one of two groups: one continued with their usual high frequency (130 Hz) settings; the other was changed to 80 Hz. Medications were not changed. After three weeks of stimulation they returned to hospital for two consecutive days of testing. On Day 1, they were assessed

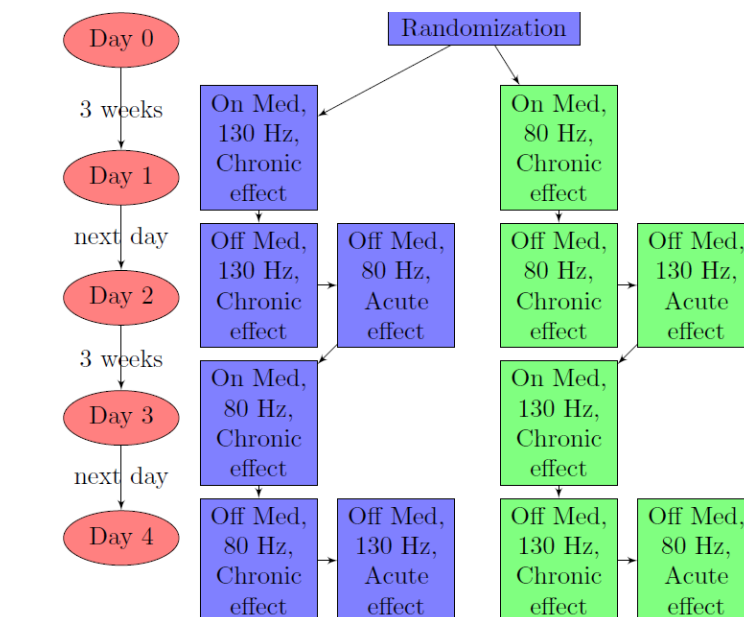
ON medication with stimulation at the assigned frequency (ON med chronic effect). On the following day they were assessed after overnight withdrawal of medication (OFF med chronic effect). After this, the stimulus frequency was changed (to 80 or 130 Hz respectively), and the patients assessed again (OFF med acute effect). The reason for doing this was to probe whether acute assessment of a new frequency would be predictive of long term effects. The time between sessions on this second day was at least 30 minutes in order for motor scores to stabilise (Temperli *et al.*, 2003). Following the adjustment of frequency, patients remained on the new settings for the next 3 weeks and returned to hospital for two final days of testing. The intensity of each pulse during 80Hz stimulation was increased in order to deliver the same amount of electrical energy to the brain (Koss *et al.*, 2005).

Total electrical energy delivered (TEED):

$$= 1 \text{ second} * \text{voltage} * \text{frequency} * \text{pulsewidth} / \text{impedance} \quad (2.1)$$

We allowed a small window of voltage modification so that the patient could modify voltage if there was excessive dyskinesias or a lack of effect of the new setting.

**Figure 2.1: Study flow chart**



## 2.3 Statistical analysis

All data were evaluated for normality of distribution. Normal data were analysed with mean and standard deviation, t-tests and repeated measures ANOVA. Non-normal data was analysed using non-parametric statistics. Two-tailed tests were used in all cases except for the comparison of actual intensity used at 80 Hz with the calculated TEED. In this instance we had prior experience that patients preferred a reduced intensity.

In total, each patient was assessed 6 times each differing in medication status, stimulus frequency and chronic/acute testing. Our analysis was therefore designed to address the following questions: (a) since patients were tested on multiple occasions using the same tests, was there an order effect? (b) did it matter whether patients were assigned to 130 or 80 Hz at the start of randomisation? (c) in the OFF med state only, were assessments in the acute phase the same as those after 3 weeks of stimulation (chronic)? (d) was there a difference in the chronic effect of 130 vs 80 Hz DBS when ON meds? Analysis of variance for repeated measures was carried out using R software (R Core Team, 2016). To address the question of an order effect, all six assessments were included irrespective of medication status with frequency as a within-subject factor. . In case the ANOVA was significant, an additional T-test pairwise comparison between each means in the different assessments was performed, and a linear regression to figure out if a trend due to repeating the task had appeared. To address questions (b) and (c) rmANOVA was applied to OFF meds data only (4 total sessions per person). Acutness (acute-/chronic change of setting) and frequency (80 Hz/130 Hz) were within-subject factors, the between-subject factor was group (starting the study with 130 Hz or 80 Hz), the interaction between acutness and frequency was also calculated. Finally, for question (d) we conducted a separate analysis ON meds for high vs low frequency. If the normality of data assumption was confirmed, paired t-test (or, if not, Wilcoxon test) was then performed.

## Chapter 3

# Study I: Bradykinesia study

### 3.1 Introduction

#### 3.1.1 Bradykinesia

Bradykinesia is a key symptom in PD, mandatory to retain this diagnosis (Hughes *et al.*, 1992). This term depicts particular type of slow movement. Clinically, when patients are asked to produce repetitive movement, one can see a slow decrease in the movement amplitude: the decrement. Luckily, at the beginning of PD, this symptoms respond very well to levodopa therapy (Berardelli *et al.*, 2001). It is also one of the symptoms responding well to STN-DBS (Pollak *et al.*, 1992; Limousin *et al.*, 1995; Weaver *et al.*, 2012b).

The physiopathology leading to bradykinesia is not solved. Nevertheless, according to the basal ganglia model this phenomenon could be as a consequence of excessive GABAergic stimulation from SNr and GPi towards the thalamus. (Berardelli *et al.*, 2001). Interestingly many electrophysiological and imaging studies involving EEG, MEG, PET, functional MRI and magnetic stimulation demonstrate an under-activity in the midline cortical motor regions, especially the SMA region. The latter represent the actual projection from the thalamus back to the cortex in the motor loop see fig 1.1.

Bradykinesia parallels the nigrostriatal loss in PD (Vingerhoets *et al.*, 1997); it is directly linked to functional disability and to poor quality of life (Muslimović *et al.*, 2008). This symptoms is also correlated with symptoms of depression, sleeping dif-

ficulty and suicidal thoughts (Koerts *et al.*, 2008). Finally this symptom, when tremor is absent, is more correlated with poor prognosis.

Our hypothesis regarding this particular symptom is that reducing the frequency to 80Hz might be less effective on bradykinesia and therefore patients' performance might deteriorate

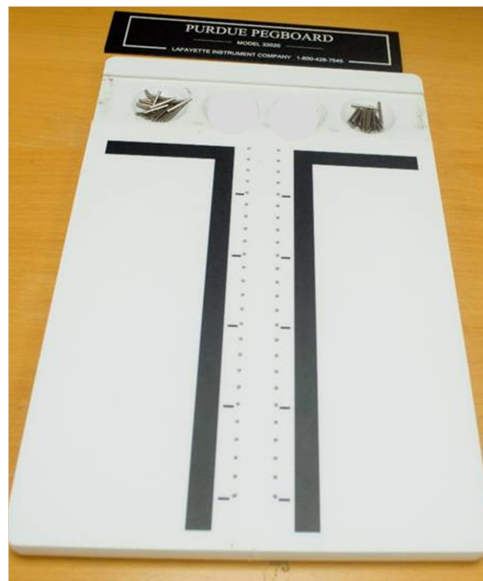
## 3.2 Method

### 3.2.1 UPDRS III

The UPDRS III was measured when the participant attended the study with the stimulation On in both high and low frequency conditions as well as in Off medication states, altogether 6 times see figure 2.1.

### 3.2.2 Purdue pegboard task

This task involves peg placement using the Purdue pegboard. Patients had to pick up metal pegs 25 mm on each side from a board in front of them. One by one, pegs were placed on a vertical row of holes drilled into a board. This task was performed with each hand separately and with both hands together. The goal was to place as many pegs as possible in 30 seconds on vertical rows.



**Figure 3.1: Purdue Pegboard**

The task provides: objective measurements from fine motor function to assess bradykinesia (Hietanen *et al.*, 1987), and good correlation ( $r = 0.7$ ) with nigrostriatal loss (Vingerhoets *et al.*, 1997). Moreover, normative scores have been established for age, sex and lateralisation (Agnew *et al.*, 1988). Compared to healthy control group and mild cognitive impaired subjects, Alzheimer disease group performed less well during this task.

### 3.2.3 Finger-tapping task

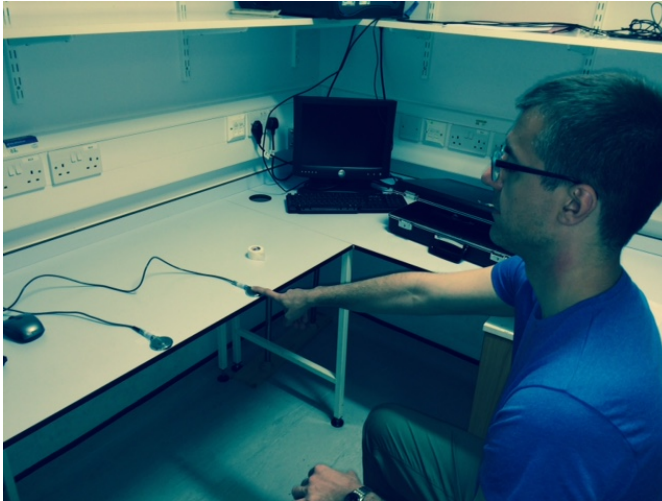
Finger tapping was evaluated with the V900S evaluation system (Biometrics Ltd, UK). Patients tapped as rapidly as possible on a force transducer with their index finger. The amplitude excursion of the finger and the force of tapping was recorded for 30s. The task was performed with each hand alone and then bimanually. Data was analysed with an in-house script. We have looked at: the number of taps for each hands alone; and at each hand separately when patients were tapping bimanually.

### 3.2.4 Combined task

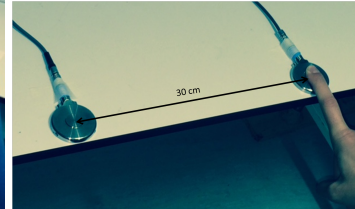
The patient was asked to tap with one hand while placing pegs with the other one. Both hand combinations were assessed. The number of pegs placed by one hand combined with the taps of the other hand were counted. The combined task is more complex as it involves bilateral movement of two different types (finger tapping and putting pegs in the board). We expected this more complex task would lead to poorer performance (Kluger *et al.*, 1997) and included it specifically because other groups have found it to be particularly affected in patients with cognitive problems in MCI and Alzheimer's disease. Since STN DBS can produce mild cognitive problems in some PD patients, we reasoned that their deficits might be particularly evident in complex rather than simple tasks.

### 3.2.5 Shoulder movement

The patient was asked to move his outstretched arm as quick as possible between two force sensors attached to a table. While moving, he was asked to touch the middle of the sensor. We counted the number of tap produced in 30 s. see fig 3.2.



**Figure 3.2: Shoulder movement assessment:** the participant is moving his arm outstretched between two sensors spaced 30 cm apart.



**Figure 3.3:** Zoom on the sensors: the distance between the two sensors is 30 cm

### 3.3 Results

As noted in the General Methods chapter, eligible patients were randomised into two groups, having an initial 3 weeks stimulation at 130 or 80 Hz. We refer to these as Group 1 and Group 2 respectively.

#### 3.3.1 Demographic data

Demographic results are shown in table 2.1. Median time after DBS was 4 years with a minimum of 6 months and maximum of 5 years post implantation. Altogether patients tolerated the change in stimulation frequency well apart from one patient who withdrew from the study after 3 weeks of stimulation at 80Hz because of deterioration in his tremor. In 8 patients, it has been possible to leave them on a somewhat lower frequency of stimulation for the long term as they felt a benefit from it especially on gait or speech. At the end of the sessions, the patients were assessed by an unblinded neurologist to try to find the best setting. 5 of them ended up on 80Hz and 3 on 100Hz and the remaining participants came back to 130Hz. Interestingly, adaptation of the voltage of those who have stayed with 80Hz stimulation required a lower voltage as summarized in table 3.1.

### 3.3.2 Voltage adjustment

All the patients tolerated the theoretical voltage as an adjustment for 80 Hz frequency. As we built up progressively the voltage after switching frequency, we noticed that all the patients needed an increase in the voltage either because they felt their gait slower or because the bradykinesia or tremor was insufficiently controlled. It was not necessary to go beyond the theoretical voltage in most of the patients. In general, a somewhat lower voltage was admissible in the patients with good clinical outcome.

	130 Hz	80 Hz	Theoretical voltage	t test	p value	C.I
Left side	2.73(0.71)	3.41(0.96)	3.48(0.91)	-1.72	0.1	-0.15 - 0.02
Right side	2.68(0.66)	3.33(0.81)	3.42(0.84)	-2.54	0.02*	-0.16 -0.01

**Table 3.1: Voltage adjustment** The voltage at 80 Hz was slightly reduced compared to the voltage planned for the left side on the test two-sided. The results are meant in Volts. In brackets, the standard deviation

### 3.3.3 UPDRS III Score Baseline

At baseline, group 1 and 2 were similar in on states (group 1: mean = 16.1 (4.5) ; group 2: mean= 19.5, (5.95) ,  $F(1,13) = 1.4$ ,  $p=0.45$ ) as well as in off states ( group 1: mean= 21 (5.4) ; group 2: mean= 26.4 (7.5),  $F(1,13) = 2.5$ ,  $p=0.14$ ) .

#### 3.3.3.1 Order effect

The order effect analysis showed statistically significant change in UPDRS scores which was due to the anticipated medication effect. Pairwise comparison without Bonferroni correction between the different assessments confirmed differences between On and Off medication states. A simple linear regression was calculated to predict the UPDRS score based on the assessment time point. No trend ( $b = 0.6$ ,  $t(88) = 1.24$ ,  $p= 0.22$  C-I= -0.37-1.6) was retrieved what allowed us to disclose any learning effect. . From a clinical point of view, patients remained stable throughout the study as shown from the global UPDRS scores in table 3.2

#### 3.3.3.2 Frequency effect

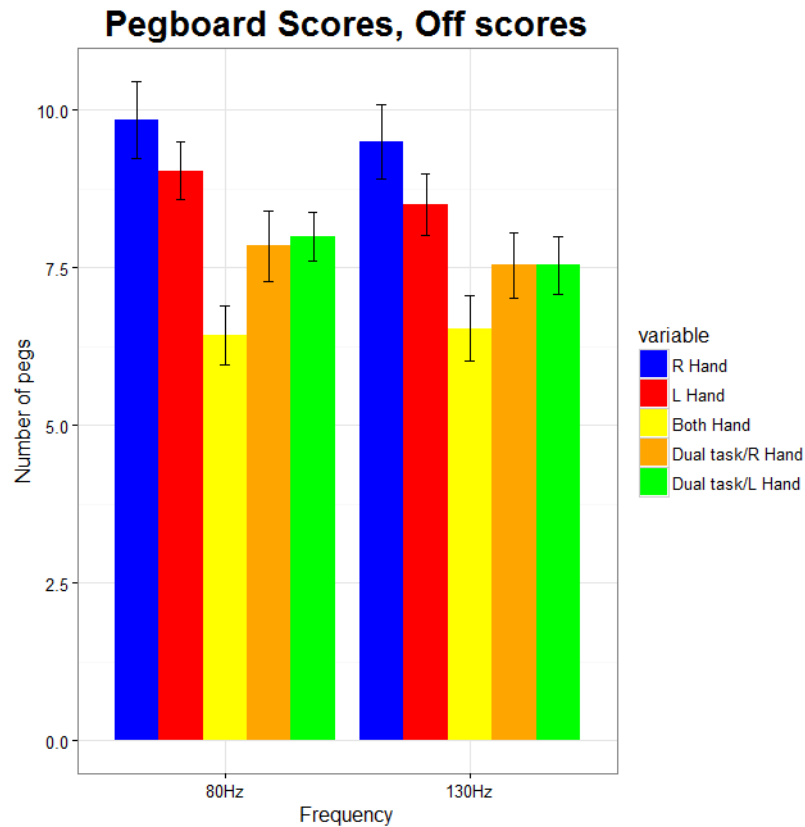
The effect of frequency was first explored with a 2-way ANOVA in the 4 off medication states, with acute/chronic as one factor and 80/130 Hz as the other. For the

total UPDRS III there were no main effects nor interaction terms, implying that the UPDRS remained constant in the OFF med state whether chronic or acute or using 80 or 130 Hz DBS. The group analysis did not show any significant results. A t-test comparison of the ON meds chronic effect of 80 v 130 Hz also revealed no significant effect. Thus, UPDRS III ratings were not worsened by reducing DBS frequency to 80 Hz.

We also conducted a post hoc analysis on subscores of the UPDRS scale: there were no frequency specific effects in either ON or OFF meds state for tremor (sum of items 20 and 21), rigidity (item 22), axial scores (sum of items 27-30) and distal bradykinesia (sum of items 23 and 24). However, there was a significant frequency effect on proximal movement (Item 25; Wilcoxon test), with performance at 80 Hz better than at 130 Hz in the OFF (but not ON) meds state, see table 3.2.

### **3.3.4 Purdue pegboard task**

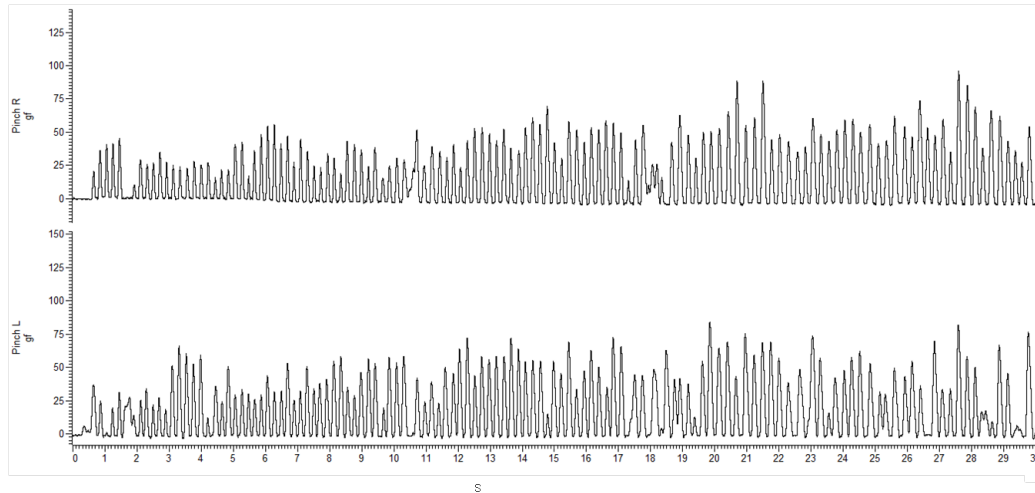
The normal distribution assumption was not met. In order to assess the frequency effect, we analysed only the off med conditions to avoid the effect of medication. We then combined data from the acute and chronic measurements before comparing the two frequencies with the Wilcoxon test. Overall performance in these tasks was similar for both frequencies. As expected, performance deteriorated in the complex tasks (combined and bimanual task) see figure 3.4 and table 3.2



**Figure 3.4:** Distal movements as assessed with the Purdue Pegboard (patients off medications). No differences across the tasks between 80Hz and 130Hz.

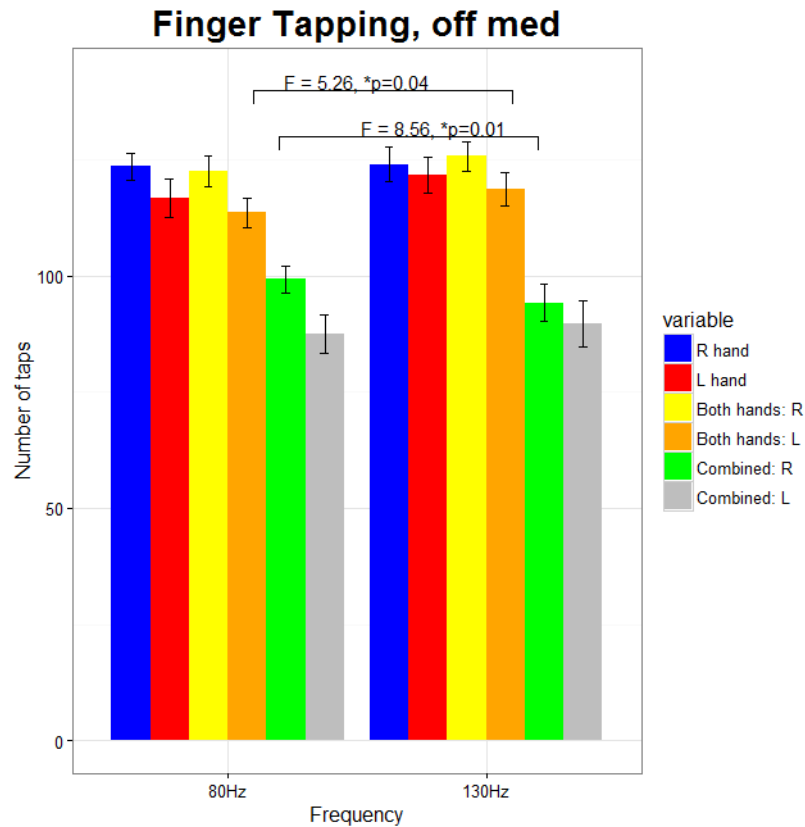
### 3.3.5 Finger-tapping task

Figure 3.6 is an example of a patient tapping with both hands together. The taps' amplitude varies significantly during the performance, and some decrement is visible on the left hand while the taps are becoming slower. We did not analyze the amplitude decrement here as the interindividual variation during tapping varied greatly. Interestingly, patients' performances while tapping with both hands together uncovered asymmetrical impairment (See figure: 3.5).



**Figure 3.5:** Both hands tapping at the same time. Upper part of the figure is showing the right hand and the lower part the left hand. Asymmetrical tapping rate and performance can be seen as well as a slight decrement after 17 s, more clearly visible on the left side.

Details of the statistical analysis of the data can be found in the table 3.2. The only significant finding was that there was an effect of DBS frequency when OFF meds for left hand while both hands were tapping at the same time. Slightly more taps were performed on 130Hz than 80Hz (approximately 4 more taps). However, given the number of comparisons made across the 4 different tasks, this is non-significant corrected for multiple comparisons. We conclude that DBS frequency had no effect on finger tapping performance. Figure 3.6 presents the grand average tapping rates across group, medication and acute/chronic states separately for 80 and 130 Hz stimulation.



**Figure 3.6:** The numbers of taps as assessed with finger tapping does not show any differences across the tasks between 80Hz and 130Hz- There is a slight advantage using higher frequency for finger tapping in terms of number of taps.

### 3.3.6 Combined task

#### 3.3.6.1 Order effect

The ANOVA on the order effect analysis revealed a statistical difference between the assessments when putting pegs with the right hand. The pairwise comparison disclosed any differences on the different assessment except the fifth assessment due to a patient performing quite badly on this task. The linear regression, nevertheless, did not show any trend ( $b = -0.2$ ,  $t(88) = -1.26$ ,  $p = 0.21$  C-I =  $-0.5-0.11$  ), see table 3.2.

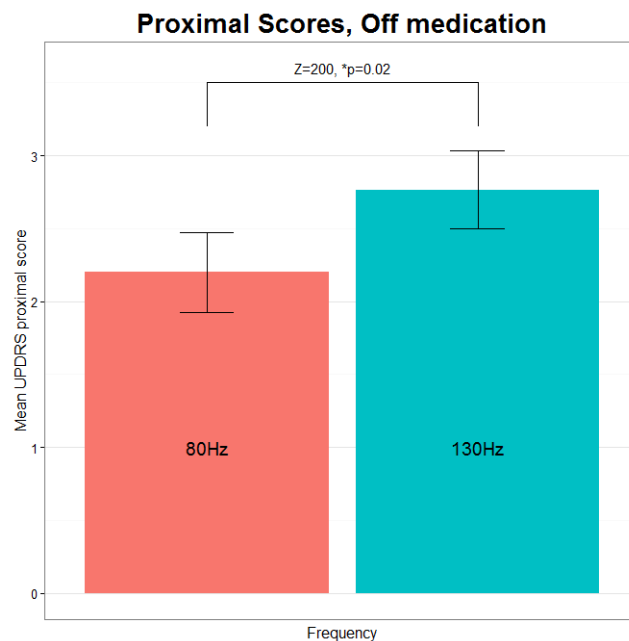
#### 3.3.6.2 Frequency effect

Details of the statistical analysis are given in Table 3.2. There were no significant main effects or interactions apart from in the OFF meds state when tapping with the right hand and placing pegs with the left. In this case, tapping was faster ( $P = 0.02$ )

after chronic (3 weeks) stimulation than acutely and slightly better ( $P = 0.04$ ) with 80 Hz DBS. However, correcting for the multiple comparisons within this data set means that these effects were probably not significant. We conclude again that 80 Hz DBS does not impair performance in this task or can even improve it slightly.

### 3.3.7 Shoulder movement

Related effects of acute/chronic and DBS frequency were seen for right (but not left) shoulder movements. Analysis of the OFF meds data showed that movements were faster with 80 Hz DBS ( $P = 0.02$ ). A significant interaction of chronic/acute and Frequency ( $P = 0.04$ ) was due to the fact that acute 80Hz stimulation improved performance more than chronic 130 Hz stimulation whereas acute 130 Hz was worse than chronic 80 Hz. Figure 3.7 illustrates the average data across group, medication, and acute/chronic state for the two different frequencies and arms (i.e. left and right). 80 Hz stimulation produced a slight advantage over 130 Hz stimulation for the right arm.



**Figure 3.7:** Proximal scores are sum of UPDRS item 26. Shoulder movements were improved more by 80Hz compared to 130Hz

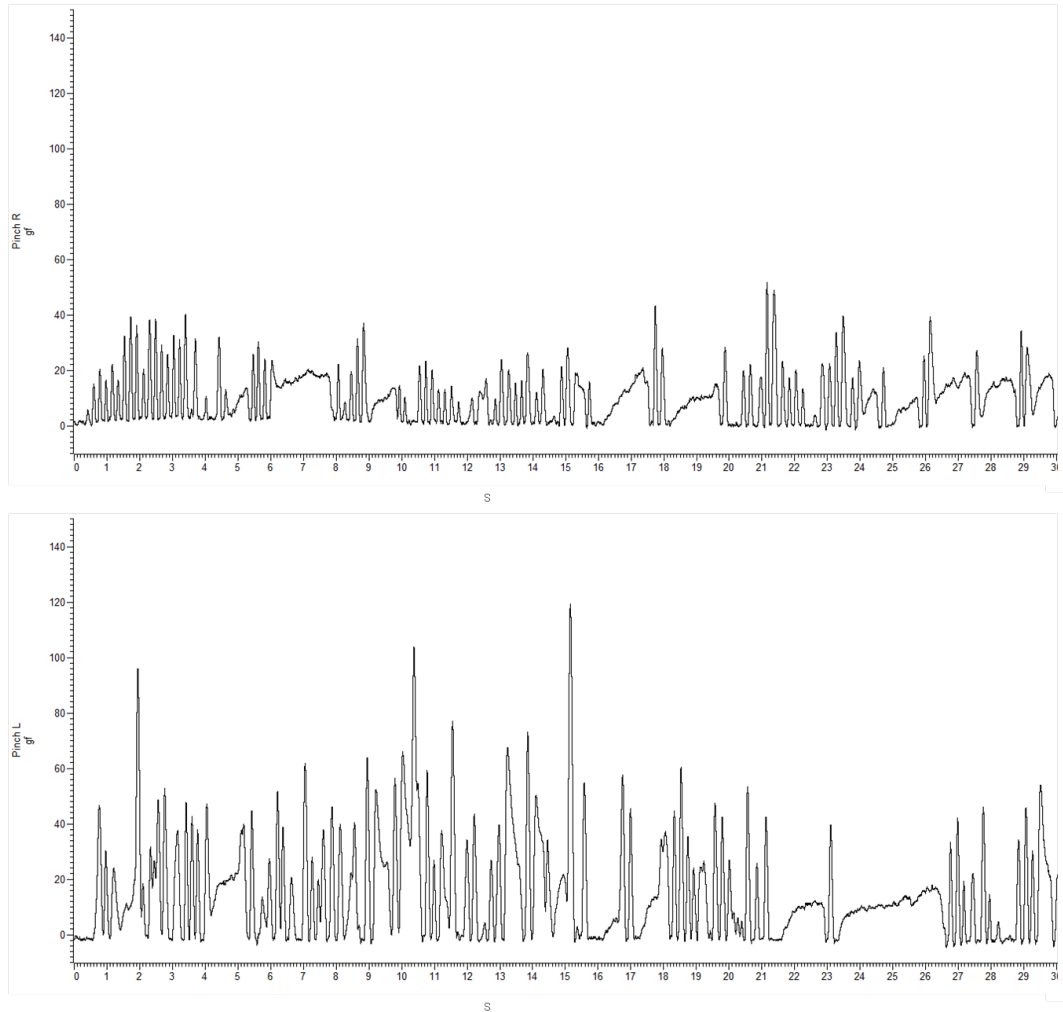
	On med 130 Hz Chronic	Off med 130 Hz Chronic	Off med 80 Hz Acute	On med 80 Hz Chronic	Off med 80 Hz Chronic	Off med 130 Hz Acute	Order	P value	Group Off med	P value	Frequency Off med	P value	Ac vs.Chr Off med	P value	Interaction Off med	P value	Frequency On med	P value
<b>UPDRS Assessment :</b>																		
UPDRS III score	17.93 ( 5.51)	23.87(6.95)	21.33(8.64)	19.13 (7.44)	22.93 (9.08)	24.00 (8.87)	F= 4.85	< 0.01*	F= 0.8	0.38	F= 2.16	0.17	F= 2.49	0.14	0.48	0.5	Z= 50	0.7
Speech	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1.5)					Z = 20	0.2						
Distal movement	5 (2.5)	7 (2)	5 (3)	6 (3)	6 (2.5)	6 (3.5)					Z= 200	0.3						
Proximal movement	2 (2)	3 (2)	2 (2)	2 (2.5)	2 (2)	2 (3)					Z=200	0.02 *						
Tremor	1 (2.5)	1 (2)	1 (2.5)	1 (2.5)	1 (3)	1 (2.5)					Z=100	0.8						
Rigidity	3 (2.5)	4 (3.5)	3 (4.5)	3 (5.5)	4 (4)	3 (5.5)					Z = 90	0.6						
Axial	2 (2)	2 (2.5)	2 (2)	2 (2.5)	2 (3.5)	3 (2.5)					Z=100	0.6						
<b>Pegboard :</b>																		
Right hand	11 (3.5)	10 (2.5)	11 (2.5)	10 (2)	9 (2.5)	9 (3.5)					Z = 100	0.3						
Left hand	8 (2)	8 (1.5)	9 (3)	9 (3.5)	9 (2)	9 (2.5)					Z = 100	0.2						
Both hand	6 (2.5)	7 (2.5)	6 (3)	7 (2)	7 (1.5)	7 (3.5)					Z = 100	0.5						
<b>Finger Tapping:</b>																		
Tapping right hand	123.53 (22.32)	119.33 (22.87)	119.53 (18.07)	119.93 (23.3)	116.67 (24.32)	118.73 (22.36 )	F= 1.03	0.4	F= 0.01	0.9	F= 0.03	0.9	F= 0.44	0.52	F= 0.48	0.56	F= 0.79	0.39
Tapping left hand	115.47 (21.47)	117.07 (24.12)	116.33 (20.56)	111.2 (24.64)	111.73 (22.11)	119.4 (16.88)	F=1.81	0.12	F= 0.76	0.4	F= 3.83	0.7	F= 1.09	0.31	F= 0.09	0.77	F= 0.85	0.37
Bimanual, right hand	121.46 (18.27)	127.23 (19.15)	125.54 (18.15)	122.92 (18.69)	119.77 (16.26)	124.46 (13.97)	F= 0.51	0.7	F= 0.41	0.53	F= 1.1	0.31	F= 0.23	0.6	F= 3.68	0.81	F=0.07	0.8
Bimanual, left hand	117.38 (22.75)	120.46 (21.09)	115.38 (18.92)	112.46 (16.59)	111.92 (13.2)	116.92 (16.04)	F= 0.18	0.7	F= 1.19	0.3	F= 8.56	0.01*	F=0.01	0.99	F= 1.0	0.34	F=1.97	1.84
<b>Combined task:</b>																		
Tapping right hand	93.27 (26.96)	91.53 (23.65)	90.13 (20.66)	87.8 (26.38)	93.93 (27.35)	83.4 (28.01)	F= 1.73	0.14	F= 0.01	0.9	F= 5.26	0.04*	F= 7.16	0.02*	F= 0.38	0.55	F= 1.28	0.3
Peg left hand	7.67 (1.76)	7.27 (1.75)	8.2 (1.78)	7.53 (2.9)	7.4 (2.16)	7.6 (2.59)	F= 1.8	0.12	F= 1.25	0.3	F= 1.56	0.23	F= 4.77	0.05*	F= 0.39	0.54	F= 0.07	0.8
Tapping left hand	86.93 (25.42)	87.47 (27.32)	86.4 (24.7)	84.13 (23.93)	81 (22.76)	84.07 (26.5)	F= 0.3	0.91	F=0.13	0.72	F= 0.43	0.53	F= 0.04	0.84	F= 1.63	0.22	F= 0.44	0.52
Peg right hand	8.27 (2.63)	7.33 (2.66)	8.27 (2.91)	8 (2.51)	7 (2.45)	7.6 (2.41)	F=4.24	< 0.01*	F= 0.09	0.8	F=0.14	0.7	F= 12.11	< 0.01*	F= 3.11	0.1	F= 0.3	0.6
<b>Shoulder task:</b>																		
Right shoulder	54.07 (11.78)	52 (12.92)	58.57 (11.28)	55.14 (10.93)	51.57 (10.97)	49 (11.35)	F=1.18	0.33	F= 0.08	0.09	F= 8.36	0.01*	F= 1.84	0.2	F= 6.32	0.03*	F= 4.10	0.07*
Left shoulder	49 (9.6)	49.5 (9.8)	54.07 (8.97)	49.36 (7.19)	48.07 (8.43)	48.14 (9.58)	F=1.18	0.33	F= 3.67	0.08	F= 1.82	0.2	F= 2.4	0.12	F= 3.5	0.09	F= 1.08	0.32

**Table 3.2: Summary table** Means and standard deviation in brackets for parametric data, median and interquartile range in brackets for non-parametric data. \* indicates significant differences. Order: order in which the test have been done, Group off med: comparison between patients starting the study at 130 or 80Hz, Frequency off med: Comparison for frequency as a main effect in Off medication, Ac vs Chr Off med: Acute vs chronic effect as a main effect, Interaction: interaction between acutness and frequency.

### 3.3.8 Freezing of tapping

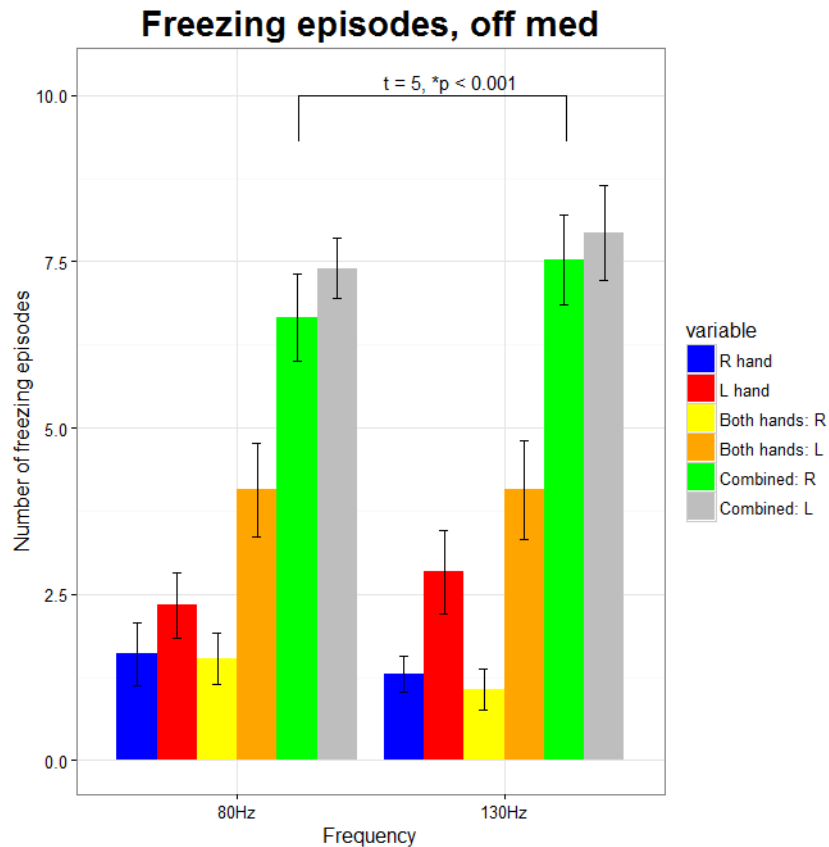
One common behaviour seen in PD is freezing of gait. This phenomenon was also seen during the finger tapping task. In figure 3.8 the taps occur regularly in the first half of the traces, but about half way there is a freezing episode where the patient is failing to remove his finger from the force plate completely. It appears from this example that the period of time spent during a freezing episode is longer than the time spent during a normal tap.

As the patients were asked to make two tasks in the same time namely putting pegs in the pegboard and tapping, the freezing episodes became frequent 3.8



**Figure 3.8:** Freezing episodes are seen while the patients are asked to perform two tasks in the same time: in this example the two traces are showing on the upper part the right hand and on the lower part the left hand. While the participant was tapping with the right hand, the left hand was placing pegs in the pegboard. the freezing episodes happen usually in the same time than putting a peg in the board.

A freezing episode was defined as a tap episode lasting longer than 1.5 times the mean tap duration. This definition appears to correlate well with visually identified episodes of freezing. High frequency stimulation produced more freezing in the right hand than low frequency stimulation but only when the right hand was tapping and the left hand was placing pegs (dual task mode) ( $t = 4$ ,  $p = 0.0005$  (IC= 1.2-4.0)).



**Figure 3.9:** Freezing episodes results: during dual task the number of pegs was significantly reduced on 80 Hz for the right hand

### 3.4 Discussion

Overall the data show a slight advantage of low frequency DBS on the speed of shoulder movement and freezing, as well as a tendency for better performance in more complex behavioural tasks, such as the combined task. Interestingly, there was a slight right side preference: low frequency DBS improved shoulder movement more on the right side than the left, and also improved freezing during right hand but not left hand tapping. This is similar to previous data from Moreau et al (Moreau *et al.*, 2008) who also found a slight right side advantage. In contrast, high and low frequency had similar effects on performance of distal movements such as finger tapping and pegboard performance, indicating that low frequency DBS at 80 Hz has no detrimental effect on function. Indeed the global UPDRS on scores on 80Hz or 130Hz were similar (see also Moreau et al (Moreau *et al.*, 2008)).

Speech (another symptom known to improve on low frequency DBS) and shoulder movement involve axial muscles. It may therefore be that the connectivity of the STN favours effects on axial control. Freezing of gait is another symptom that has been reported to respond better to lower frequency DBS, so it was of interest that low frequency DBS reduced freezing episodes during a complex tapping task in the present patients. Also a more important relationship to the left STN have been made by Tripoliti et al where speech was more impaired in relationship with stimulation of the left STN. (Tripoliti et al., 2008). Therefore the left STN stimulation appears to be critical in those patients experiencing speech or freezing of gait.

Regarding very low frequency and finger tapping, Chen et al found an asymmetrical results with more important finger tapping deterioration on the best side when stimulating at very low frequency (20Hz) compared to baseline (Chen et al., 2007). In our study, proximal performance was improved at a somewhat lower frequency. This underline the fact that even if some over synchronization on beta band could explain impaired result at very low frequency, the opposite happen for proximal movement. STN lesion can lead to hemiballismus (ie high amplitude ballistic movement usually involving either the shoulder and/or the hip) (Bergman *et al.*, 1994). This kind of movement involves by definition more proximal movement. Moreover, it is true that even if not significant, our finger tapping data tend to show better performance at 130Hz than 80Hz. This, nevertheless, stresses out the fact that axial symptoms are possibly not directly linked to beta band synchrony. It can be that DBS inhibits too much existing preserved loop addressing more axial performance such as gait speech or shoulder movement and provoking freezing events.

Many authors have suggested that DBS works by suppressing output from an overactive STN. However, in PD, subcortical circuitry degenerates at different rates, meaning that DBS must be adjusted to suppress only specific, non-functioning outputs with minimal interference with other, functioning outputs. Indeed, stimulation at too high a level may produce secondary side-effects which can disappear on reducing the voltage (Fleury et al). It is therefore possible that decreasing the frequency may allow valid loops to carry on exercising their physiological role while

a higher frequency would not. The clinical picture of PD patients mirrors this fact since patients develop speech and gait problems later in their history indicating that the circuitry involved in gait and speech degenerates slower than the other neuronal circuitry involved in more distal tasks such as finger tapping. Reducing the frequency of stimulation may be one way of “focussing” the effect of DBS to achieve maximum effects on distal control whilst avoiding detrimental effects on speech, gait and axial control.

## Chapter 4

# Study II: DBS frequency and its impact on cognitive tasks

### 4.1 Introduction

#### 4.1.1 General considerations

This chapter will focus on the effect of the frequency of stimulation on different cognitive functions. To some extent, some of these functions are impaired in PD patients already at an early stage. Their modulation by 130 Hz STN DBS could deteriorate some of them. Some reports advocate some benefit, on those functions, of a decreased frequency of stimulation.

PD patients can be impaired in many cognitive domains such as working memory and executive function already in early stages (Elgh *et al.*, 2009; Foltynie *et al.*, 2004); for review see (Dirnberger & Jahanshahi, 2013). It has been advocated that these impairments could be linked to several processes, the mesocortical dopamine denervation (decrease dopamine output from the ventral tegmental area to the frontal lobe), a deficient subcortical loop at the caudate level resulting in a decreased frontal lobe activity (Gabrieli *et al.*, 1996) and the loss of cortical cholinergic innervation (Gratwicke *et al.*, 2015).

Several approaches have been used to look at STN DBS's effect on specific cognitive functions either by comparing them before/after STN DBS or on/off stimulation. The effect of STN or GPi DBS on global cognitive functions is debated.

Most studies have shown stability in the short term (Williams *et al.*, 2010; Odekerken *et al.*, 2013) but one study has shown some decline after STN DBS on the Mattis Dementia Rating scale while patients who had GPi DBS stayed cognitively stable at six months (Weaver *et al.*, 2012b). The effects of manipulation (On vs. Off stimulation) of STN DBS on a range of tasks requiring cognitive processing reveal either no change (semantic and phonetic fluency (Jahanshahi *et al.*, 2000)) or improvement (reaction time, (Ballanger *et al.*, 2009) or worsening (Go no-go task ((Ballanger *et al.*, 2009; Hershey *et al.*, 2004)), Stroop test, ((Jahanshahi *et al.*, 2000))). However, semantic and phonetic fluency were impaired in several, confirmed by two meta-analyses (Parsons *et al.*, 2006; Combs *et al.*, 2015). The effect of STN DBS was a fewer words' production for both phonetic and semantic fluency, but to a larger extent for the former. Based on the known cognitive impact of STN DBS, we decided to study the role of stimulation frequency on three tasks, the simple reaction time, the go no-go, and the verbal fluency.

#### 4.1.2 Verbal fluency

PD patients have impaired verbal fluency as part of their executive dysfunctions. This has been measured in different studies with a trend showing the semantic (category) fluency being more impaired than the phonetic (letter) one (Foltnie *et al.*, 2004; Aarsland *et al.*, 2009). While STN-DBS has been consistently shown as efficient on motor symptoms, several studies have found a reduced verbal fluency to variable extents. In the COMPARE trial (comparing Gpi DBS vs. STN-DBS), the STN arm showed a reduced phonetic fluency of about six words (although it did not reach a significant difference) seven months after surgery while the semantic fluency remained stable (Okun *et al.*, 2009). Furthermore, a meta-analysis by Parsons *et al.* showed that semantic and phonetic fluency are worsened by STN (Parsons *et al.*, 2006).

Widespread neuronal networks subtend the functional anatomy of verbal fluency. The word productions can be divided between the frontal, temporal and parietal lobe. On one side, the frontal lobe is involved in the word production for both phonetic and semantic fluency (Costafreda *et al.*, 2006), while the semantic flu-

ency is more linked to the left temporal cortex (Mummery *et al.*, 1996), and the parietal regions are more involved in switching between retrieval strategies (Gurd *et al.*, 2002). Costafreda pointed out different sub-specialized parts in the lower inferior frontal lobe; its dorsal part showed a higher BOLD response during the phonetic fluency task, while its ventral part showed a higher BOLD response during the semantic fluency task (Costafreda *et al.*, 2006). Consequently, different networks are involved in these two tasks. As specified by Anzak *et al.*, semantic or phonetic fluency performances are associated with specific power bands in the STN recorded during microrecording during the surgical procedure. While both tasks' performance is associated with an increase in the gamma band, some additional desynchronization in the beta band is seen in semantic VF only. Therefore, some specific local changes seem to occur in the STN during the performance of verbal (phonetic and semantic) fluency tasks. Changes to gamma band activity in the left STN were significantly correlated with total correct responses and measures of switching during verbal fluency (Anzak *et al.*, 2011). Consequently, a subtle balance between gamma and beta band might be necessary to achieve the best verbal fluency performance. We hypothesize that if 130Hz is overriding any STN activity, this subtle balance cannot be reached. Lower verbal fluency could be correlated to a too high frequency (130Hz) inhibiting the STN too much, while 80Hz stimulation could allow this subtle balance to appear.

#### 4.1.2.1 Hypothesis:

Consequently, we hypothesize that reducing the frequency of stimulation to 80Hz of the STN could improve phonetic fluency.

### 4.1.3 Simple reaction time

The simple reaction time (the time needed to respond quickly to a stimulus) is a task encompassing the reaction time itself and the movement time. Both parameters are altered in PD compared to controls: the movement time is slower and the reaction time somewhat longer (Berardelli *et al.*, 2001). According to Jahanshahi *et al.*, the timing for an auditory warning cue was optimally set if given not later than 200 ms

until 3200 ms before the imperative cue (it speeded up the reaction time from about 100 ms in the PD group, but did not modify the movement time) (Jahanshahi *et al.*, 1992). Several studies looked at the reaction time in patients with DBS. Brown *et al.* described 12 patients, 6 with STN DBS and 6 with GPi DBS, while both groups showed quicker reaction (71 ms) and movement time (195 ms) as compared to no stimulation, no differences were found between both groups. Interestingly, the movement time was more improved when DBS was On than the reaction time, indicating DBS as facilitating the movement itself more than the preparation for the movement (Brown *et al.*, 1999). A quicker reaction depending on stimulation was also found by Ballanger *et al.*, although the difference was only about 50 ms (Ballanger *et al.*, 2009). However, some studies did not find a difference regarding reaction time (Georgiev *et al.*, 2016) for the simple reaction time, despite a shorter movement time on stimulation ( $\geq 110$  ms). In a more complex task such as the go no-go (GNG) task (requiring to inhibit an unwanted response); the reaction time was unchanged between on and off STN DBS stimulation (Van Den Wildenberg *et al.*, 2006).

We used a simple reaction time task with an auditory cue. This design was planned to promote the fastest movement and keep participants focused on the reaction time task. We hypothesize that the reaction time and the movement time would be quicker at 130 Hz than 80 Hz because bradykinesia has been shown mostly improved at higher frequencies (Limousin *et al.*, 1995).

#### 4.1.4 Go no-go

The effect of DBS stimulation on the GNG task was assessed in On and Off stimulation in several studies. In Hershey *et al.*, patients with STN DBS were assessed as off levodopa medication, either in Off or On stimulation. The study looked at the GNG, set with two levels of difficulty: high frequency of go trials (80%), compared to low frequency (50%). The discriminability of no-go stimuli vs. go stimuli was lower in the case of strong prepotent responses (65%, vs. 75%) and was correlated to the reaction time: higher reaction time leading to more errors ((Hershey *et al.*, 2004)). Moreover, the error rate tends to fade on a low level of prepotent responses

(van den Wildenberg *et al.*, 2006). Ballanger *et al.* looked at On vs. Off STN-DBS's effect in a population of patients being operated on average 47 months earlier. They assessed the cortical correlation between the GNG (40% of no-go stimuli) and the cerebral blood flow measured by positron emission tomography. They found that the number of commission errors (the number of patients' failure to withhold themselves from pushing the response key during a no-go trial.) increased from 4% in off states to 10% in on states (Ballanger *et al.*, 2009). From the imaging perspective, it appeared that a set of cortical regions were differently activated or deactivated: activation was more pronounced at the ventral anterior cingulate cortex. Simultaneously, deactivation was seen on cerebral structures more involved in motor action (motor, premotor areas, and the pre-SMA) and the inferior frontal cortex involved in reactive and proactive inhibition (Ballanger *et al.*, 2009). A recent study showed that the discriminability rate (the number of commission errors divided by the number of no-go stimuli) was lower in STN-DBS patients if the percentage of go signals was as high as 80% (Georgiev *et al.*, 2016). Therefore we have chosen a ratio go/no-go of 80/20 to try to be more sensitive to uncover a GNG deficit related to DBS frequency.

Local field potentials are a measure of neuronal discharge synchrony, which represents probably the sum of local postsynaptic potentials expressed as an oscillatory activity (among other the beta and gamma activities) (Levy *et al.*, 2002; Tinkhauser *et al.*, 2018). Some studies looked at the modification in local field potentials during the GNG task. Gamma synchronization was increased in the STN when a patient was involved in the no-go part of the GNG task. This synchronization may represent the brake to the movement allowing more time to respond correctly to the situation (Hammond *et al.*, 2007). The same kind of beta-band behaviour was found in Kuhn *et al.* Here, the beta band's power was decreased just before a go signal (removing the break to start a movement) while the beta was restored in the no-go trials (Kühn *et al.*, 2004). Hershey highlights the importance of ventral electrode in the STN able to disrupt functional connectivity for the network connecting STN to anterior cingulate and inferior cingulate (Hershey *et al.*, 2010).

The current spreading from the more ventral electrode can modulate those fibres and modify response inhibition patient capacity during the GNG task.

We hypothesize that the same is true for high frequency STN DBS: 130 Hz could lead to a too strong inhibition on the associative network, hence to increase impulsivity, in comparison to 80 Hz. Regarding the GNG task, we hypothesize that a lower frequency of STN stimulation will decrease the reaction time and decrease the number of commission errors compared to a high frequency.

## **4.2 Methods**

### **4.2.1 Verbal fluency**

Both phonetic and semantic fluencies were assessed. For the phonetic fluency, the patient was asked to find as many different words as possible beginning with a specific letter during three consecutive trials lasting 1 minute each. Three trials were run with the letters F, A, or S, respectively. Patients were asked to avoid proper nouns or derivatives from previous words. The sum of each letter trial was calculated, excluding intrusion errors and repetitions. Semantic fluency involved generating words belonging to a category such as animals and boys' names within one minute. We measured the number of words generated in one minute for each category, excluding intrusion errors and repetitions. Parallel forms were used to minimize the practice effect. (Alternative letters: B, H, R, alternative forms for semantic fluency: Items of clothing and girl names). The raw scores were then converted to a scaled score according to the D-kef table conversion (Delis *et al.*, 2001a)

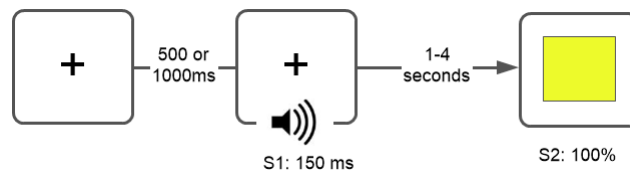
### **4.2.2 Simple reaction time**

During this task, the patient holds a box with two keys (the home and the response key). The participant is asked to fixate a cross projected on a screen for 1000 ms. An auditory warning stimulus is then given. S1 is a warning tone (800 Hz, 150 ms) randomly presented 500 ms or 1 second before S2 the actual go signal. After a variable interval of 1 second to 4 second, a second stimulus S2, go signal a green box is presented over the fixation point. The patient is asked to release the home

key and move and press the response key when the green appears on the screen as quickly as possible see figure 4.1. There are altogether 100 trials. Many variables are measured

1. The mean reaction time: (mRT) interval is calculated between the onset of the stimulus S2 and the patient lifting their index finger from the home key.
2. The mean movement time: the time when a patient has left the finger from the home key and pressed the response key.

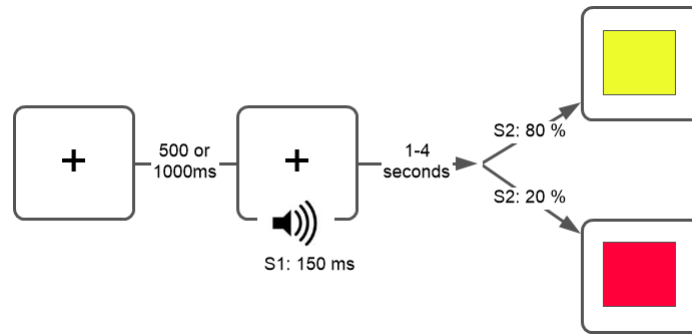
The reaction time reflects the time to make a decision, and movement time the actual time to execute the movement (Jensen, 1988). The movement time has been included as an important component describing bradykinesia.



**Figure 4.1:** Simple reaction time task, schematic representation

### 4.2.3 Go no-go Task

The same box as for the previous task is used. During this task, the patient presses the response key when a green square (Go trials) appears on the screen as quickly as possible. During no-Go trials, a red square appears on the screen. The patient is asked to withhold a response, hold down the home key, and not move the hand until a Go trial (green square) appears on the screen. The proportion of go to no-go trials in a block of 100 trials was 80/20. Only the dominant hand was used during these two tasks, see figure 4.2.



**Figure 4.2:** Go no-go task, schematic representation

In addition to mRT and mean movement time, we measure also:

1. anticipatory errors: Go trials with RTs of 100 ms
2. commission errors: Patients' failure to withhold themselves from pushing the response key during a no-go trial
3. omission errors are: Go trials on which participants omit to respond
4. partial response errors: releasing the home key on no-go trials but without pressing the response key
5. long response: responses with RTs of 2 seconds or longer

We computed the commission error rate (CER) : the proportion of commission errors out of the total number of no-go trials, the hit rate (HR) : the proportion of correct Go trials out of the total Go trials, and the anticipation error rate: anticipation errors out of the total number of Go trials. The discriminability index is the difference between HR and CER.

## 4.3 Results

### 4.3.1 Verbal fluency

#### 4.3.1.1 Letter fluency

This analysis was based on 14 patients; one patient refused to participate in this particular task. The patients are described in table 2.1. The main effect of frequency,

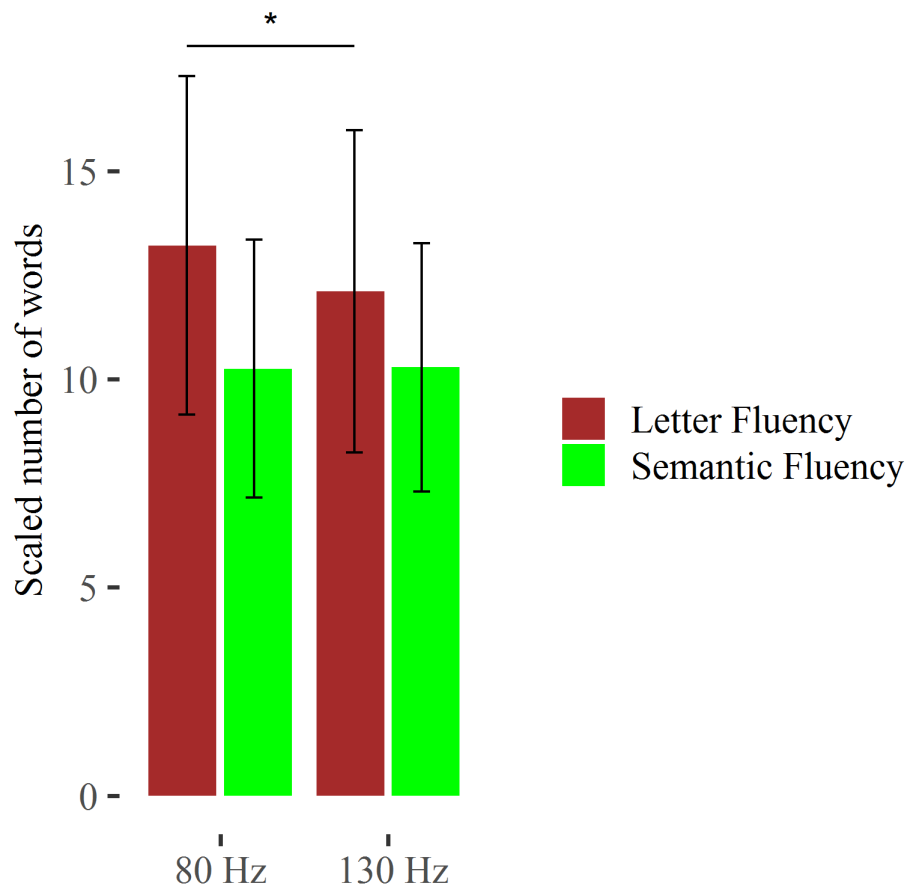
130 vs. 80 Hz, was significant, in favour of 80 Hz, for the number of correct words generated by the patients during the phonetic fluency task ( $F=5.12$ ,  $p=0.04$ ). According to the Pearson correlation coefficient calculation, the effect size was 0.4, accounting for about 20% of the effect. The main effect of changing frequency acutely versus the chronic stimulation was not significant. The interaction of these two factors was not significant either. The results do not show a significant group effect between patients starting the study at 80 Hz or 130 Hz, see table 4.1.

#### 4.3.1.2 Semantic fluency

The main effect of frequency of stimulation on semantic fluency, the acute change of frequency, and interactions were all non-significant for semantic fluency. The results did not show a significant group effect between patients either. See table 4.1

	On med 130 Hz Chronic	Off med 130 Hz Chronic	Off med 80 Hz Acute	On med 80 Hz Chronic	Off med 80 Hz Chronic	Off med 130 Hz Acute	Order	p-value	Group Off med	p-value	Frequency Off med	p-value	Ac vs.Chr Off med	p-value	Interaction Off med	p-value	Frequency On med	p-value
<b>Verbal fluency assessment</b>																		
Scaled phonetic Fluency	12.29 (4.18)	11.93 (3.87)	13.21 (4.23)	12.50 (4.03 )	13.21(4.04)	12.29 (4.01)	0.75	0.59	0.18	0.7	5.12	0.04 *	0.24	0.6	0.2	0.7	5.56	0.04*
Scaled Category Fluency	9.07 (3.52)	10.21(2.86)	10.50 (3.61)	11.07(3.12)	10.00(2.60)	10.36(3.20)	0.48	0.79	0.006	0.9	0.02	0.9	0.3	0.6	0.3	0.6	2.1	0.2
Scaled phonetic vs Category	3.21 (3.42)	1.71 (3.69)	2.71(4.01)	1.43(4.59)	3.21(3.12)	1.93 (4.14)	0.2	1	0.22	0.6	6.22	0.03 *	0.04	0.84	0.45	0.51	0.3	0.6
Intrusions in phonetic fluency	0.50 (1.75)	1.00(2.75)	1.00 (1.75)	0.50(1.75)	1.00 (1.00)	0.00 (1.75)					Z= 120	0.6						
Repetitions in phonetic fluency	2.00 (1.75)	2.00 (3.50)	1.50 (1.75)	1.50 (2.75)	1.50 (2.75)	1.50 (2.75)					Z= 120	0.2						
Intrusions in Semantic fluency	0.00 (0.75)	0.00 (0.00)	0.00 (0.75)	0.00(0.75)	0.00(0.00)	0.00 (0.00)					Z= 43	0.8						
Repetitions in Semantic fluency	1.00 (1.50)	0.00 (2.00)	0.00(1.00)	1.00(0.75)	0.50(1.75)	1.00(1.00)					Z =54	0.6						
<b>Simple Reaction Time</b>																		
Mean reaction time (ms)	421.71 (90.31)	444.87 (88.02)	421.43 (79.02)	442.12 (68.62)	449.91 (85.66)	461.14 (105)	1.13	0.35	0.01	0.94	1.81	0.2	0.5	0.49	4.1	0.1	0.04	0.8
Mean movement time (ms)2	269 (140.23)	268.46 (90.4)	253.73 (83.3)	249.42 (70.14)	275.53 (106.24)	321.38 (179.59)	2.16	0.14	0.54	0.48	4.40	0.06	1.33	0.27	4.4	0.06	2.55	0.13
Anticipation errors	2 (2)	1 (1)	2 (2.5)	2 (2.5)	1 (2)	2 (1)					Z = 100	0.8					40	0.9
Partial responses	0 (1)	0 (1)	0 (1)	1 (1.5)	0 (1.5)	1 (2.5)					Z = 70	0.9					2	0.06
Omissions	4 (5)	2 (2.5)	1 (3.5)	3 (5)	1 (1.5)	2 (3)					Z = 200	0.2					40	0.9
<b>Go no go</b>																		
Mean reaction time	560.79(144.47)	560.18(126.12)	521.79(133.99)	571.34(118.1)	590.77(151.06)	588.84(153.56)	1.43	0.22	0.07	0.8	4.04	0.07	2.6	0.13	15.95	0.002	1.39	0.26
Mean movement Time	261.5(118.93)	250.5(72.72)	246.95(124.16)	248.36(53.25)	250.1(58.02)	280.03(131.12)					Z=300	0.1					Z=70	0.5
Commissions errors	1(1.5)	0(1)	1(1)	1(1.5)	0(1)	0(0.5)					Z = 60	0.2						
Anticipation errors	0(1)	0(0)	0 (0.5)	0(1)	0(0)	0(0.5)					Z = 20	1					6	0.8
Long response	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.50)					NA	NA						
Partial response	0 (0)	0 (0.5)	0 (0.5)	0 (0.5)	0 (0.5)	0 (2)					Z = 60	0.2					4	0.4
Omissions errors	0.00( 0.00)	0.00(0.50)	0.00(0.00)	0.00(0.00)	0.00(1.00)	0.00(0.50)					NA	NA						
Commission error rates (%)	5 (7.5)	0 (5)	5 (5)	5 (7.5)	0 (5)	0 (2.5)					Z = 60	0.1					Z=20	0.7
Hit rate (%)	98.75 (2.5)	98.75 (3.12)	97.5 (1.88)	98.75 (3.75)	98.75 (2.5)	98.75 (3.75)					Z = 100	0.7					Z=50	0.5
Anticipation errors rate (%) 2	0 (1.25)	0 (0)	0 (0.62)	0 (1.25)	0 (0)	0 (0.62)					Z = 20	1					Z=6	0.8
Discriminability (%)	93.75 (10)	95 (10)	93.75 (6.25)	93.75 (13.12)	97.5 (6.88)	96.25 (6.25)					Z = 200	0.4					Z=50	0.6

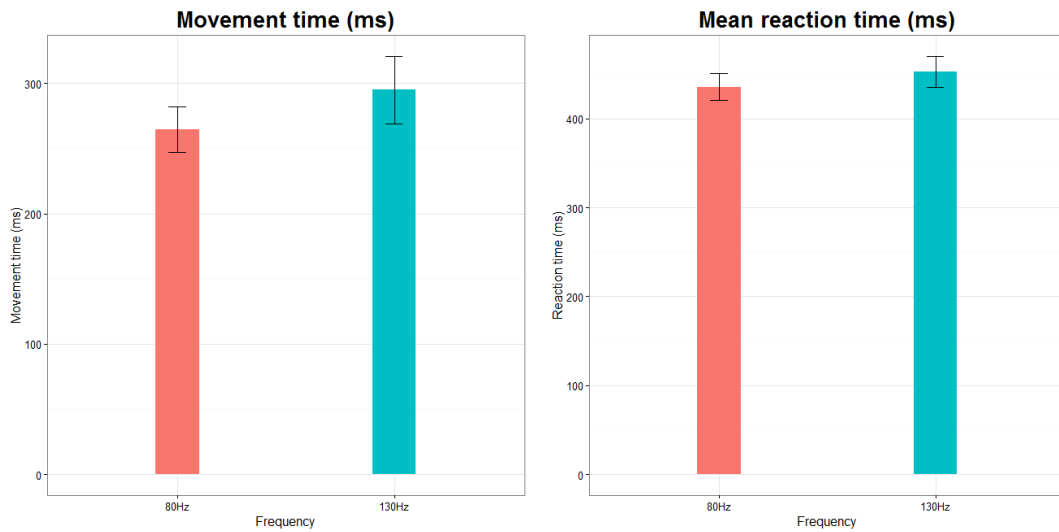
**Table 4.1: Verbal fluency data.** Means and standard deviation in brackets for parametric data, median and interquartile range in brackets for non-parametric data. \* indicates significant differences. Order: order in which the test have been done, Group off med: comparison between patients starting the study at 130 or 80Hz, Frequency off med: Comparison for frequency as a main effect in Off medication, Ac vs Chr Off med: Acute vs chronic effect as a main effect, Interaction: interaction between acutness and frequency.Repeated measure ANOVA is displayed for parametric data. For non-parametric-data: median and interquartile range are displayed as well as Wilcoxon paired test only for the main effect of frequency.



**Figure 4.3:** Verbal fluency results (semantic and phonetic) fluency. Scaled numbers of words (Phonetic fluency: 3 letters, semantic fluency: 2 categories) generated by each patient during 1 minute for patients in off medication condition. In green: semantic fluency, in brown: phonetic fluency.  $n = 14$  patients, Error bars are standard error of the mean. Phonetic fluency was significantly better at 80Hz compared to 130Hz, while semantic fluency was unchanged ( $F=5.12$ ,  $p=0.04$ ).

### 4.3.2 Simple reaction time

The reaction time differed neither across On and Off conditions nor between 130Hz, and 80Hz see table 1.1. We did not find a practice effect, no group differences, no effect of acute change of frequency, and no interactions. Nonetheless, the patients were on average quicker On medication compared to Off medication.

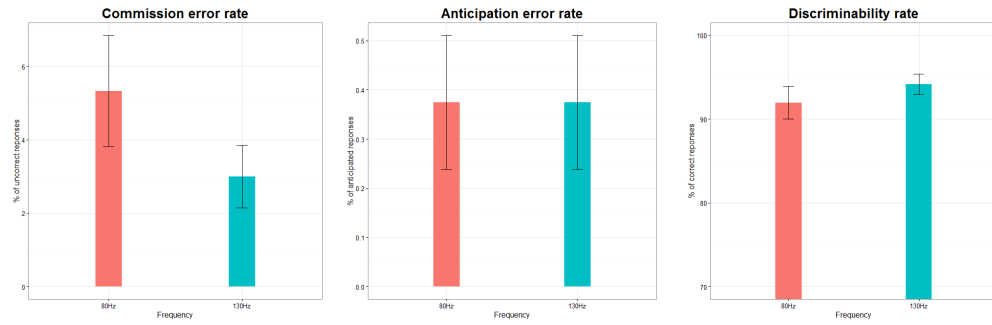


(a) Simple reaction time task: Movement time. Error bar are standard error of the mean.  $F=1.81$ ,  $p=0.2$   
 (b) Simple reaction time task: Reaction time. Error bars are standard error of the mean.  $F=4.4$ ,  $p=0.06$

**Figure 4.4:** Results for movement and reaction time during simple reaction time task. Pooled data on either 80 Hz or 130 Hz in off medication patients.

### 4.3.3 Go-no-go

The reaction time was slower in the go no-go task than the simple reaction time, but the mean movement time was similar. However, we did not find an effect of frequency on mean reaction movement time or errors, see table 4.1. Patients made fewer commission errors (although non-significant) on 130 Hz. The latter did not increase the anticipation rate. The discriminability rate was similar between both frequencies but toward an advantage for high frequency.



- (a) Commission errors. Number of patients' failure to withhold themselves from pushing the response key during a no-go trial. Maximum of 20 no-go trials. Error bars are standard error of the mean.  $Z = 50$ ,  $p = 0.2$
- (b) Anticipation errors are the number of Go trials with reaction time of  $\leq 100$  ms. Error bars are standard error of the mean.  $Z = 20$ ,  $p = 1$
- (c) The discriminability rate: difference between the hit rate and the commission error rate. Error bars are standard error of the mean.  $Z = 200$ ,  $p = 0.4$

**Figure 4.5:** Go no go results. Pooled data on either 80 Hz or 130 Hz in off medication patients.

## 4.4 Discussion

Our results confirm an improvement of 80 Hz on phonetic fluency but not on semantic fluency. The frontal lobe (especially the left Inferior frontal gyrus) being more involved in phonetic production (Costafreda *et al.*, 2006), some lower frontal activation might explain a potential discrepancy between semantic fluency preservation (more parietal) and phonetic fluency deterioration (Pihlajamaki *et al.*, 2000). One could argue that the effect is quite small (the effect size was 0.4), but this result subtends the theory that DBS at the usual high frequency setting might worsen this cognitive ability. Therefore 130Hz DBS may alter the verbal production further than 80Hz. In Wojtecki *et al.*, 10Hz frequency provided a better verbal fluency than 130Hz (Wojtecki *et al.*, 2006). The authors did calculate the effect of frequency by mixing the number of words produced in both phonetic and semantic fluency (48.3 (9.7) vs. 42.3 (11.1)). Therefore, this study was not designed to disentangle a difference between phonetic and semantic fluency. However, the motor outcome at 10 Hz frequency was detrimental. Hence, a higher frequency of stimulation is necessary to achieve a motor improvement (as shown many times in the literature ((Limousin

*et al.*, 1995; Krack *et al.*, 1998; Weaver *et al.*, 2012b; Odekerken *et al.*, 2013)); 80Hz could consequently be a good compromise. Other studies looking at the DBS effect on verbal fluency (pre vs. post-surgery) tend to show a deleterious effect of the procedure on verbal fluency: either on semantic fluency (GPi stimulation: 56.1 vs. 46.9 words, unscaled data) (Tröster *et al.*, 1997), or letter fluency (12.1 vs 10.7) (Ardouin *et al.*, 1999). Nevertheless, another study revealed no change in both semantic and letter fluency (On vs. Off stimulation) (Jahanshahi *et al.*, 2000). The difference in the number of words generated in our study (13.2 vs. 11.9) is smaller than on and off stimulation. Those studies tend to show diverse outcomes, possibly due to the experimental setup (on or off medication), the quality of the off medication assessment, or the amount of Levodopa reduction occurring after surgery. The strength of this study is attributable to its double-blinded assessment.

We did not observe any effect of the DBS frequency on the reaction time in the simple reaction time task. This confirms our earlier finding that 130 Hz and 80 Hz have a comparable effect on bradykinesia except for more complex tasks such as dual tasking or more proximal movements. Nevertheless, for simple movements, both DBS frequencies lead to an equivalent outcome. The same was true for the reaction time in the GNG task; although more complex, we did not show a difference between both frequencies. One might have predicted a decreased number of commission errors on 80Hz if the associative network is more sensitive to 130 Hz than to 80 Hz. However, despite having a strong prepotent response in our design, we did not notice a change regarding commission errors (although a trend was visible in favour of 80 Hz) and discriminability rate. This may be due to the fact either that 80 Hz is still inhibiting too strongly the associative. When comparing to previous studies on this topic, Hershey assessed go no-go in two different studies. The reaction times were similar between contact locations (ventral vs. dorsal) and between On and Off stimulation (Hershey *et al.*, 2004, 2010). However, the reaction time was a bit shorter in the presence of a strong prepotent response and lead to more commission errors. Moreover, Ballanger *et al.* reported a quicker reaction time when comparing on and off stimulation, but at the cost of more commission errors

on go no-Go tasks (Ballanger *et al.*, 2009).

In conclusion, both frequencies are similar regarding reaction times and movement times but may differ regarding a more cognitive task such as phonemic fluency. This underlines that a specific neuronal network might respond differently to a different frequency of stimulation. For example, it might be that other cortico-basal loops, such as the oculomotor loop being more sensitive to a specific frequency than the go no go task. Another task, such as the antisaccades task involved in inhibiting unwanted response, might indeed reveal a difference in reaction times or error rate.

## Chapter 5

# Study III: Cortical excitability and Frequency of stimulation

### 5.1 Introduction

As mentioned in the previous chapter, DBS is a surgical technique (used routinely to improve PD patients experiencing motor fluctuations not easily treated with optimal medication) which leads to a substantial quality of life improvement (Pollak *et al.*, 1992; Limousin *et al.*, 1995; Weaver *et al.*, 2012a; Williams *et al.*, 2010; Deuschl *et al.*, 2006; Odekerken *et al.*, 2013). While its mechanism of action is still unresolved; there is no doubt that DBS modulates STN and fibers in its neighborhood. However, the effects of DBS can also be verified at the cortical level: DBS increased cortical blood flow pattern on positron emission tomography on cortical structures related to cortico-basal circuitry (DLFPC, SMA, and cingulate cortex) (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999), although conflicting results were found where, instead, a decreased blood flow was found at several cortical levels (frontal, parietal and temporal) (Hershey *et al.*, 2003; Payoux *et al.*, 2004); DBS modifies thalamocortical connectivity as assessed on functional magnetic resonance studies (Kahan *et al.*, 2014) and neurophysiological studies showed  $\beta$  synchronization between the cortex and the basal ganglia in off medication state (Tinkhauser *et al.*, 2018). TMS is a tool used to measure cortical excitability through various paradigms such as Short interval intracortical inhibition (SICI) and Long interval

intracortical inhibition (LICI). Several studies looked at DBS's effect on cortical excitability by comparing it pre and postoperatively or On and Off stimulation in patients with DBS implanted. Those studies are detailed below. TMS gives unique access to measure brain excitability; consequently, we decided to assess if there were differences in cortical excitability according to the DBS frequency.

### 5.1.1 General consideration

TMS machines generate a time-varying magnetic field that will produce an electrical current (according to the Faraday Law), able to excite neuronal tissue. Animal experiments with the exposed motor cortex's direct electrical stimulation show that a single stimulus can produce repetitive activation of neurons in the cortex. This causes the corticospinal neurons that conduct the spinal cord activity to fire repetitively up to 4-5 times at a high frequency (1.5ms between each wave of activity). The first of these waves is caused by direct excitation of the axon of the corticospinal neurons (the D-wave), whereas the latter activity is produced by synaptic activation of the same neurons within the cortex (indirect or I-waves) (Patton & Amassian, 1954). Anesthesia can abolish I waves but not D waves, the reason why some authors advocated that I waves relate to GABAergic tone (Florian *et al.*, 2008; McDonnell *et al.*, 2007; Patton & Amassian, 1954). We have used two well-known paired-pulse paradigms to assess brain excitability: SICI and LICI. These techniques are based on applying on the brain scalp both a conditioning stimulus (CS) and a test stimulus (TS). CS and TS amplitudes and their interval will produce a certain amount of cortical inhibition, as described below.

### 5.1.2 Safety of TMS in DBS

Usage of TMS in DBS patients is considered safe for research purposes providing safety recommendations (Rossi *et al.*, 2009). This assumption is based on 1) studies looking at physical effects such as the electrical current produced in a DBS lead and the heat generated by TMS, 2) studies that have involved both TMS and DBS did not disclose any side effects. Regarding physical aspects: DBS in animal studies have established that the maximum charge density (for an electrode surface of

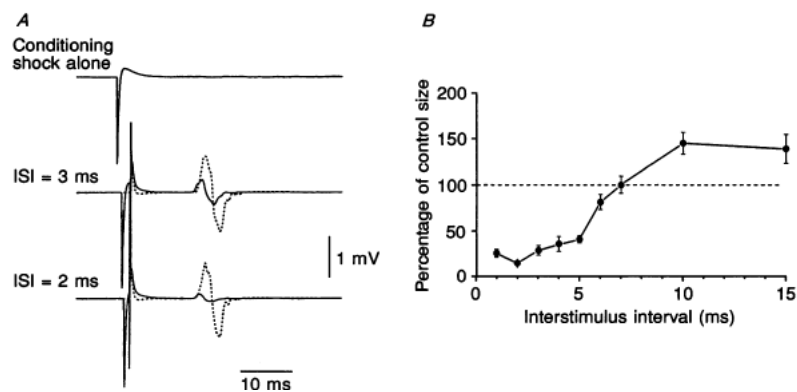
0.06 cm<sup>2</sup>) should not exceed 30  $\mu\text{C}^2/\text{cm}$  in order to avoid tissue damage, (DBS devices cannot overcome this limit) (Kuncel & Grill, 2004). The voltage produced by TMS at the electrode contact, as measured in a conducting gel (Kumar *et al.*, 1999), or with an oscilloscope (Kühn & Huebl, 2011), varied between 0.08 V and 2.8 V respectively (i.e., type of voltage reached in clinical routine). Shimojima showed, in a phantom model, no temperature increase in the DBS lead when applying continuous TMS. However, the current induced in the DBS lead increased: 1) linearly with the increase of the output stimulator and 2) when TMS was firing closer to the lead. When the TMS coil was placed on the loops formed by the DBS lead on the top of the phantom head, voltages could reach up to 34 V when stimulating at 50% of the maximal output, the charge density calculated was no more than 20  $\mu\text{C}/\text{cm}^2$  (below the maximal charge density admitted). These authors calculated that 75% of the maximum output could be beyond the safety limit (Shimojima *et al.*, 2010). A thorough review performed by Von Loh *et al.*, including five studies (involving TMS in PD patients and STN-DBS patients during 2002 and 2010: about 122 patients), disclosed no side effects related to TMS (Vonloh *et al.*, 2013).

For all these reasons, we have conducted this study by applying specific rules in addition to guidelines published by the safety consensus group (Kühn & Huebl, 2011; Rossi *et al.*, 2009): A) The TMS coil was placed behind the DBS electrodes' loop to avoid overheating them. B) The TMS maximum output limit was set at a maximum of 70%. C) A specific attention was drawn to keep a safety distance of 15 cm between the TMS coil and the DBS battery. D) An aeroplane cushion was put around the neck's patient to protect the DBS battery from direct damage (figure 5.4.)

### 5.1.3 Short-latency Intracortical Inhibition (SICI)

Paired pulse TMS reflects cortical excitability (Kujirai *et al.*, 1993; Florian *et al.*, 2008; McDonnell *et al.*, 2007; Di Lazzaro *et al.*, 1998). During SICI, two pulses are delivered on the scalp in the region in front of the hand muscles. Single pulses are set suprathreshold to elicit a controlled MEP (e.g., on the FDI), while paired pulses produce a smaller MEP (inhibited): the conditioned MEP. The latter occurs when a

subthreshold CS is set at 90% of RMT and precedes TS for 1.5 ms (Kujirai *et al.*, 1993). Figure 5.1 shows (on the first trace) that CS on its own does not produce an MEP, while paired-pulse reduces MEPs dramatically at a short interval between CS and TS. Pharmacological studies have shown that this inhibition is usually attributed to an activation of the GABA<sub>A</sub> receptor (Florian *et al.*, 2008; McDonnell *et al.*, 2007). On the contrary, near or suprathreshold CS and interstimulus longer than 10 ms may provoke bigger MEP as shown in figure 5.1. The amount of inhibition depends on the interstimulus interval: at 1 ms interstimulus interval: inhibition is attributed to refractoriness effect; while between 1.5 and 4 ms: the inhibition effect is attributed to the modulation of the GABA A receptor by modulating the presence of late I waves. (Di Lazzaro *et al.*, 1998).

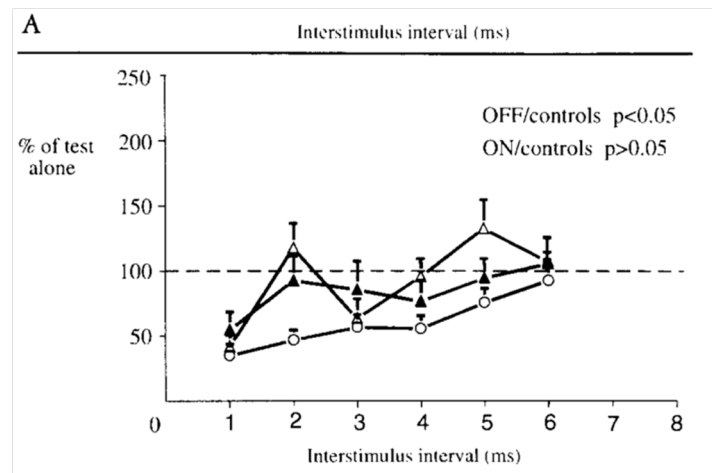


**Figure 5.1:** SICI example in Kujirai *et al.*: A dramatic inhibition of the test stimulus occurs when a conditioning stimulus precedes the test stimulus from 1.5 ms (Kujirai *et al.*, 1993)

### 5.1.3.1 SICI in PD patients

SICI is reduced in PD most of the time when patients were assessed relaxed (Ridding *et al.*, 1995b; Bareš *et al.*, 2003; Strafella *et al.*, 2000; Hanajima *et al.*, 1996). On the contrary, when patients kept some active muscle during SICI assessment, SICI in Off medication patients was not different from controls. However, the inhibitory effect was slightly lower in PD patients as if their excitability was lower than controls (Ridding *et al.*, 1995b; Berardelli *et al.*, 1996). Nonetheless, no significant differences were found between on and off Dopa conditions (Ridding *et al.*, 1995b; Bologna *et al.*, 2018) (See figure 5.2) (Ridding *et al.*, 1995b). The effect

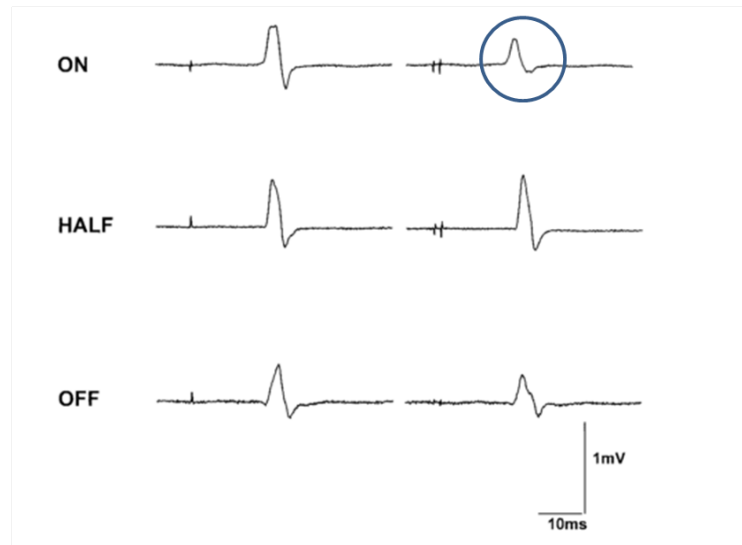
of subthalamic nucleus stimulation on SICI in PD showed variable results: either increased (Cunic *et al.*, 2002a) or unchanged (Fraix *et al.*, 2008). Altogether, SICI appears as being decreased in PD patients (Berardelli *et al.*, 2008; Ridding *et al.*, 1995b) and restored after STN-DBS (Cunic *et al.*, 2002a). It is not known how is affected SICI by DBS frequency.



**Figure 5.2:** Changes in motor cortical excitability in patients with Parkinson's disease according to interstimulus interval, (Ridding *et al.*, 1995b)

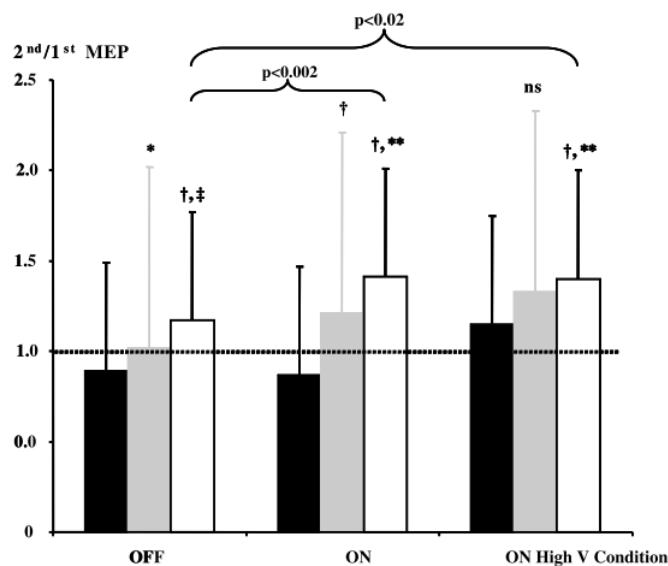
### 5.1.3.2 SICI in STN-DBS patients

The effect of subthalamic nucleus stimulation on motor cortex excitability in PD showed variable results: In Cunic: patients were assessed on dopaminergic medication. This study showed an increased SICI (CS at 95% AMT, TS at 1 mV at rest, inter-stimulus interval: 2 ms) when STN DBS was On compared to Off and half stimulation (Cunic *et al.*, 2002a). In Fraix *et al.*, no differences were found in SICI (interstimulus interval three and 5 ms, CS at 80% AMT, TS at 120% AMT). Altogether, SICI appears as being decreased in PD patients (Ridding *et al.*, 1995b; Berardelli *et al.*, 2008) and restored after STN-DBS (Cunic *et al.*, 2002a).



(a) Patients assessed on dopaminergic medication.

Top graph : On stimulation. Middle graph: Half stimulation. Bottom graph: Off stimulation. The circle points the SICI effect in patients having their stimulation turned on (Cunic *et al.*, 2002b)



(b) Paired pulse paradigm at 3, 5 and 15 ms showing no difference in SICI at 3 ms interstimulus interval in off med patients but increased facilitation at 15 ms interstimulus interval (Fraix *et al.*, 2008)

**Figure 5.3:** Short cortical Inhibition in STN-DBS patients

It is not known how is affected SICI by DBS frequency.

#### 5.1.4 Long-latency intracortical inhibition (LICI)

Long intracortical inhibition (LICI) is another way to measure cortical excitability.

This paradigm is built as follow: two stimuli (CS and TS) are set to provoke an MEP

at 120% of the RMT when given in isolation; however, when these are given within a time interval between 60 ms and 200 ms the MEP after TS is inhibited. Valls-Solé *et al.* have explored a large panel of stimulation options by varying interstimulus interval as well as stimuli intensities and showed a specific pattern of inhibition arising when stimulating between 60 to 200 ms at more than 100% RMT for both conditioning and test stimuli (Valls-Solé *et al.*, 1992). The maximum inhibition being reached at an interval of 100 ms. LICI is usually associated with GABA<sub>B</sub> (metabotropic) receptor (McDonnell *et al.*, 2007; Florian *et al.*, 2008). Indeed, the interstimulus time needed to evaluate this inhibition and its duration fits well with the metabotropic architecture of the receptor and to the building of the inhibitory postsynaptic inhibition (McDonnell *et al.*, 2007).

#### 5.1.4.1 LICI in PD

One study has found that LICI enhanced in the PD population (Berardelli *et al.*, 1996): (on non-operated patients) LICI (CS: 150% of RMT, TS: 125% of RMT) was higher in Off dopaminergic medication than control (Berardelli *et al.*, 2008). Five of these patients were also assessed on and off medication: LICI was shown as similar.

Several studies looked at LICI in the PD population as reviewed by Latorre *et al.* (Latorre *et al.*, 2019). LICI was found as decreased in the PD off medication (non-DBS patients) population (Berardelli *et al.*, 1996; Chu *et al.*, 2009) compared to healthy controls. Five patients from the Berardelli study were also tested in On medication, where LICI was shown as restored, while it was not the case in the Chu study. Another study compared healthy controls to LRRK2 PD patients and sporadic PD patients, while LICI was decreased in the LRRK2 population, no significant differences were found between healthy and sporadic PD patients in off medication (Kojovic *et al.*, 2017). As a consequence, LCI is variable in the PD population.

#### 5.1.4.2 LICI in STN DBS

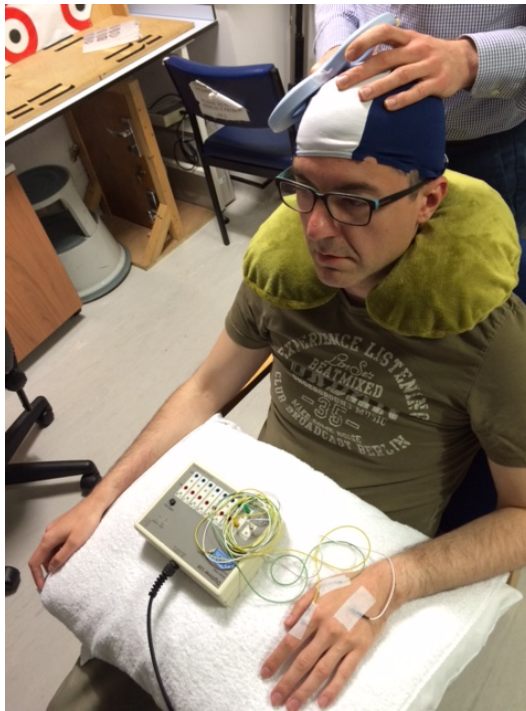
Cunic *et al.* reported no effect on LICI when comparing On, half On and off stimulation (patients were assessed on Dopa), (Cunic *et al.*, 2002a) It has not been assessed

when changing DBS frequency stimulation.

## 5.2 Method

### 5.2.1 Recordings techniques

During TMS, subjects were seated relaxed in a chair. TMS was performed using 2 Magstim 200 stimulator and a figure-of-eight-shaped coil, external wing diameter 9 cm (Magstim, Dyfed, UK). The output of two magnetic stimulators was connected to one Bistim module see figure 1.4. The coil handle was pointing posteriorly and laterally, approximately  $45^\circ$  to the sagittal midline, to evoke an anteriorly directed current in the brain to provoke an anteromedial current, see figure 5.4.



**Figure 5.4:** TMS montage

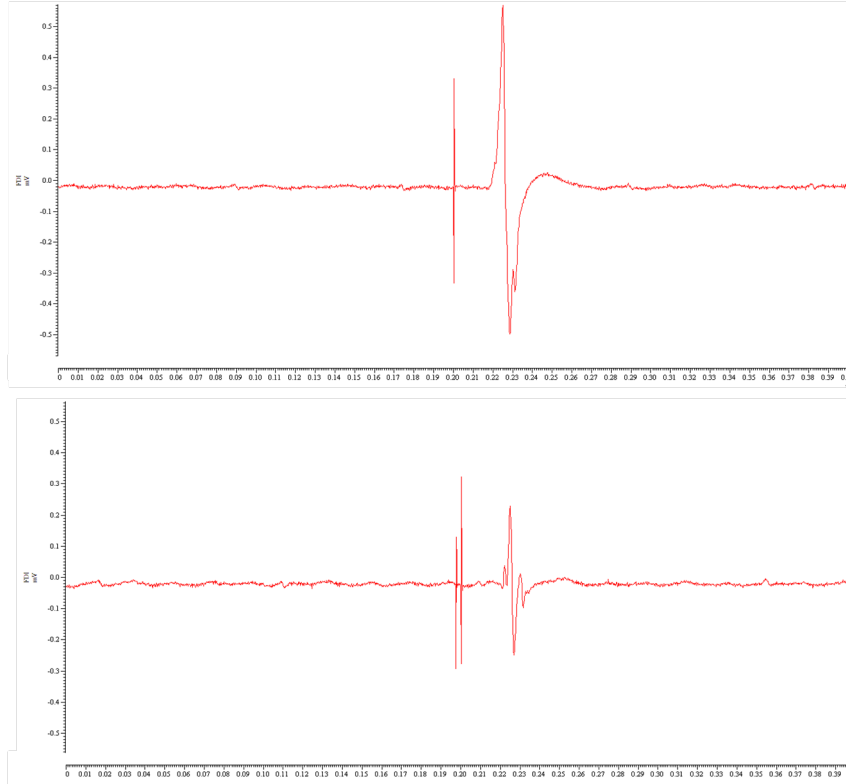
Surface EMG activity was recorded with a 10 mm Ag-AgCl surface electrode using a belly-tendon montage between the first dorsal interosseous (FDI) muscle and the corresponding metacarpophalangeal joint. The ground was placed on the third metacarpal bone (figure 1.4). EMG signal was acquired through the Digitimer D360 and transferred onto a computer via the analog-digital converter 1401 (Cambridge Electronic Design). Sweeps duration was of 400 ms. The TMS impulse was

given at 20 ms. The signal was amplified, filtered, and analyzed with the Signal software version 4.00 (Cambridge Electronic Design). The peak-to-peak amplitude was measured with dedicated scripts written on the Signal software language to capture an MEP between 20 and 40 ms after the TMS artifacts.

The optimal coil position for activating the contralateral FDI was determined as the site where stimulation produced the largest MEP in five consecutive trials. This site was marked with a pen on a cap to keep the coil's same placement throughout the experiment. Rest motor threshold (RMT) was calculated using the lowest intensity to evoke an MEP of more than 50  $\mu$ V in at least 5 out of 10 consecutive trials in the FDI. The active motor threshold (AMT) is evaluated while the subjects are contracting FDI at 10% of the maximal voluntary contraction. It is defined as the lowest stimulus intensity able to elicit motor evoked potentials with an amplitude of 100  $\mu$ V, in at least five consecutive trials.

### 5.2.2 SICI

SICI was evaluated in the FDI muscle of the more affected hand. Recordings were done at rest as attested by surface EMG control. The intensity of the conditioning stimulus (CS) varied (70%, 80%, and 90% of the AMT) to guarantee the CS remains subthreshold. The test stimulus (TS) was set at 1 mV and given 2.5 ms after CS (i.e. ISI: 2.5 ms). The choice of 1 mV was based on different studies confirming that the most important inhibition occurs at this intensity (Peurala *et al.*, 2008). Two trials are shown in figure 5.1. The graph on the top of the diagram shows the TS alone and the unconditioned MEP; on the bottom, two artifacts representing both CS and TS followed by a dramatic MEP inhibition.

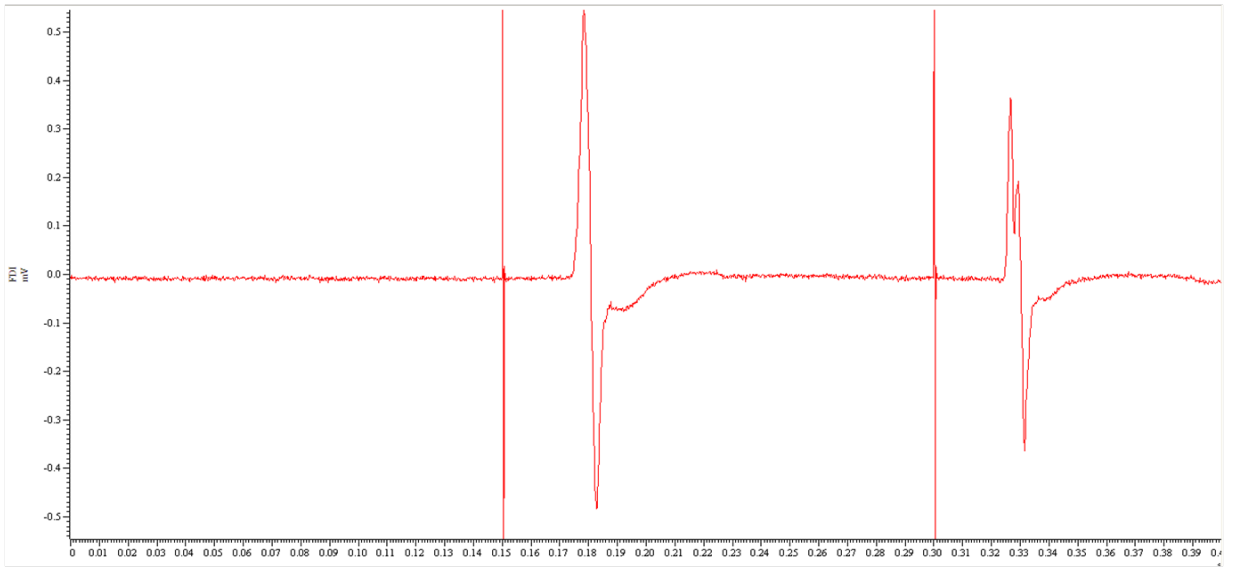


**Table 5.1: Short Intracortical inhibition example(SICI)** Example of SICI on a 400 ms sweep. The MEP is recorded on the FDI, its amplitude is expressed in mV. The diagram on the top shows a test stimulus (TS) set at 200 ms followed by a 1 mV MEP. The diagram on the bottom shows CS set at 200 ms at 80% of the AMT followed 2.5 ms later (interstimulus interval) by TS. The resulting MEP is about 40% smaller than the unconditioned MEP.

We have acquired 15 trials per condition. Our different sweeps were analysed through a custom script written in MatLab. For a given patient, each sweep was considered as an independent measure and compared to the other MEPs of the same subject in the given condition (e.g., On or Off medication and 80 Hz or 130 Hz). We set two specific rules to reject a given MEP: 1) if the amplitude of the conditioned MEP was  $\geq$  three standard deviations, 2) if the amount of contraction was  $\geq$  3 SD compared to other sweeps of the same patient and condition. Some patients had some difficulties being fully relaxed during the session due to their medical condition, and some TMS was performed off medication.

### 5.2.3 LICI

The same setup as described above was used to assess LICI. The FDI muscle of the most affected hand was assessed during a complete muscle relaxation using surface EMG as control. The conditioning and the test stimuli were set at 1 mV at 2 different interstimulus intervals: 100 ms and 150 ms. The same number of sweeps was acquired. Also, a given sweep was kept if no muscle contraction was seen before the CS.



**Figure 5.5: Long intracortical inhibition example** Example of LICI on a 400 ms sweep. The montage is the same than for SICI. The diagram on the top shows a test stimulus (TS) set at 200 ms followed by a 1 mV MEP. The diagram on the bottom shows CS set at 200 ms at 80% of the AMT followed 2.5 ms later (interstimulus interval) by TS. The resulting MEP is about 40% smaller than the unconditioned MEP.

### 5.2.4 Statistical analysis

This analysis was designed to determine which parameters are contributing to the measured cortical inhibition. Therefore, we identified four potential variables: the intensity of the CS for SICI (or the ISI for the LICI), the frequency of stimulation, the acute versus the long-term effect of stimulation, and the medication (the patient is on or off medication). We have conducted a general linear mixed model analysis. This method deals well with missing data. Besides, it allows taking into account interindividual variability and the fact that the assessments were repeated

using random factors. Finally, this method considers the variance of peripheral factors compared to the factor of interest and the intertrial variability. Models followed the gamma distribution reason why we have chosen to fit our models accordingly. We performed the analysis stepwise: firstly, we assessed all these variables' main effects and their interaction. Frequency, CS (or ISI for LICI), acute vs. chronic stimulation, and medication were implemented as fixed effects and the subjects as random effects. The main effects of the parameters investigated and the two-ways, three-ways, and four-way interactions were investigated. The models were compared according to both the Aikake Information Criteria and Bayesian Information Criteria that assessed each variables' contribution to the variance. The interaction analysis delivered several p-Values (one for each comparison), which were then gathered and adjusted according to the "false discover rate" method to reduce the type 1 error rate due to multiple comparisons.

## 5.3 Results

The demographic data are shown in table 2.1 in the general method chapter. Fifteen patients were assessed six times, as shown in the flow chart. (see figure 2.1). One patient has participated partly in the TMS experiment because he could not stand being off medication. We have reviewed participants in this study as part of their usual clinical routine follow-up on many occasions. We observed neither any damage to the DBS system nor any side effects except some participants' discomfort when receiving TMS pulses.

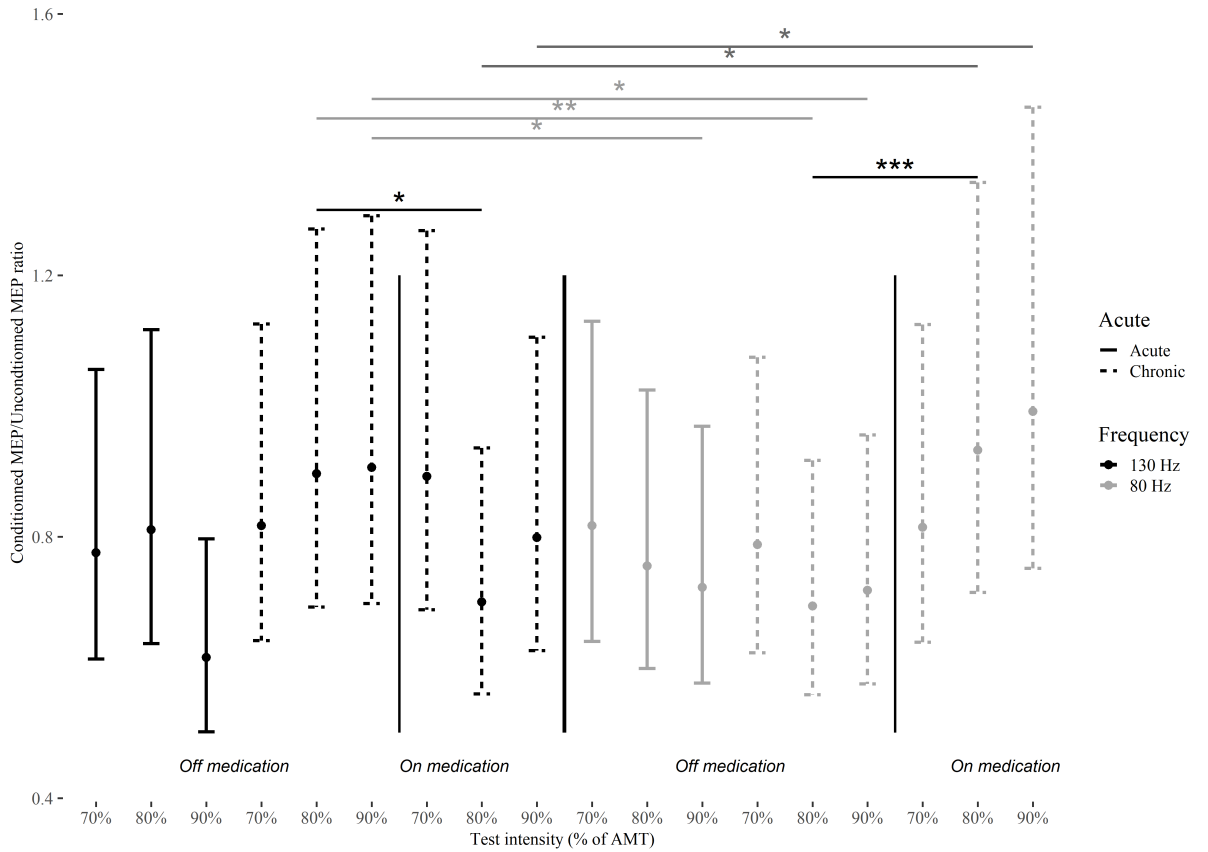
### 5.3.1 Short intracortical inhibition (SICI) results

2256 sweeps were available to assess SICI (8.4 sweeps per condition). A main effect was found for medication ( $\chi^2_{(1)} = 8.42$ ,  $p = 0.0037$ ), but not for CS ( $\chi^2_{(2)} = 0.11$ ,  $p = 0.95$ ) and frequency ( $\chi^2_{(1)} = 0.16$ ,  $p = 0.68$ ). The three-way interaction (medication \* frequency \* CS) was significant ( $\chi^2_{(2)} = 20.7122$ ,  $p < 0.0001$ ) showing a significant effect of medication and frequency on the SICI. Furthermore, the two ways interaction ISI\*State taking into account the acute-versus chronic stimulation on the effects reported above (see methods) was significant  $\chi^2_{(10)} = 40.85$ ,  $p < 0.0001$ .

The main findings and contrast analysis shows that the influence of DBS frequency on the MEP inhibition is strongly influenced by dopaminergic medication (figure 5.6, Table 5.2). Indeed, patients on medication displayed less MEP inhibition at 80Hz (i.e., less effective SICI), while the opposite pattern (a better MEP inhibition at 130Hz ) was observed off medication (5.6, Table 5.2)).

Contrast	Interaction 1	z	p value (FDR method)
Medication	main effect	8.4227	0.0140
130-on - 130-Off-chronic	80 % AMT	3.0372	0.0130
130-on - 80-On	80 % AMT	3.5355	0.0030
130-off-chronic - 80-off-chronic	80 % AMT	-3.5256	0.0030
80-off-acute - 80-on-chronic	80 % AMT	2.8716	0.0143
80-on - 80-off-chronic	80 % AMT	-4.0776	0.0004
130-on - 80-On	90 % AMT	2.9470	0.0131
130-on - 130-off-acute	90 % AMT	-2.9799	0.0131
130-off-chronic - 80-off-acute	90 % AMT	-2.9546	0.0131
130-off-chronic - 80-off-chronic	90 % AMT	-3.2607	0.0068
80-off-acute - 80-on-chronic	90 % AMT	4.2866	0.0002

**Table 5.2: Contrasts analysis** The contrast analysis for the triple ways interaction for SICI comparing frequency while patients being stimulated for a few hours: acute effects (acute), vs. during 3 weeks: chronic effect (chronic); being On medication (On) or Off medication (Off); and a given interaction with the actual conditioning stimulus during SICI. The table displays only statistically significant results after adjustment with the "False discovery method" (FDR method) for multiple comparisons.



**Figure 5.6:** Short intracortical inhibition represented as the ratio: conditioned MEP/unconditioned MEP, bars representing interval confidence. AMT: Active motor threshold. All three conditioning stimuli are: 70%, 80%, and 90% at both frequencies, acute vs. chronic stimulation and On and Off medication. A lower mean represents more inhibition

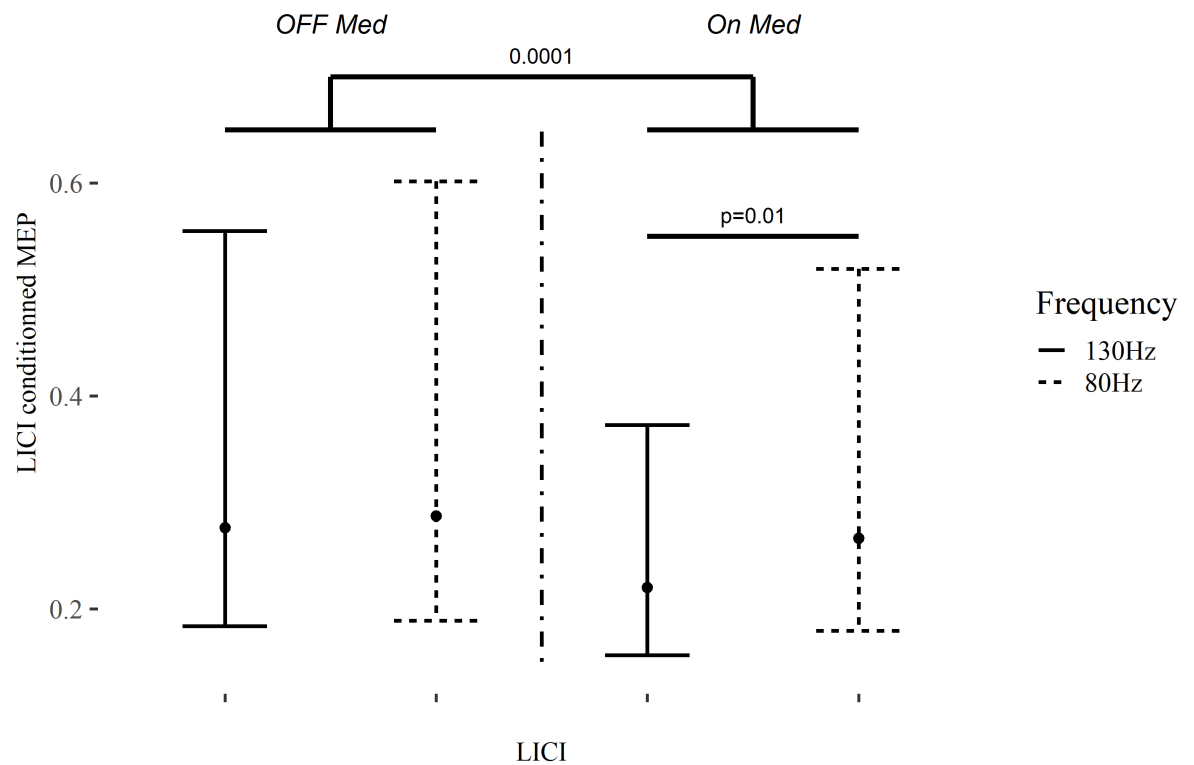
### 5.3.2 Long intracortical inhibition (LICI) results

1490 sweeps were available to assess LICI (8.3 sweeps per condition). An example of the Long intracortical inhibition is shown in figure 5.5. The principal effects were significant for ISI ( $\chi^2_{(1)} = 7.31$ ,  $p = 0.0333$ ) and medication ( $\chi^2_{(1)} = 19.24$ ,  $p = 0.0001$ ) but not for ISI ( $\chi^2_{(1)} = 4.77$ ,  $p = 0.0723$ ). The three ways interaction: Frequency\*ISI\*Medication ( $\chi^2_{(1)} = 1.35$ ,  $p = 0.4921$ ) and two ways interactions State\*ISI ( $\chi^2_{(14)} = 5.00$ ,  $p = 0.7699$ ) failed to reach significance. We however observed a two ways interaction between Frequency and medication, showing a differential effect of DBS frequency according to dopaminergic medication irrespective of ISI ( $\chi^2_{(1)} = 6.64$ ,  $p = 0.0333$ ). The Contrast analysis showed a stronger inhibition effect on 80 Hz DBS compared to 130 Hz DBS for patients on medication. Such

effect was not observed in patients off medication.

Contrast	Degree of freedom	$\chi^2$	p value (FDR method)
Principal effect Medication	1	19.2400	0.0001
Principal effect Frequency	1	7.3100	0.0333
Frequency medication interaction	1	6.6400	0.0333

**Table 5.3: Contrasts analysis for the two ways interaction between Frequency and medication LICI** The contrast analysis for LICI showing both medication and frequency as principal effect and the interaction between frequency and medication. The table displays statistically significant results after adjustment with the "False discovery method" (FDR method) for multiple comparison.



**Figure 5.7: Two ways interaction results for LICI.** Means on long intracortical inhibition are shown, comparing both frequencies with a higher amount of inhibition at 130 Hz and in On Med

## 5.4 Discussion

130Hz shows a more effective inhibition than 80Hz according to both SICI and LICI in On medication state. For SICI, the contrast analysis regarding interactions

shown in the table 5.2 revealed that the amount of inhibition is mainly driven by the medication status and 130Hz. Indeed 130Hz alters the amount of inhibition, especially in On med condition, as well as CS. The biggest CS (90% of test stimulus) showing maximal inhibition. However, in Off medication, the inhibition becomes bigger at 80 Hz. As mentioned earlier, SICI is known to be reduced (Ridding *et al.*, 1995b; Berardelli *et al.*, 1996) in PD patients and restored after DBS (Cunic *et al.*, 2002a; Däuper *et al.*, 2002; Pierantozzi *et al.*, 2002; Fraix *et al.*, 2008). Therefore we confirm that 130Hz is normalizing cortical excitability similarly to previous studies (Bologna *et al.*, 2018; Ridding *et al.*, 1995b; Fraix *et al.*, 2008) and to a greater extent than 80 Hz when patients are On medication. The reason why SICI is more effective at 130Hz could be due to several reasons. Early explanatory theories on DBS were related to its potential inhibitory effect on the STN and its connection with cortical structures (Beurrier *et al.*, 2001) through both the thalamocortical loop and the hyperdirect pathway. It might be that the fact that SICI is directly dependant on the frequency of stimulation is indeed directly linked to the higher inhibitory power of 130Hz compared to 80Hz. As such, this is corroborated by the clinical outcomes (bradykinesia and rigidity being slightly improved at a higher frequency) (Limousin *et al.*, 1995) and more sustained clinical effect (Ricchi *et al.*, 2012). Eighty-hertz frequency of stimulation was more efficient in normalizing the cortical inhibition in Off medication states; this raises the question of whether an adaption of the frequency should occur when the medication effect is fading up to keep the cortical inhibition stable.

The amount of inhibition measured by the SICI depends on many variables such as the interstimulus interval, conditioning stimuli intensity, and whether SICI is assessed at rest or with some muscular activity (Latorre *et al.*, 2019; MacKinnon *et al.*, 2005). In a previous study, when SICI was assessed in the active state (actively contracting FDI at 20% of maximal contraction); SICI was similar between healthy controls (52% of inhibition) and PD patients (45% of inhibition) (Berardelli *et al.*, 1996), however in studies where SICI was performed at rest, the amount of inhibition was about 75% inhibition in healthy controls compared to 50% in PD off

medication (Ridding *et al.*, 1995a). Both rigidity and active contraction increase the muscle tone. Therefore the difference in the amount of SICI could be due to a failure to relax (due to rigidity) in PD patients. Therefore, PD patients keep, to a certain extent, a permanently active state, which will directly influence the amount of SICI. In the present case, while we checked that patients were as relaxed as possible, a certain amount of contraction mirroring their rigidity was inevitable. Our data showed an opposite result while the patients being off medication: 80 Hz normalizing cortical inhibition better than 130 Hz. It might be that some networks depend more heavily on the dopaminergic status to achieve a synergistic effect of both dopaminergic and electrical stimulation leading to a better SICI normalization when patients are on medication. This is corroborated by a) DBS's efficiency relies on a dramatic response to dopaminergic medication (Charles *et al.*, 2002) and b) the amount of SICI is similar between dopaminergic and 130 Hz stimulation (Pierantozzi *et al.*, 2002), c) the amount of SICI is more pronounced when combining both DBS and dopaminergic medication than only stimulation (Däuper *et al.*, 2002). These facts are emphasizing that DBS modulates networks highly dependent on dopaminergic status. However, the contrary becomes true (in our study) when those networks are not under an efficient dopaminergic stimulation: avoiding any synergy. This highlights that continually stimulating with the same parameters might be less efficient than adapting stimulation to the actual dopaminergic status.

Interestingly, our data presented in the previous chapters showed that DBS's effect is not uniform and that some tasks can be improved and others aggravated by the same frequency. For example, in the previous chapter, distal movements were slightly improved at 130 Hz, but more proximal movements were improved at 80 Hz. Our results regarding SICI tend to corroborate the effect of 130 Hz on a distal muscle (FDI), the very same muscles used to assess bradykinesia during finger tapping. It is unsure if SICI would have been the same for the deltoid muscle, for example. This subtle difference needs to warn the clinicians of a possible better effect of 130Hz on distal movement even if not recordable from the clinical point of view. However, 80Hz seems to improve better proximal movements (in

the present study), complex movement (Momin *et al.*, 2018), speech (Grover *et al.*, 2019) and gait Ricchi *et al.* (2012) and is better restoring on intracortical inhibition when patients are off medication. Therefore, 80 Hz is probably modulating different pathways less responsive to dopaminergic stimulation, such as the hyperdirect pathway.

In summary, the amount of SICI results from different influences: a) being modulated by the thalamocortical loop and b) being modulated by the hyperdirect pathway (retrograde stimulation). There is a synergy when adding both 130Hz and medication from both an electrophysiological and clinical perspective. In the case of no medication (off med), the magnitude of modulation by 130Hz becomes lower, and 80hz could be better modulating some other networks less influenced by Dopa, such as the hyperdirect pathway. Because 80Hz is apparently slightly better at improving symptoms less improved by Dopa (speech and gait), other networks are being stimulated.

As in Cunic *et al.*, the amount of inhibition obtained from LICI increased with the interstimulus interval. The condition (80 vs. 130 Hz) showed a significant difference and was driven for SICI by the medication effect. In Cunic *et al.* On and Off STN DBS achieved no difference in LICI (Cunic *et al.*, 2002a); however, data on non-operated PD patients confirmed an effect of Dopa (Berardelli *et al.*, 2001). Therefore, it seems that LICI responds more to medication than to DBS. This could be because LICI deals with a different Gabaergic (GABA<sub>B</sub>-mediated) profile than SICI (GABA<sub>A</sub>-mediated). Moreover, although LICI represents cortical excitability, an effect at the spinal level is probably also participating. It is unknown if the effect of DBS (in addition to modulating the cortical level) is also modifying the descending volleys behavior, therefore, modifying the real LICI modulation at the cortical level.

Our results have several limits due to technical aspects: patients may exhibit a prominent cap on their head-protecting DBS-lead. On several occasions, the cap was on the way to the optimal hot spot, leading to unstable MEPs. SICI is challenging to obtain in STN-DBS patients. An important number of trials have been

rejected based on muscle activation (visible on the MEG recording) occurring before TMS or because huge facilitation was obtained. In conclusion, it is uncertain whether the improvement in SICI is due to a direct effect of STN stimulation at the cortical level or a more general clinical effect.

## Chapter 6

# Impact of deep brain stimulation frequency on eye movement and cognitive task

### 6.1 Introduction

DBS affects oculomotor function due to the STN modulation. Given how well-characterized the eye movement pathways are in animals and humans, assessing how DBS affects eye movements can offer insights into the mechanisms by which DBS is acting, and how a disease process and its modulation with DBS alters neural functioning.

#### 6.1.1 Ocular movement physiology

Saccades are of two types : (1) visually guided saccades that enable rapid foveation of an object of interest in the environment are thought to arise within the collicular-parietal pathway (Gaymard *et al.*, 2003); and (2) voluntary internal saccades such as antisaccades, that are embodied in the collicular-DLPFC pathway (Gaymard *et al.*, 2003; Condy *et al.*, 2004). The superior colliculus is like a bottleneck where is converging pathways arising from the PEF and FEF. While the former is directly linked to the CS, the latter is directly and indirectly linked to it via its relays in the basal ganglia (Gaymard, 2012), as described below.

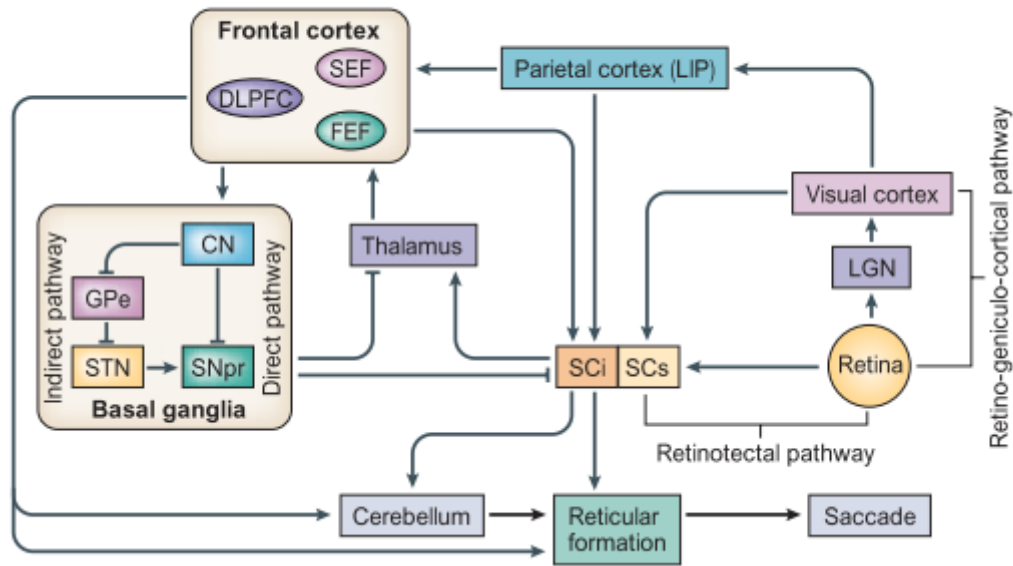
Technically, a saccade is an eye movement that includes the following features: a)

a minimal amplitude:  $\geq 2^\circ$ ; b) it is considered as completed when it reaches its first landing point; c) the fixation time: the duration between the landing point and the start point where the eye comes back to the fixation point; d) the latency: the time between the appearance of a cue and the beginning of the saccades. The usual range of saccades' reaction time is between 90 and 450ms, on average 200ms see (Westheimer, 1954). Interestingly the minimum time conduction from the retina to the generation of a saccade is 60 ms; the additional time is related to processing the information between the different cortical areas. Saccades  $\leq 90$ ms are considered express saccades; their shortness is attributed to the direct by retino-tectal pathway, bypassing the cortical level (Munoz & Everling, 2004).

### 6.1.2 Saccades

The saccades generation is a complex movement involving many cortical and sub-cortical areas involved on the one hand on visual processing, on the other hand, on the saccade generation. The visual signal related to the saccades goes through the parieto-tectal pathway, which is connected to V4. The lateral intraparietal area (in the monkey) has neurons with receptive fields (linked to a specific stimulus location in the visual field) that respond specifically to salient objects (Gottlieb & Goldberg, 1999). The saccades generator is located in the brainstem modulated mainly by the superior colliculus and to some extent by the FEF (Watanabe & Munoz, 2011). The critical node releasing a saccade is the superior colliculus. It is controlled by both cortical (the DLPFC, the FEF, and the SEF) and subcortical (SNr, STN) areas. The cortical influences are as follow: The FEF initiates the saccades (its inhibition will abolish saccades (Schiller *et al.*, 1980)), the DLPFC is inhibiting unwanted saccades (Condy *et al.*, 2004) and the SEF is involved in saccades preparation. The subcortical area influences are as follow: SC is continuously braked by tonic inhibition coming from the SNr (Matsumura *et al.*, 1992), while the STN and caudate nucleus act as additional brakes to the saccades, see 6.1. A saccade is triggered when a particular threshold activity is reached in SC and FEF (Paré & Hanes, 2003). Antoniadou *et al.* summarize the saccades generation by formulating the "double-loop hypothesis," which encompasses on the one side: the fronto-basal

loop and on the other side the oculomotor loop. The first loop modulates the second. While the second loop can trigger reflexive saccades, the first play a higher-order role by modulating the decision to trigger a saccade (Antoniades *et al.*, 2015). This was nicely depicted by Munoz et al (Munoz & Everling, 2004), see figure 6.1



**Figure 6.1:** Saccade generation diagram: functional network implicated in generating a saccade, (Munoz & Everling, 2004)

Part of the networks implicated in the oculomotor loop is the caudate-nigro-collicular pathway linked to the STN's ventral part as shown in Matsumura's work on non-human primate, see 6.2 (Matsumura *et al.*, 1992), which has been confirmed during Micro-recording of the STN-DBS in PD patients. (Fawcett *et al.*, 2005). In addition, contraversive saccades can be generated when stimulating one STN at a time (Sauleau *et al.*, 2007) implying a lateralized neural organisation. The reason for this phenomenon to happen was alternatively attributed either to the STN's intrinsic property or to its link to the FEF. An animal study supported the first hypothesis: GABA inactivation of the STN itself (but not outside the STN) provokes the same behaviour (contraversive saccade) (Baron *et al.*, 2002). The second hypothesis was based on the assumption that STN DBS stimulates fibers from the FEF (on the internal capsule medial aspect). Similar findings were described simul-

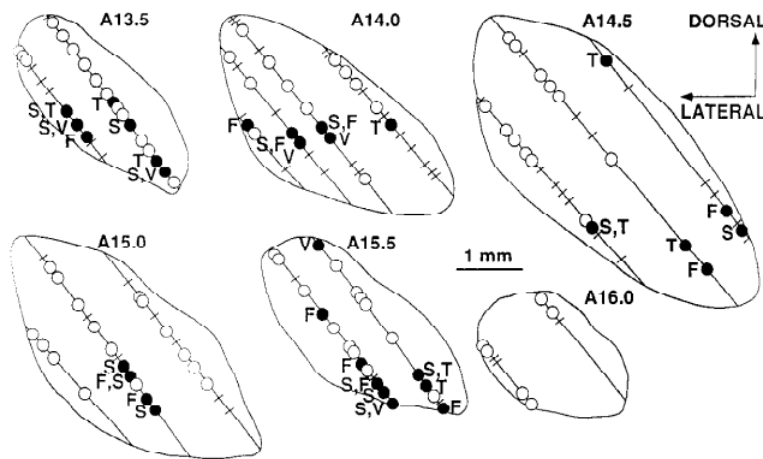


FIG. 4. Locations of neurons with visuoculomotor activities (●) and neurons with skeletomotor activities (○) that were recorded from the left STN of monkey Je. Bars: locations of neurons that showed no response. They are plotted along the reconstructed electrode penetrations obtained from the coronal histological sections. The sections are arranged in caudal-to-rostral sequence [from A13.5 to A16.0, on the basis of the atlas of the brain of *M. fuscata* (Kusama and Mabuchi 1970)], each separated by 0.5 mm. The identified electrode tracks were projected on the nearest section. Symbols along the electrode tracks indicate the types of response: F, fixation; S, saccade; V, visual; T, target and reward. Neurons with 2 types of activity are indicated by conjugated symbols (e.g., S, V). Calibration bar: 1 mm.

**Figure 6.2:** Visuomotor cells in STN in the monkey are found mainly in the ventral part. One can see that some cells are more specialized in specific eye-movements' attributes (fixation, saccades) (Matsumura *et al.*, 1992)

taneously by another study, which reproduced contraversive saccades in 9 patients when stimulating lateral and superior aspects of the STN (Shields *et al.*, 2007).

Moreover, some neurons in the STN could respond to both saccade and passive limb movement. These specific properties highlight that in PD patients, neurons' receptive field may encompass several segments of the body (Fawcett *et al.*, 2005)

STN-DBS is thought to decrease the degree of inhibition generated by the SNr upon the superior colliculus (Terao *et al.*, 2011), itself responsible for saccadic initiation. Several studies have assessed STN-DBS effects on eye-movement, in the On or Off medication state (Klarendic and Kaski for review (Klarendic & Kaski, 2020)). STN-DBS reduces pro-saccadic latency and improves the gain for visually-guided saccades compared to off stimulation (Sauleau *et al.*, 2008; Yugeta *et al.*, 2010; Goelz *et al.*, 2017).

The oscillation model of basal ganglia oculomotor (Yugeta *et al.*, 2010; Antoniadis *et al.*, 2012; Shaikh *et al.*, 2018; Tokushige *et al.*, 2018) best accounts for the STN-DBS effects on eye movements: beta-band oscillations are increased in PD patients, and because desynchronization of beta-band is required to initiate a motor command, motoric thresholds in PD are elevated. STN-DBS thus decreases pathologic oscillations and facilitates a motor command, but simultaneously stabilizes activity within the superior colliculus and restores inhibitory saccadic control

(Yugeta *et al.*, 2013) , leading to the coexistence of decreased latency and improved fixation.

Antisaccades (looking in the opposite direction to a suddenly appearing target) are of particular interest in PD as a measure of disinhibition (Van Stockum *et al.*, 2012). Antisaccades are mediated by the frontal eye field (FEF) and the superior colliculus (SC) (Munoz & Everling, 2004; Pierrot-Deseilligny *et al.*, 2004) , with additional top-down influence from the supplementary eye fields and the dorsolateral prefrontal cortex (DLPFC) (Munoz & Everling, 2004), thus adding cognitive layers on top of the final oculomotor execution and offering insights into executive function.

DBS has been shown to improve both the gain (Fawcett *et al.*, 2010; Goelz *et al.*, 2017) and latency (Yugeta *et al.*, 2010) of antisaccades in PD. The number of errors during antisaccades was found to be greater at high frequency STN-DBS in some (Goelz *et al.*, 2017) but unchanged (Rivaud-Péchoux *et al.*, 2000; Yugeta *et al.*, 2010) in other studies. These data suggest that STN's over-activity may be modified by DBS such that, altogether, eye movements are facilitated. Executive processes are impaired in PD, with deficits across planning (initiation, maintenance, and monitoring) and attention that disrupt goal-directed behaviour (Dirnberger & Jahanshahi, 2013). In addition to assessing antisaccadic performance, executive dysfunction can be probed using the Stroop test which requires suppression of a strong prepotent response of reading words (Stroop, 1935). Both the antisaccade and Stroop tests require inhibitory control of prepotent responses for correct performance (Miyake *et al.*, 2000). Such tasks are altered in PD (Dirnberger & Jahanshahi, 2013), and can be worsened by STN-DBS (Ballanger *et al.*, 2009; Jahanshahi, 2013; Jahanshahi *et al.*, 2015b,a). Thus, patients made significantly more errors on the Stroop Interference task On vs. Off DBS stimulation (Jahanshahi *et al.*, 2000), with longer reaction times found in pre vs. post DBS at 130Hz (Dujardin *et al.*, 2001). Although a few studies have looked at the effect of STN DBS on eye movements and cognition, there is little data on how different DBS frequencies may modulate specific eye movements and executive function. Given the overlap be-

tween the neural circuits for gait and eye movement (Ewencyk *et al.*, 2017) , and the fact that lower frequencies (60-80Hz) were shown to improve gait, we sought to compare the effect of 80Hz and 130Hz STN-DBS on eye movements. We hypothesized that visually-guided saccades might respond similarly to the appendicular motor system across different STN-DBS stimulation frequencies; that is, reduced saccadic latency (reaction time) for high frequency stimulation. We also predicted that more complex eye movements such as antisaccades may be more affected by 130Hz STN-DBS than by 80Hz (decreased saccadic latencies and increased errors). Similar effects of STN-DBS frequency would also be expected on the control and interference subtests of the Stroop task. These predictions are based on previous evidence showing that a) tasks with higher cognitive load were shown to be impaired by high frequency DBS (Anne Williams *et al.*, 2015; Georgiev *et al.*, 2016; Pote *et al.*, 2016) but better accomplished when lowering DBS frequency (Momin *et al.*, 2018) and b) gait, which shares common brainstem and cerebellar pathways to those used for saccadic control (Srivastava *et al.*, 2018) - was shown to improve with lower frequency stimulation (Moreau *et al.*, 2008; Ricchi *et al.*, 2012; Xie *et al.*, 2018).

## 6.2 Method

### 6.2.1 Participants

We enrolled 21 consecutive PD patients with STN DBS and 16 age-matched healthy controls (HC). The patients had received chronic STN DBS for more than six months at either the National Hospital for Neurology and Neurosurgery London or the Geneva University Hospital and were recruited from the respective outpatient clinics. Patients were implanted bilaterally with standard DBS electrodes (model 3389; Medtronic). Patients were on a variety of DBS settings at baseline. Exclusion criteria were the presence of spatial neglect or ophthalmological disorders as assessed clinically. In order to assess the effect of the stimulation alone, patients were tested off medication after overnight withdrawal of dopaminergic treatment. Stimulation parameters were changed such that two frequencies of stimulation were

tested: 80Hz and 130Hz. These frequencies were selected as 130Hz is the most routinely used stimulation frequency, and 80Hz stimulation has been used to address the long-term gait dysfunction in STN-DBS treated patients. When the frequency was modified, the voltage was adjusted in order to keep the same energy equivalence (Koss et al., 2005). Both the examiner and the patient were blinded to the stimulation setting. All participants gave informed consent. Controls were either patients' spouses or recruited from a volunteer list. They had no history of any psychiatric or neurological condition and were matched for age, sex, and education (see 6.1). The study was conducted according to Helsinki declaration and approved by both local ethical committee

The demographic and clinical details of the sample are presented in Table 6.1. The two groups were well-matched for age, gender, and global cognitive function on the Mini-mental state examination (Folstein MF, Folstein SE, 1975). Mean Frontal assessment battery test (Dubois *et al.*, 2000) scores were lower in the PD population showing higher executive dysfunction than controls, as expected.

	Controls	Patients	p value
n	16	21	
Age	66.06 (5.37)	63.71 (9.16)	0.8
Gender (M F)	10   6	15   6	0.2
Handedness (R L)	16   0	19   2	0.2
Benton Score	48.81 (3.73)	44.29 (4.39)	0.002*
MMSE	28.7 (1.4)	28.8 (1.2)	0.9
Education	1.68 (0.74)	1.75 (0.84)	0.84
FAB	17.06 (1.34)	15.1 (2.95)	0.04*
UPDRS total		14.52 (6.7)	
Time since DBS		3.87 (1.5)	
LEDD (mg)		560.81 (298.5)	
Frequency STN Right (Hz)		112.86 (24.73)	
Frequency STN Left (Hz)		115.71 (29.08)	
Voltage STN Right (V)		3.03 (0.73)	
Voltage STN Left (V)		2.85 (0.72)	
Pulse width (µs)		60 (0)	
Impedance Right STN (Ω)		1190 (238.64)	
Impedance Left STN (Ω)		1071.4 (199.3)	

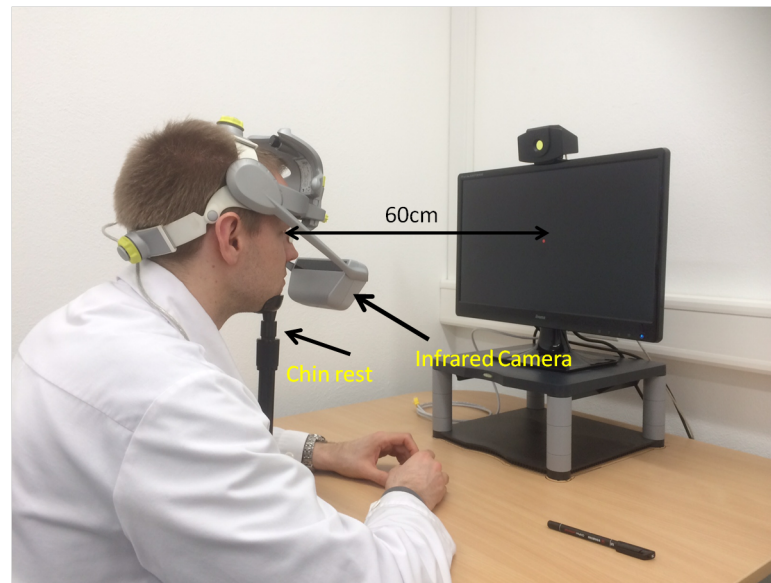
**Table 6.1:** Baseline results eye movements, MMSE: mini mental state, FAB: Frontal assessment battery. Patients and controls were fairly similar in terms of age and cognition at baseline except of FAB being lower in PD population

### 6.2.2 Baseline visit

Potential participants were identified through the movement disorders outpatient clinic, before being enrolled in the study. A baseline visit was then organized in order to administer the MMSE and the FAB to exclude patients with major cognitive impairment ( $\text{MMSE} < 24$ ) and dysexecutive function ( $\text{FAB} < 12$ ). This screening visit happened usually 1 to 2 weeks before testing the participants.

### 6.2.3 Experimental setup

The study was designed double-blinded. The settings were randomized and adjusted by a neurologist not taking part in the assessments. Patients and controls completed 2 separate testing sessions on 2 consecutive days. Patients were tested after a 12-hour over-night withdrawal from dopaminergic medication under a) 130Hz, or b) 80Hz (Koss *et al.*, 2005). Patients were stimulated at least 20 hours at each frequency before testing was started. The order of the frequency of stimulation was randomized across patients using a random number generator at the end of the baseline assessment. Recording of Eye Movements We used a head-mounted eye tracker system (Mobile EBTH, e(ye)BRAIN, [www.eyebrian.com](http://www.eyebrian.com)) with an infrared camera to capture eye movements which simultaneously captures head movement. Participants wore a padded helmet which kept the camera fixed in front of their eyes without obscuration of the visual field. The recording frequency was 300 Hz. A chin rest was used to reduce head movements, see Figure 6.3.



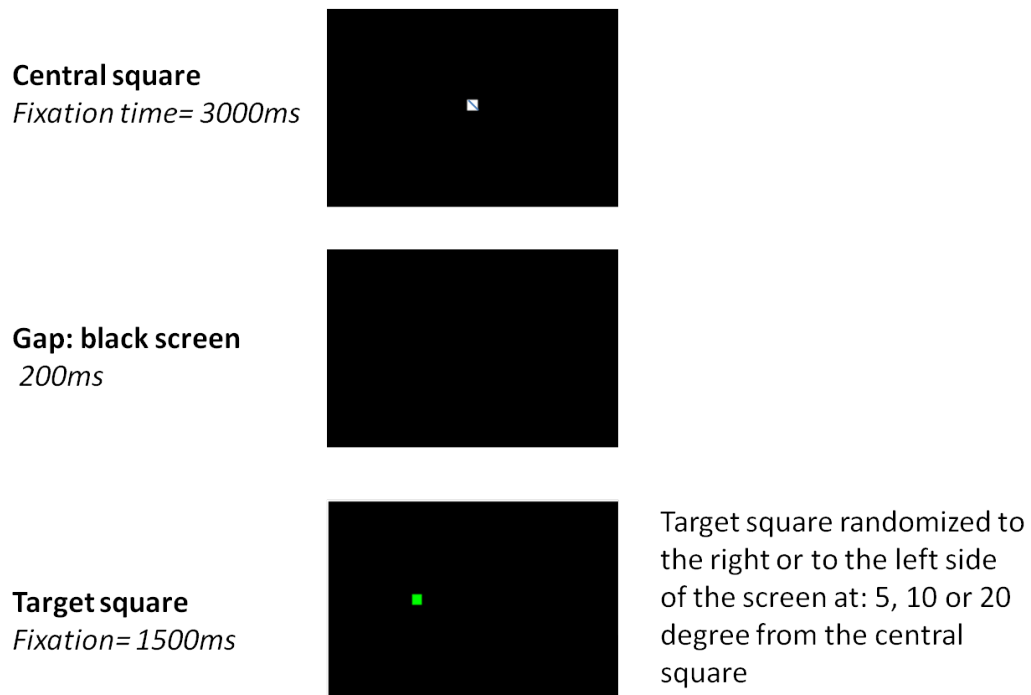
**Figure 6.3:** Eye tracker montage. The subject is sitting 60 cm away from the screen, his head being maintained still by a chin rest. The infrared camera being positioned just under the eyes in order to avoid visual obliteration.

### 6.2.4 Motor testing

We performed a UPDRS part III score to assess patients from the motor perspective. We defined subscores as follow: bradykinesia, items: 23, 24, 25, 26, Rigidity, items: 22, axial score, items: 27, 28, 29, 30 and tremor score, items: 20 and 21. This assessment was done while the researcher was unaware of the current setting

### 6.2.5 Prosaccades – gap condition

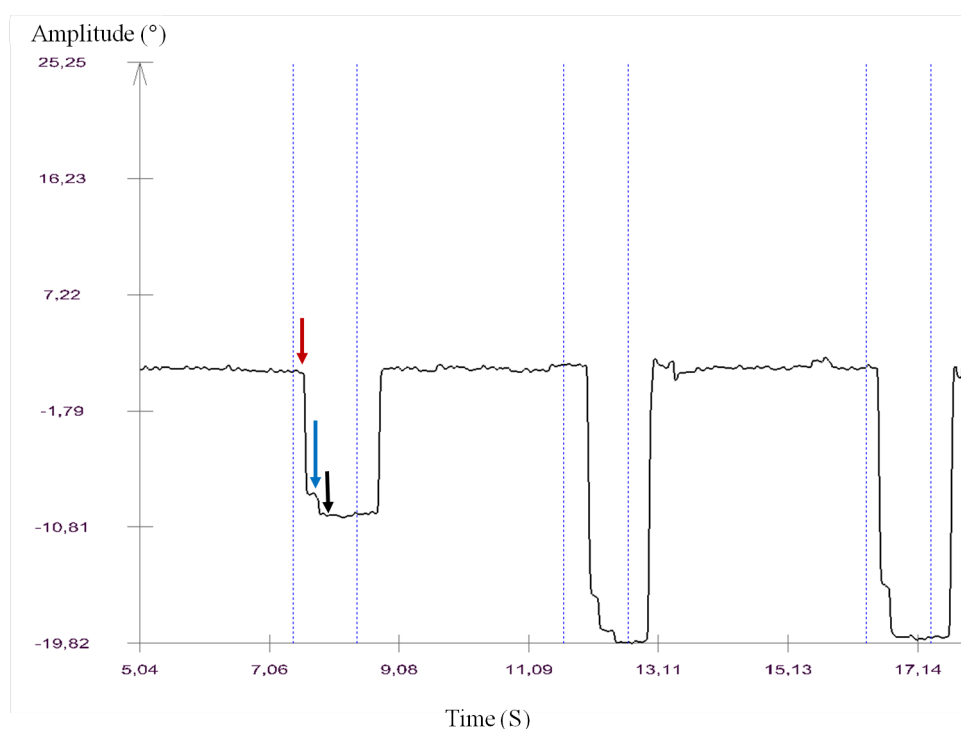
We recorded 24 trials per condition. A trial was built as follows: a) a white central fixation square appeared on a black screen for 3000 ms; b) a black screen appeared for 200 ms which represented the gap, then; c) a target green square was randomly assigned either to the right or to the left of the central fixation square, for 1500 ms, at 5°, 10° and 20° of visual angle. (See Figure 6.4) The instructions were as follows: “Look at the green squares when they appear as quickly and accurately as possible. Try to make one eye movement to the target.”



**Figure 6.4:** Gap paradigm: a central square appears on the screen for 3000 ms followed by a black screen representing a gap lasting for 200 ms. Then, a target square appears randomly on the right or left part of the screen at 5, 10 or 20 degrees from the central square. The sequence of events was the same between the prosaccades and antisaccades trial. For prosaccades: instructions were: look as quick as possible to the target square when it appears and come back the central dot: during antisaccade: When the green square comes on, please look to the mirror-image location, in the opposite direction, as quickly and accurately as possible. Try to make one eye movement to the target without moving their head.

Saccades were detected automatically by an algorithm within software Meye-Analysis, provided with the eye tracker. Saccades were defined as follows: an abrupt eye movement reaching a velocity threshold of  $\geq 30^\circ/\text{s}$  and within the range amplitude of  $2\text{-}40^\circ$ . Only the first saccade occurring after peripheral stimuli on-set (the cue) was taken into account, the latency for the saccade's initiation was  $\geq 80\text{ms}$  (shorter latencies being considered as anticipatory). The detected saccades were checked visually and discarded if a blink occurred at the beginning of the saccade or if the gaze did not return to the baseline before the next cue appeared on the screen. Gain, latency, and amplitude were calculated. The gain was defined as the ratio between the actual saccade divided by the maximum saccade amplitude to the given target. The latency of the saccade was defined as the time between the

cue and the start of the saccade. The amplitude of the saccades was defined as the distance (in degree) between the start of the saccade and the first landing point.

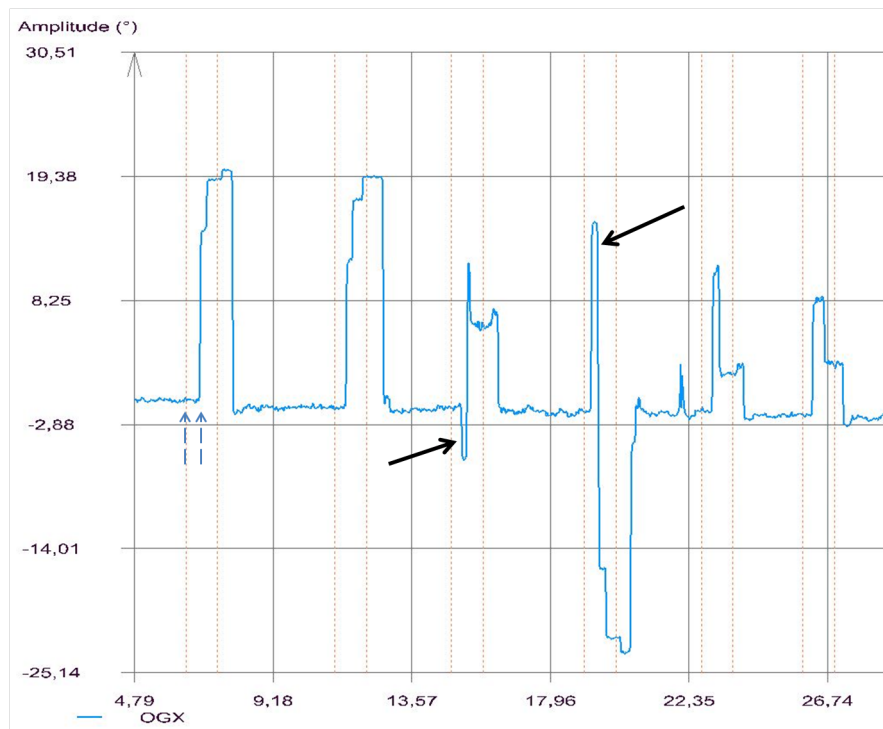


**Figure 6.5:** Oculographic recording from the left eye in a representative patient with PD, undergoing STN-DBS stimulation at 130Hz. Blue traces represent horizontal eye movements (downward deflection corresponds to a leftward directed eye movement). The start of a saccade (vertical red arrow) was automatically detected using the eye tracker software, but all traces were visually inspected for consistency and accuracy. The blue arrow denotes the first landing point of the saccadic trajectory, and the black arrow denotes the end of the saccade. Saccadic latency was measured as the time between the stimulus onset (not shown) and the start of the saccade (red arrow). Saccadic gain was calculated as the ratio between the first saccadic landing point amplitude (approx. 7.5 degrees, blue arrow), and the maximum saccadic amplitude (approx. 10 degrees, for the saccade in this example).

### 6.2.6 Antisaccades

The same gap paradigm was used for the antisaccades task. However, the participants were asked to look in the opposite direction to where the square appeared. The instructions were as follows: "When the green square comes on, please look to the mirror-image location, in the opposite direction, as quickly and accurately as possible. Try to make one eye movement to the target." This task was completed in

one block of 24 trials per condition. We computed the number of erroneous prosaccades, saccadic latencies (the time between the stimulus appearance and the start of the saccade) for both the correctly executed antisaccades and the erroneous saccades, and the gain (the ratio between saccade amplitude and stimulus amplitude) for correct antisaccades, see Figure 6.6.



**Figure 6.6:** Antisaccade example. Black arrows shows two antisaccades errors, dotted arrows show the latency between the cue and the start of the saccade.

### 6.2.7 The Stroop test

The Stroop colour word interference task from the Delis-Kaplan battery (Delis *et al.*, 2001a) encompasses four subtests as follow: 1) "Control naming task": naming the colour of individual rectangles appearing on the screen as quickly as possible; 2) "reading task": reading the colour words red, blue and green printed in black ink as quick as possible; 3) the "inhibition task": naming the color of the colour words red, green, blue - and not reading the word itself - as fast as possible, where the words are printed in an inconsistent color ink (e.g. the word "red" is printed in green ink); 4) "Inhibition/switching task: the patient is again presented with the words "red," "green," and "blue" written in inconsistent colours of red, green, or

blue ink. Half of these words are enclosed within boxes. As for the "inhibition task", the patient is asked to say the color of the ink in which each word is printed, but to read the word aloud (and not name the ink color) when a word appears inside a box, as quickly as he/she can without making mistakes (Delis *et al.*, 2001a), see figure 6.7. The latter task was included because it appears to involve more working memory than the inhibition trial and also captures set switching abilities (Delis *et al.*, 2001b; Lippa & Davis, 2010; Berg *et al.*, 2016). The functional network involved in the Stroop task is quite extensive: Cortical areas have been identified such as the Anterior cingulate cortex and the angular gyrus for encoding words and the critical node at the subcortical level is the STN. Stimulation of the latter changes the modulation from ACC on the angular gyrus probably through the associative thalamocortical network linking the STN and the ACC (Schroeder *et al.*, 2002b), leading to an increased number of self-corrected errors (Jahanshahi *et al.*, 2000) and increased reaction time (Dujardin *et al.*, 2012).

Participants are instructed to complete each subtest as fast as possible and to correct themselves if they make any errors. The total time taken to complete each subtest and the number of self-corrected and uncorrected trials are recorded. We also calculated the Stroop effects defined as the time difference between the control naming task and the inhibition task (Stroop effect 1) and between the control naming and reading tasks and the inhibition/switching task (Stroop effect 2). We then calculated the switching component by subtracting the inhibition/switching time from the inhibition time task.



**Figure 6.7:** Actual Stroop test from the Kaplan Delis system (Delis *et al.*, 2001a) encompasses four subtests: 1) colour naming, 2) reading, 3) inhibition and 4) the Inhibition/Switching task

### 6.2.8 Statistics

The analysis was divided into three steps: 1) we assessed for a possible learning effect since all tests were performed twice by both groups; 2) we assessed whether controls' performances differed across tasks from that of patients; 3) we evaluated the effect of frequency of stimulation in the patient group. For each step, we checked the distribution assumptions and used a generalized mixed-effect regression model that takes into account missing data (Hedeker & Gibbons, 2006). We used the statistical package lme4 (Pinheiro *et al.*, 2013) for the R software (R Core Team, 2013). Finally, the effect of stimulation was set as a fixed effect (130Hz vs. 80Hz). Significance value was two-sided, set at  $p \leq 0.05$ . When data were not normally distributed, we performed a Wilcoxon test.

## **6.3 Results**

### **6.3.1 Motor testing**

The UPDRS motor score and subscores were similar between the different stimulation settings (Table 6.2).

### **6.3.2 Prosaccades**

No repetition effect was observed for the gain or latency of saccades in either group. However, latencies were higher in patients with a wider distribution compared to controls as shown in table 6.2. There was no significant difference in latencies across stimulation frequencies. Gain, in the patients' group was similar to controls but was significantly higher at 80Hz compared to 130Hz, representing improved accuracy.

### **6.3.3 Antisaccades**

As for prosaccades, no repetition effect was found in either group for correct and erroneous antisaccades latencies, error rate, or gain of correct antisaccades. Overall, the latencies for correct antisaccades were prolonged in patients compared to controls; however, erroneous antisaccades latencies were similar between patients and controls. Antisaccadic error rate was increased in patients compared to controls. Patients being stimulated at 80Hz had longer latencies for correct antisaccades compared to 130Hz but this did not reach significance ( $p = 0.07$ ) and similar latencies for incorrect antisaccades ( $p = 0.59$ ). The gain of correct antisaccades was similar between the two frequencies. We observed a greater error rate (15 % difference, SD 15,  $p < 0.0019$ ) at 80Hz compared to 130Hz.

### **6.3.4 Stroop test**

Of the 21 patients, three patients were excluded from the Stroop test analysis, one patient because of poor performance on the control task, the second was illiterate, and the third patient did not tolerate the change in frequency from his usual 60Hz to 130Hz and 80Hz because of worsening gait impairment. A learning effect was observed for the control group for the time taken to complete the test both for the

inhibition task (7.8s (SD=10.7s)) and for the inhibition/switching task (3.3s (SD=16s) after the first assessment). However, the number of errors did not change across the two administrations. No repetition effect was found in the patient group. While all Stroop subtests showed similar total completion times and error rates across the two stimulation frequencies, only the inhibition/switching task was completed faster ( $p=0.07$ ) and with fewer errors at 80Hz ( $p=0.0011$ ), see Table 6.2.

	<i>Patients</i>		<i>Controls</i>		Repetition Patients	Repetition controls	Group comparison	Frequency comparison
	130 Hz mean (SD)	80 Hz mean (SD)	Day 1 mean (SD)	Day 2 mean (SD)	p value (t)	p value (t)	p value (t)	p value (t)
<b>Motor testing</b>								
	130Hz (n=20)	80Hz (n=20)						P value (F)
UPDRS III Total	19.2 (9.06)	16.9 (10.51)						0.234 (1.51)
Bradykinesia	8.7 (5.1)	7.7 (5.6)						0.4 (t = 0.9)
Rigidity	3.6 (3.4)	7.7 (5.6)						0.5 (z = 72)
Axial	2.45 (2.19)	2.15 (2.11)						0.3 (z = 60)
Tremor	1.3 (1.42)	1.5 (1.82)						0.5 (z=40)
<b>Saccades analysis</b>								
Latency (ms)	170.25 (32.65)	163.77 (37.46)	135.83 (24.39)	151.81 (39.28)	0.4167 (0.86)	0.1069 (-1.74)	0.0359 (-2.19)	0.3261 (1.02)
Gain	0.88 (0.1)	0.92 (0.09)	0.92 (0.04)	0.92 (0.04)	0.3228 (-1.05)	0.8844 (-0.15)	0.2968 (1.06)	<b>0.0041 (-3.26)</b>
<b>Antisaccades analysis</b>								
Latency Correct (ms)	317.35 (88.22)	366.94 (130.45)	284.38 (57.09)	281.67 (71.24)	0.9602 (0.05)	0.9247 (0.1)	0.0375 (-2.17)	0.0748 (-1.91)
Latency Errors (ms)	171.37 (36.29)	177.44 (40.2)	155.62 (52.14)	164.43 (36.75)	0.4489 (-0.8)	0.687 (-0.41)	0.1657 (-1.42)	0.5942 (-0.54)
ErrorRate	44.41 (26.29)	59.52 (23.2)	23.5 (15.53)	21.8 (14.59)	0.799 (1.01)	0.923 (0.1)	<b>0.0002 (-4.14)</b>	<b>0.002 (-3.75)</b>
Gain	0.9 (0.2)	0.95 (0.3)	0.95 (0.3)	1.01 (0.31)	0.496 (-0.7)	0.398 (-0.87)	0.488 (0.7)	0.547 (-0.62)
<b>Stroop analysis</b>								
	mean (SD)							
Inhibition task (s)	68.83 (23.23)	71.44 (21.78)	66 (19.47)	58.25 (13.31)	0.76 (0.31)	0.01 (2.89)	0.22 (0.22)	0.53 (-0.64)
Inhibition task (number of errors)	1.89 (3.76)	1.94 (3.89)	0.38 (1.5)	0.38 (1.02)	0.34 (3.5)	0.85 (4)	0.03 (0.03)	0.93 (15)
Switching task (s)	94.22 (41.04)	87.28 (39.32)	71.25 (19.93)	67.94 (27.38)	0.8 (-0.26)	0.42 (0.83)	0.07 (0.07)	0.06 (2.03)
Switching task (number of errors)	2.67 (3.41)	1.56 (2.89)	1.38 (2.6)	1 (2)	0.0705 (1.81)	0.3324 (0.97)	0.2848 (0.28)	0.0234 (2.27)
Stroop Effect 1 (s)	32.83 (18.86)	35.06 (15.52)	30.06 (20)	23.25 (10.21)	0.1206 (37.5)	0.0359 (109)	<b>0.0394 (0.04)</b>	0.9058 (73.5)
Stroop Effect 2 (s)	30.44 (32.93)	23.06 (34.6)	10.81 (15.15)	8.75 (23.33)	0.887 (73)	0.2764 (89.5)	<b>0.0038 (0.0038)</b>	0.1326 (120.5)
Stroop Effect 3 (s)	25.39 (27.24)	15.83 (26.59)	5.25 (15.77)	9.69 (20.1)	1 (59.5)	0.248 (28.5)	<b>0.0177 (0.0177)</b>	0.0928 (112.5)

**Table 6.2: Eye movements vs. stroop results' table.** Summary of the comparison between 130130 Hz and 80 Hz for motor testing, saccades, antisaccades and stroop test.

### 6.3.4.1 Correlation between antisaccade errors and latency

In an attempt to verify the correlation between antisaccadic latency and the error rate, we first confirmed a tight correlation between the erroneous and correct response latencies, for both the patients and the control group ( $r=0.5$   $p<0.001$ , for both groups). We further explored the correlation between antisaccade error rate and the grouped antisaccade latency (for both erroneous and correct saccades) for both groups and both frequencies of stimulation (Pearson's method). No correlation was found in the control group. However, error rate in patients negatively correlated with saccadic latency at both 130Hz ( $r= -0.62$ ,  $p= 0.0072$ ) and at 80 Hz ( $r=-0.56$ ,  $p= 0.0201$ ) (more errors linked to shorter latency saccades). The linear regression showed that 34 % of the variance in the error rate was explained by the saccade latency when patients were stimulated at 130Hz and 27% when stimulated at 80Hz. Correlation between the Stroop effect 2 and antisaccadic error rate To assess whether antisaccades' performance was correlated with the Stroop effect, we computed Spearman correlations between the error rate during antisaccade task and both Stroop effects. No correlations for the Stroop effect 2 were found either at 130Hz ( $r = 0.3$ ,  $p= 0.2$ ) or at 80Hz ( $r= 0.28$ ,  $p=0.25$ ), nor indeed in the control group ( $r=0.00$ ,  $p=0.79$ ). The same was true for the Stroop effect 1 (inhibition vs naming control subtest), at 130Hz, ( $r= 0.4$ ,  $p=0.11$ ), at 80Hz ( $r= 0.4$ ,  $p=0.12$ ) and in the control group ( $r=0.1$ ,  $p=0.58$ ).

## 6.4 Discussion

We explored the influence of STN DBS stimulation at 130Hz and 80Hz upon oculomotor saccadic function and cognitive control. We show that eye movement performance was dependent upon stimulation frequency: saccadic gain was enhanced, but antisaccades error rate increased, with 80Hz stimulation relative to 130 Hz stimulation. As such, patients receiving 80Hz frequency stimulation can generate more accurate saccades but perform less well in an antisaccades task. Pro-saccadic latencies were higher in patients than controls but did not differ between stimulation frequencies. Interestingly, whilst 80Hz stimulation led to greater antisaccade errors,

by contrast, the number of errors during the Stroop switching/inhibition subtest was slightly decreased relative to 130 Hz stimulation. These results suggest a differential modulation of oculomotor and cortical executive cognitive control by STN-DBS.

There is a consensus that in PD; DBS STN decreases pro-saccadic latency – the time taken to initiate a saccade - and increases velocity and amplitude of visually-guided saccades (Temel *et al.*, 2008; Yugeta *et al.*, 2010, 2013; Nilsson *et al.*, 2013; Shaikh *et al.*, 2018; Dec-Ćwiek *et al.*, 2017). Other studies report a positive effect of STN DBS on visually guided and voluntary saccades (Yugeta *et al.*, 2010; Nilsson *et al.*, 2013; Dec-Ćwiek *et al.*, 2017), whereas in certain studies specific parameters (e.g. latency) are improved only for visually guided saccades, and other parameters (gain of the first saccade) only for voluntary saccades (Rivaud-Péchoix *et al.*, 2000; Temel *et al.*, 2008; Fawcett *et al.*, 2010; Antoniadou *et al.*, 2012; Pinkhardt *et al.*, 2012; Fischer *et al.*, 2016; Tokushige *et al.*, 2018). We observed a slightly higher gain at 80Hz compared to 130Hz for prosaccades but no difference for antisaccades.

The pulse-step innervation is the neural command responsible for all types of eye movement and allows the generation of a saccade towards a target, and gaze-holding at a given position. Many neural structures including the cerebellar flocculus, medial vestibular nucleus, and nucleus prepositus, are involved in this neural integration and facilitate accurate saccades (Leigh & Kennard, 2004). Given the reported improvement in saccadic gain with STN-DBS, the stimulation may modulate connectivity between the STN and these centers (Lambert *et al.*, 2012) or arise as a consequence of modulation of fibers of passage in the vicinity of the STN. Here we show that saccadic latencies were higher in patients compared to controls and similar between the two DBS frequencies. A possible explanation would be that the difference in beta desynchronization associated with 130Hz and 80Hz STN DBS frequency is not large enough to produce a measurable saccade latency difference.

#### **6.4.1 STN stimulation and anti-saccadic error rate**

Whilst it is generally accepted that STN-DBS increases antisaccadic latency in PD patients (Vidailhet *et al.*, 1994; Briand *et al.*, 1999), there is a wide variability of reported STN-DBS effects on antisaccade error rate. We found higher antisaccade

error rates in patients receiving 80Hz STN-DBS stimulation, which could either be due to a direct effect upon eye movement facilitation, or more general impairment of executive control and more specifically loss of inhibitory control leading to disinhibition and higher impulsivity. The underlying mechanism linked to this result may be attributable to the fact that indeed SC is disinhibited by STN-DBS (Yugeta *et al.*, 2010; Terao *et al.*, 2011) and according to our results even more so at 80Hz than 130Hz (better prosaccade accuracy but more errors during antisaccades at 80Hz). Increased facilitation of prosaccades (improved gain) at the lower stimulation frequencies would in turn induce greater anti-saccadic errors, perhaps due to reduced time within which to inhibit a visually-guided saccade. The cortical areas involved in generating a saccade during the antisaccades task include the FEF and the DLPFC (Leigh & Kennard, 2004; Pierrot-Deseilligny *et al.*, 2004; Antoniadis *et al.*, 2015). Lesions of the former lead to increased latencies but not errors, while lesions to the latter lead to an increase in saccadic errors without altering the latency (Munoz & Everling, 2004). The fact that both errors and latencies were increased during antisaccades compared to controls would argue against a direct effect of STN on SC (since only latencies should have been increased) but would argue instead for an alternative mechanism. It has been suggested that STN-DBS interferes with the interloop transfer: transfer between the oculomotor loop and the prefrontal oculomotor loop at the level of the striatum. The prefrontal oculomotor loop involves the DLPFC and basal ganglia oculomotor centers (STN, striatum, and ventrolateral thalamus). This loop has been proposed to account for the control of complex eye movements (including both initiation of volitional prosaccades and also inhibition of prosaccades in the antisaccade task) by acting upon the oculomotor loop (originating in FEF/SEF, going to STN and striatum then to oculomotor thalamus and back to FEF/SEF), as part of a double loop hypothesis (Antoniades *et al.*, 2015).

#### **6.4.2 STN stimulation and cognitive control**

We hypothesized that because antisaccades are a cognitively more demanding task, they would be less affected by 80Hz than 130 Hz stimulation. Indeed, high frequency STN-DBS is known to impair executive functions such as verbal fluency

(York *et al.*, n.d.; Parsons *et al.*, 2006; Williams *et al.*, 2011; Combs *et al.*, 2015) , the Stroop test (York *et al.*, n.d.; Jahanshahi *et al.*, 2000); and go-no-go tasks (Hershey *et al.*, 2004; Ballanger *et al.*, 2009; Georgiev *et al.*, 2016). In contrast, studies on lower frequency stimulation showed an improvement of verbal fluency (Wojtecki *et al.*, 2006) and freezing of gait (Moreau *et al.*, 2008; Ricchi *et al.*, 2012). Moreover, the latter has been tightly linked to antisaccade performance (Walton *et al.*, 2015). Contrary to prediction, we found a marginal improvement of executive control at 80Hz on the Stroop test, but an aggravation of the error rate in the antisaccade task. The reason for this discrepancy could be because the antisaccade task involves not only working memory but also requires an efficient fixation system able to retain a saccade despite the gap. Indeed, a study illustrates this fact when comparing antisaccades and the Stroop test: no correlation were found between corrected antisaccades and the stroop effect (Bowling *et al.*, 2012). This results emphasizes the fact that despite both antisaccade and stroop test are representing the inhibition ability their modulation by STN-DBS may differ. It has been shown that STN-DBS can modify the speed-accuracy trade-offs in favor of speed (Frank *et al.*, 2007; Pote *et al.*, 2016) , and this would account for reduced saccadic latencies in the face of increased saccadic errors. Jahanshahi *et al.* confirmed that 130Hz STN-DBS influences upon different executive tests are not uniform such that both verbal fluency and Stroop test were unaffected while Trail-Making test and Wisconsin Card Sorting were improved (Jahanshahi *et al.*, 2000). Whether this is due to differences in the anatomical, electrophysiological, and/or functional properties of affected cortical and subcortical networks across cognitive domains remains to be defined (Bouthour *et al.*, 2018). Interestingly, as part of our findings, we report that our control group has a learning effect when repeating the Stroop test for the time completion while the patients' group did not. While the learning effect is expected in the control group, this finding reflects an expected higher executive dysfunction in the patient group (Lemay *et al.*, 2004).

### 6.4.3 Clinical implications

From a clinical perspective, our data show that lowering the frequency of stimulation from 130Hz to 80Hz can modify eye movement performance without effects on motor symptoms, and thus offering a wider range of stimulation parameters that may reduce specific DBS-related side effects without compromising motor outcomes. Of particular clinical relevance, the motor UPDRS shows that different settings were equivalent, and importantly, tremor did not worsen at lower stimulation frequencies.

Gait dysfunction remains a therapeutic challenge in Parkinson's disease, being partly unresponsive to Levodopa treatment (Schaafsma *et al.*, 2003), and responding variably to STN-DBS (Tommasi *et al.*, 2007), as opposed to the three core symptoms of PD (bradykinesia, rigidity, and tremor) (Limousin *et al.*, 1995; Williams *et al.*, 2010). Even in patients treated with DBS, gait tends to deteriorate over time and whether this is related to disease progression or a deleterious effect of the stimulation is debated (Adams *et al.*, 2011; Fleury *et al.*, 2016). Recent reports on STN-DBS showed that lowering DBS frequency could improve gait (Moreau *et al.*, 2008; Ricchi *et al.*, 2012; Xie *et al.*, 2018). Freezing of gait, a significant component in gait dysfunction in PD, has been associated with an increased rate of errors during antisaccades in PD patients suggesting a link between gait and eye movement circuitry (Walton *et al.*, 2015). Indeed, visual exploration and saccades are impaired in PD and have been linked to both cognitive decline (Archibald *et al.*, 2013; Stuart *et al.*, 2019) and gait dysfunction (Anastasopoulos *et al.*, 2011; Lohnes *et al.*, 2011; Lohnes & Earhart, 2012; Ewencyk *et al.*, 2017). The latter can be improved for some patients by low frequencies (60Hz and 80Hz) (Moreau *et al.*, 2008; Xie *et al.*, 2018). Thus, the beneficial effects of 80Hz on prosaccades may translate to similar effects on gait, possibly related to the enhancement of networks involved in visual exploration.

## Chapter 7

# General Conclusion

This project has made possible to analyse in details how 130Hz or 80Hz can modulate different cortico-subcortical networks. General conclusions can be made from our behavioural measures.

## 7.1 Effect of frequency of stimulation on the motor loop

Parkinson's disease has been for a long time described as being mainly (if not only) a disease affecting motor performances. While the literature has invalidated this statement, it remains that the motor issues are prominent. As a result, being able to improve for example bradykinesia is not only a desirable but mandatory goal. It was known that frequency lower than 130Hz can have a benefit on the three cardinal symptoms (bradykinesia, rigidity and tremor), however our studies showed that 80Hz has a similar acute and long-lasting benefits three weeks later on the motor scores, as also replicated in the literature (Momin *et al.*, 2018; Xie *et al.*, 2018). Movement assessment can be divided on motor performance and assessment of the movement speed. In the first and fourth chapter: acute and chronic effect (three weeks later) of both frequencies were alike on the UPDRS motor subscores, on the number of finger taps, on the number of pegs placed in the pegboard and the reaction and movement time during the go no go task apart from the comparison of proximal movement being better performed at 80Hz.

## 7.2 Effect of frequency of stimulation measured by TMS

From the neurophysiological aspect, 80Hz and 130Hz modulation has a measurable impact. Indeed, the short intra-cortical inhibition was decreased at 80Hz compared to 130Hz. This is pointing out that, to some extent, the modulation of different frequencies has an impact on cortical inhibition in a way that it is making this inhibition more physiological at 130Hz. This can be an expected results since the connectivity between STN and SMA is a) directly linked to the motor cortico-subcortical network (Nambu *et al.*, 1996), b) a coupling  $\beta$  activity has been shown ((Tinkhauser *et al.*, 2018; Horn *et al.*, 2017)) between these two structures. In addition, imaging studies showed that the laterally located cortices linked to reactive and voluntary behaviours have an increased activity while the medial areas have a decreased one, for a review see (Grafton, 2004; Samuel *et al.*, 1997) . Interestingly, our measures were taken from the FDI, a muscle dealing with voluntary fine movements. As a consequence, 130Hz may be a better setting when it comes to try to improve fine movement, even if this was not measurable from our behavioural data.

## 7.3 Effect of frequency of stimulation on the associative loop

From the cognitive point of view, the verbal fluency and the stroop were better at 80Hz. This interesting findings goes along with the fact that numerous studies have shown a decreased semantic and phonemic fluency performance (Parsons *et al.*, 2006; Combs *et al.*, 2015). In addition, very low frequency (10Hz) has been shown to restore to some extent verbal fluency (but being detrimental from the motor point of view) (Wojtecki *et al.*, 2006). Here we show that an "intermediate" frequency of 80Hz might improve certain cognitive task without losing substantial benefit on the motor counterpart. Consequently, a lower frequency might represent a compromise.

## **7.4 Effect of frequency of stimulation on the oculomotor loop**

From the oculomotor point of view: we have focused our analysis on two main features: saccades' latencies and gain. When patients were performing actual saccades, their latencies (their reaction time) were similar (the same was true for the go-no-go task ) but their gain was improved at 80Hz. However, during antisaccades, the gain remained similar between both frequencies but the number of errors and their latencies were increased at 80Hz. This was an unexpected result since we have predicted a higher errors' rate at 130Hz. A possible reason for this finding is: the network dealing with antisaccades is wider and needs to mix oculomotor network on one side, but also the working memory and the spatial memory. Interestingly, the strategy used by the patients to achieve the antisaccades had a cost: an increased latency. This means that some compensatory phenomenon are taking place to allow the correct answer, namely: to prevent looking to the strong contralateral stimulus. This findings were not corroborated by our go-no-go task where no effect of the frequency were visible. The reason is probably linked to the fact that oculomotor movement are finer movement where more effects could be measurable.

As a consequence, one frequency of stimulation does not enhance all tasks, some being better restored at 130Hz (motor functions, antisaccades) and other by 80Hz (saccades, stroop).

## **7.5 How the frequency of stimulation modify different networks**

Altogether, we can confirm that 130Hz is a good frequency when it comes to deal with pure motor issues, but some tasks seems to be more prone to be better restored with some different frequencies. This is also subtended by the current knowledge on the STN's neurophysiology. Indeed, the local field potential measurable in the STN shows different power of frequency across its structure in PD patients : its dorso-lateral part being richer in the  $\beta$  band (12-30Hz) and its ventral part being

richer  $\gamma$  band (30-100hz). These neurophysiological subdivisions are replicating the anatomical ones: motor tasks being mapped on its dorsolateral aspect and emotional tasks being mapped on the ventral one. (Eitan *et al.*, 2015) . Numerous articles are dealing with the role of the  $\beta$  local field potentials (Kühn *et al.*, 2008; Tinkhauser *et al.*, 2018). Those  $\beta$  power and their duration correlates well with the motor status. Interestingly, when patients are on medication, the  $\beta$  power is replaced by the  $\gamma$  power. The latter has been shown, in animal models, as enhancing the cortical performance (Sohal *et al.*, 2009). In addition, a subdivision of the  $\gamma$  spectrum named the finely tuned gamma (60-90Hz) has been advocated as a physiological correlate enhanced by levodopa and having coherence with the cortex (Jenkinson *et al.*, 2013). This oscillation matches well with the intermediate frequency we have applied during our study. Then, it could well be that the modulation given by DBS, is, indeed, enhancing some useful modulation in the brain. In addition a recent study confirmed that 60Hz frequency can improve bradykinesia as did 130hz by favouring  $\alpha$  and low  $\beta$  local field potential, while 130Hz replaced all the  $\beta$  band (Blumenfeld *et al.*, 2017). However, this does not mean that one frequency fits with all "physiological" oscillations. For example, the limbic system has been shown to be driven by a  $\theta$  oscillation. As a results, it is possible that the brain coordinate brain regions in the spectrum of a certain range of frequencies that can be enhanced, as opposed to be broken by high frequency of stimulation. As a consequence, one could postulate that a given  $\gamma$  oscillation may be suitable to enhance performance of a particular network.

However, it is unknown what would be the best  $\gamma$  oscillation for the oculomotor functions. From our results, while saccades were improved by 80Hz, antisaccades were not. This means: a) that when it comes with clinical practice the choice between the two frequencies is open, b) more research should be done on trying to have physiological surrogate allowing not only to measure the  $\gamma$  power but also to adapt the stimulation on-line in order to favour the actual needed oscillation.

## 7.6 Which patient will benefit from 80Hz?

Our data can't offer a definitive answer to this question. However, as most of our patients managed to go through the whole process of the study, one patient had to give away, and the amount of tremor as measured by the UPDRS scale was increased, although not significantly. Therefore, from a practical point of view choosing 80Hz in patients presenting an important burden of tremor may notice an aggravation, and should not be chosen for this strategy. On the other hand, some data tend to confirm some benefit on speech and gait, although the magnitude of this effect is small. Finally our cognitive data showed an advantage of lower frequency on cognitive functions but not on antisaccades. As a consequence, our proposal would be to try 80Hz in patients without tremor, experiencing some cognitive decline or gait and or dysarthria.

## 7.7 Future research perspectives

As stated above, our data show that a given fixed frequency of stimulation does not fit all networks; in addition, not all networks are degenerating at the same pace in PD. This is an opportunity to promote very personalized medicine. Indeed, personalizing the frequency of stimulation to a given patient may improve the therapy's efficacy. We hypothesize that the best frequency of stimulation should fit with the fine-tuned  $\gamma$ . Studies looking at the acute effect of a DBS frequency based on the fine-tuned  $\gamma$  could reveal, on the one hand, the persistence of a clinically meaningful motor effect, while on the other hand side minimizing cognitive side effects. In order to demonstrate this, several studies and adaptations could be conducted: 1) Electrodes should be adapted to be able to detect the fine-tuned  $\gamma$  frequency, 2) chronic stimulation over months or an even longer duration should also be implemented to verify that the chronic effect of a low frequency of stimulation may last if set at the fine-tuned  $\gamma$ . These studies could be set either in a cross-over fashion or prospectively. In the current perspective of adaptive stimulation, we think that deep brain stimulation should be delivered in the presence of the  $\beta$  band and adapted to enhance the fine-tuned  $\gamma$ . This would allow delivering the correct amount of stim-

ulation at a given time; 3) these studies should then verify if the modulation of the STN enhancing the fine-tuned  $\gamma$  frequency is, indeed able to minimize cognitive issues by comparing to the current mode of stimulation to the stimulation adapted solely on the  $\beta$  band detection.

**Appendix A**

**Appendix**

Date	
Time of scoring	
Examiner name	
Anti-parkinsonian medication	
DOPA mg/d	•
	•
	•
Hrs DOPA lasts	•
	•
Time of last anti-parkinsonian medication intake	
Medication	Off On
Activa® Therapy	On Off On Off
1 Mentation	
2 Thought Disorder	
3 Depression	
4 Motivation/Initiative	
Subtotal 1-4 (maximum=16)	
5 Speech	
6 Salivation	
7 Swallowing	
8 Handwriting	
9 Cutting food	
10 Dressing	
11 Hygiene	
12 Turning in bed	
13 Falling	
14 Freezing	
15 Walking	
16 Tremor	
17 Sensory symptoms	
Subtotal 5-17 (maximum=52)	
18 Speech	
19 Facial expression	
20 Tremor at rest: face,lips,chin	
Hands: right	
left	
Feet: right	
left	
21 Action tremor: right	
left	
22 Rigidity: neck	
Upper extremity: right	
left	
Lower extremity: right	
left	

Patient Name :
N°

23 Finger taps: right				
left				
24 Hand grips: right				
left				
25 Hand pronate/supinate: right				
left				
26 Leg agility: right				
left				
27 Arise from chair				
28 Posture				
29 Gait				
30 Postural stability				
31 Body bradykinesia				
Sub-total 18-31 (maximum=108)				
Total points 1-31 (max=176)				
32 Dyskinesia (duration)				
33 Dyskinesia (disability)				
34 Dyskinesia (pain)				
35 Early morning dystonia				
36 "Offs" (predictable)				
37 "Offs" (unpredictable)				
38 "Offs" (sudden)				
39 "Offs" (duration)				
40 Anorexia, nausea, vomiting				
41 Sleep disturbance				
42 Symptomatic orthostasis				
Blood Pressure: seated				
supine				
standing				
Weight				
Pulse: seated				
standing				
Total points 1-42 (max=199)				
	Best	Worst	Best	Worst
Hoehn & Yahr Stage				
% ADL Score (PD)				
% ADL (with dyskinesia)				



## Consent Form

**Agreement to participate in Research Project:** Clinical and neurophysiological assessments of DBS frequency in Parkinson's disease.

**Researchers:** Dr André Zacharia. Dr Patricia Limousin. Dr Thomas Foltynie. Dr Matteo Ciocca, Dr Isabel Sastre-Bataller. Professor John Rothwell. Professor Marjan Jahanshahi. Professor Marwan Hariz. Dr Ludvic Zrinzo.

**Version 1.0** 01/08/2013

**REC ref no:** 13/LO/1255

**Please Initial**

1. I confirm that I have read and understood the Participant Information Sheet dated 03/04/2013 (version 1.0) for the above study.
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
3. I understand that my participation is entirely voluntary and that I am free to withdraw at any time without giving reason, or my medical care or legal rights being affected.
4. I understand that relevant data collected during the study may be looked at by the research doctors, responsible individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
5. I agree to take part in this study.
6. With your permission, we will inform your GP that you will take part in the study.

☐

☐

☐

☐

☐

☐

_____ Name of Participant	_____ Date	_____ Signature
_____ Name of person taking consent (if different from researcher)	_____ Date	_____ Signature
_____ Researcher	_____ Date	_____ Signature

*When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes*



UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.



## VIDEO and IMAGE CONSENT FORM

**Version 1.0** 01/08/2013

**REC ref no:** 13/LO/1255

Title of project: **Clinical and neurophysiological assessments of DBS frequency**

Name of Principal investigator: Doctor Patricia Limousin

The participant (Name) \_\_\_\_\_

Has given his / her consent to be filmed during the above experiment and for the images to be potentially used for:

Please Initial Boxes

Analysis purposes

☐

Teaching purposes and presentation at scientific meetings

☐

Publication in scientific journals \*

☐

\*Here eyes will be obscured

\_\_\_\_\_  
Name of participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature



UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

# MINI-MENTAL STATE EXAM

PATIENT NAME: \_\_\_\_\_ DoB: \_\_\_\_\_

NHS Number: \_\_\_\_\_

DATE:

## Right / Wrong? - 30 questions for 30 points

### ORIENTATION – 10 points

Ask the following questions:

1. What is today's date?
2. What is the month?
3. What is the year?
4. What day of the week is it today?
5. What season is it?
6. What is the name of this clinic (place)?
7. What floor are we on?
8. What city are we in?
9. What county are we in?
10. What country are we in?

**Orientation subtotal = /10**

### IMMEDIATE RECALL – 3 points

Ask the subject if you may test his/her memory. Then say "ball", "flag", "tree" clearly and slowly, about 1 second for each. After you have said all 3 words, ask him/her to repeat them - the *first* repetition determines the score (0-3):

11. BALL
12. FLAG
13. TREE

**Recall subtotal = /3**

### ATTENTION – 5 points

**NB PERFORM SERIAL 7S OR 'WORLD' BACKWARDS BUT NOT BOTH!**

A) Ask the subject to begin with 100 and count backwards by 7. Stop after 5 subtractions. Score the correct subtractions.

14. "93"
15. "86"
16. "79"
17. "72"
18. "65"

## **Frontal Assessment Battery**

### **Purpose**

The FAB is a brief tool that can be used at the bedside or in a clinic setting to assist in discriminating between dementias with a frontal dysexecutive phenotype and Dementia of Alzheimer's Type (DAT). The FAB has validity in distinguishing Fronto-temporal type dementia from DAT in mildly demented patients (MMSE > 24). Total score is from a maximum of 18, higher scores indicating better performance.

### **1. Similarities (conceptualization)**

"In what way are they alike?"

- A banana and an orange

(In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are fruit"; but credit 0 for the item; do not help the patient for the two following items)

- A table and a chair
- A tulip, a rose and a daisy

**Score** (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3

Two correct: 2

One correct: 1

None correct: 0

### **2. Lexical fluency (mental flexibility)**

"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.'" The time allowed is 60 seconds.

**Score** (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

> 9 words: 3

6 -9 words: 2

3 -5 words: 1

< 3 words: 0

### **3. Motor series "Luria" test (programming)**

"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of "fist-edge-palm."

"Now, with your right hand do the same series, first with me, then alone."

The examiner performs the series three times with the patient, then says to him/her:

"Now, do it on your own."

### **Score**

Patient performs six correct consecutive series alone: 3

Patient performs at least three correct consecutive series alone: 2

Patient fails alone, but performs three correct consecutive series with the examiner: 1

Patient cannot perform three correct consecutive series even with the examiner: 0

### **4. Conflicting instructions (sensitivity to interference)**

"Tap twice when I tap once."

To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

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